QuapoS 3

Quality Standard for the Oncology Pharmacy Service with Commentary

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Table of Contents

Preface to the 3rd edition of the Quality Standard for oncology pharmacy services (QuapoS) 2003

The patient is the focus of our attention. This is a view that everyone will surely agree with, although at times some may be tempted to add "ultimately".
Because ultimately it is not enough to recognise the importance of the principle; we also require the capacity – technical and economic – to implement it.

The European Union has identified new members who are keen to join, as are their peoples. The ESOP (European Society of Oncology Pharmacy) has, since 2000, been experiencing its affinity with all European experts involved in oncology pharmacy, calling on all of them to participate actively in the unification process.
And such was the spirit at the First Conference on QuapoS in September 2001 in Luxembourg. Standardisation, as we realised early on, is both an enormous challenge and an opportunity for oncology pharmacy.
Its significance lies not only in harmonisation and the benchmarking which results, but also in the freedom we have to develop in accordance with our specific conditions – usually dependent on our social framework – and to identify and record differences.
For as we know, standards are not just about the identical things we have in common, but also about things that will remain different in future.
Nothing is more depressing than attending education courses or congresses that describe situations elsewhere which seem seductively desirable, but which cannot be implemented under conditions back home, in either the near or distant future. Sticking to the devil we know is often the regrettable consequence.
QuapoS, developed by German oncology pharmacists in both hospital and public pharmacies as members of the DGOP (German Society for Oncology Pharmacy), should be seen as an offer for progress.

• The first quality standard was published in 1997 and concentrated primarily on pharmacy services in the narrower sense, i.e. conditions to comply with in the production of cytotoxic substances.
• In 2000 the second edition reaffirmed and extended existing guidelines. It also incorporated services provided by oncology pharmacists as partners within an interdisciplinary team treating the patient. Furthermore, DGOP began certifying oncology pharmacy departments in pharmacies on the basis of QuapoS.
• Now, in the third edition, the field of pharmaceutical care has been tackled and comprehensively examined. A holistic view of the patient and the orientation of pharmaceutical services towards the patient have now been reflected in the quality standard.

Let me emphasise once more that the aim of this edition is not to apply German findings to the rest of the world. Rather we are attempting – and this is why there are so many translations – to approach any interested parties in their home country and in their own language, and to facilitate their entrance into the European debate. We are fully aware that the English language will be the bridge linking us in our common scientific purpose. I wish to express my gratitude to the delegates, members and friends who have made this possible.

When we convene once again in 2004 for the Second European Conference in Luxembourg, our ability to identify what is common and what is different will be much greater than it already is, and many new colleagues will be involved in the processes we hope to trigger among the various nations.

Klaus Meier
President ESOP

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1. Personnel
1.1. Persons Handling Cytostatics

Persons handling cytostatics under the direct influence of the pharmacy include:

Pharmaceutical personnel:
- **Pharmacists and persons being trained as pharmacists**
- **Pharmacy engineers**
- **Assistant pharmacists**
- **Pharmacy technicians and persons being trained as pharmacy technicians**
- **Pharmacy assistants**

Non-pharmaceutical personnel:
- **Pharmacy auxiliary staff**
- **Professionals employed by the pharmacy**
- **Employees in the store**
- **Cleaning staff**
- **Transport staff**

Hannelore Kreckel, Giessen

All persons handling cytostatics must receive appropriate instruction before taking up their employment and at least annually thereafter.

Pharmaceutical personnel
see Section 1.2. Persons involved in Preparation

Non-pharmaceutical personnel
Non-pharmaceutical personnel may only be entrusted with work which provides support for preparation. This includes keeping the store stocked with drugs and other materials, documentation tasks, preparation for delivery including sealing the ready-to-administer cytostatic solutions, and disposal tasks.

The type of documentation and labelling, the delivery procedures, and the disposal methods for the different materials must be clearly defined and properly explained to the staff involved.

Procedures for handling sterile disposable products and the calculation of stocks of all materials and products used, both for a single working step and for the departmental stocks, must be explained. The prescribed storage conditions must be known, observed and regularly inspected.

Persons whose qualifications are of a non-pharmaceutical nature (e.g. employees in the store) can be assisted in recognising finished medicines containing cytostatics by affixing pictures of the particular products in a clearly visible position and by appropriately labelling the place where cytostatics are stored.

Transport staff
Transport staff may accept for delivery only released, properly packaged and labelled, closed containers for conveying to the departments which have requisitioned them. They are responsible for the correct and punctual delivery of the ready-to-administer cytostatic solutions.

Cleaning staff
Cleaning staff are responsible for the cleaning and care of the floor and the surfaces of the objects in the facility. Cleaning staff must be instructed about the special problems associated with a clean room and about the particular risks and hazards presented by a preparation area for ready-to-administer cytostatic solutions.

Compliance with the hygiene and disinfection plan must be documented.

1.2. Persons Involved in Preparation

Categories of person working in the cytostatics department include:

Pharmaceutical personnel:
- **Pharmacists and persons being trained as pharmacists**
- **Assistant pharmacists**
- **Pharmacy engineers**
- **Pharmacy technicians and persons being trained as pharmacy technicians**
- **Pharmacy assistants**

Non-pharmaceutical personnel:
- **Pharmacy auxiliary staff**
- **Professionals employed by the pharmacy**
- **Cleaning staff**
- **Maintenance personnel**

These persons have access to the area where preparations are carried out.

Only pharmaceutical personnel may be employed in the preparation of ready-to-administer cytostatic solutions. Before these employees begin their work, they must be adequately educated and trained in aseptic working procedures and in the handling of hazardous substances.

Quality standards must be discussed with all employees in order to arouse and promote understanding for and awareness of the diverse problems associated with an oncology pharmacy service.

Hannelore Kreckel, Giessen

Persons working in preparation have access to the preparation room, as do persons who perform cleaning and maintenance tasks.

Job descriptions are available for all categories of person employed in the cytostatics department.

Pharmaceutical personnel

Only pharmaceutical personnel may be employed in the preparation of ready-to-administer cytostatic solutions.

The ready-to-administer cytostatic solutions produced are released for delivery by a pharmacist.

The personnel entrusted with the preparation of cytostatics must be just as competent in the handling of hazardous substances as they are in the working procedures for aseptic drug preparation. The personnel must be instructed, trained and thoroughly familiar with the tasks they have to perform and must be able to participate regularly in further education or additional training courses. (cf. Chapter 1.6 Education, Training and Further Training of Staff).

Training the employees in cytostatics preparation must be planned in respect of both duration and content in order, on the one hand, not to ask too much of the persons involved and, on the other hand, to give then the opportunity to acquire the skills required for preparation and to acquire the necessary theoretical knowledge.

It is recommended that a programme be organised in which the necessary stages are divided into modules and which enables the persons being trained to learn about the complex area of work within cytostatics preparation in a logical and systematic way. For this purpose a competent contact partner must be available. (cf. Chapter 1.6 Education, Training and Further Training of Staff).

Theoretical knowledge can be acquired both through discussion and through private study or during further training events. Basic principles should be named and examined, and distinguished from advanced knowledge.

Non-pharmaceutical personnel

see Chapter 1.1. Persons Handling Cytostatics

During the preparation process, the behaviour of both the preparation personnel and the auxiliary staff must be aligned on preparation. Unnecessary movements in the preparation room affect the air flow and should therefore be avoided.

Working steps which produce particles must be reduced to the absolute minimum. Thus, for example, packs of sterile disposable products bound together should be separated beforehand in the make ready area.

All activities likely to impair the concentration of the employees must be prevented during the preparation process.

In order to preclude uncertainty, it must be clearly known how and why the working environment and working procedures are monitored. Confident and well thought-out actions are the best prerequisite for producing good work.

The quality of the work in centralised cytostatics preparation is essentially determined by the employees working in such a department. Motivated employees are the most important guarantee for the success of the department.

Having motivated employees is of enormous benefit but cannot be achieved without effort. One promising approach is to provide the individual employee with a great deal of information, to make appropriate comments about this information and to ensure that it is disseminated. All employees in the specific problem area of a cytostatics department should feel that their questions and anxieties are taken seriously so that proper account is taken of the need for information and security.

This also includes ensuring that employees learn how the department is linked, on the one hand, to the overall structure of the pharmacy and, on the other, to the overall structure of the treatment and care of the patient. This is the only way to categorise, understand and explain the problems and wishes of the department to be supplied. In order to create the requirements for this it is recommended that employees are offered the chance during their training to spend a few days learning about everyday life on the wards and during the work to maintain constant personal contact with the units being supplied.

Dealing with problems and wishes brought to the department requires that clearly defined spheres of responsibility must exist and that employees must know the exact bounds of their authority in order to be able to perform tasks independently.

1.3. Hazard Evaluation, Working Rules and Instruction

Before starting work in cytostatics preparation, a documented hazard evaluation must be performed (law on industrial health and safety, hazardous substances regulations). The employees must be given instruction according to the results. In addition to the persons actually performing the preparation, all employees handling and using cytostatics must be given instruction in the sense of the hazardous substances regulations (s. 3 *GefStoffV*). This also includes the cleaning personnel and those working in the transport service.

Appropriate instruction must be provided for each of the different professions.

Depending on the particular requirements this will include (among others) the following points:

- **effects of drugs**
- **proper handling of cytostatics**
- **hazards and protective measures**
- **aseptic procedures**
- **disposal of contaminated materials and equipment and of cytostatic residues**
- **occupational preventive medicine**
- **action in the case of accidents.**

According to s. 20 (2) *GefStoffV* the instruction must be repeated annually; the accident prevention rules of the accident insurance providers specify instruction twice a year.

Written working rules must be prepared for each particular workplace (s. 20 (1) *GefStoffV*).

Cytostatics are classified according to their properties and included in the hazardous substances list of the pharmacy (s. 16 (3a) *GefStoffV*). This list must be extended if significant changes occur and must be

checked at least once a year. If there are changes, a new hazard evaluation must be performed.

Accidents must be documented in an accident protocol; in the case of personal injury, *RVO* (decree) s. 1552 ff. requires that the accident be either recorded in the first aid logbook (minor injuries, incapacity to work for a period of less than three days) or notified to the statutory insurance provider.

Susanne Rüggeberg, Lehrte

Hazard Evaluation

According to the provisions of the law on industrial health and safety (*ArbSchG* s. 5 (1)) the employer must perform a hazard evaluation within which the dangers associated with the work are ascertained and appropriate protective measures are defined. The employer may delegate these tasks to suitable persons; safety experts or works doctors should be available in an advisory capacity.

The recommended procedure for hazard evaluation comprises the following steps:

• **Definition** of the work areas to be evaluated
e.g. cytostatics preparation laboratory, reception of goods, store, transport, laboratory, etc.

• **Ascertainment** of hazards and burdens
e.g. classification the hazardous substances in the hazardous substances list (see above), but also mechanical dangers originated by equipment and physical and mental burdens such as fatigue, stress, monotony, noise, light, etc.

• **Evaluation** of these hazards and burdens
The protective aim is almost always specified in laws or regulations [*GefStoffV, TRGS* (technical rules for hazardous substances) 201, *TRGS* 440, *TRGS* 525, *TRGS* 905, *AOLG* (working group of the highest regional health authorities), leaflet M620 of the *BWG* (professional association for the health service and social services), *BuBaV* (procedure recognised by the professional association) (*LASI* (committee of the *Länder* for industrial safety and safety technology)), *ApBetrO* (pharmacy regulations), etc.)]

• **Specification** of the necessary measures
Hazards should be tackled as far as possible at their source. Technical protective measures should take priority over organisational measures, which in turn should take priority over measures oriented on persons.

• **Testing the Effectiveness** of the measures
If protective measures are taken these must be tested for effectiveness. It is re-ascertained whether the protective measures have achieved the intended aim or whether they have possibly resulted in the generation of new hazards.

• **Documentation**
If there are more than 10 employees the hazard evaluation must be documented in writing. The *BFW* advises that it is useful for every establishment to prepare written documentation.

A workbook intended especially for pharmacies can be ordered from the *BGW*: "GP 5,5 *Grundlagen der Prävention, Ermittlung und Beurteilung von Gefährdungen -Apotheken-*" (Principles of the prevention, ascertainment and evaluation of hazards - pharmacies). This lists all the statutory requirements and contains work tables necessary for ascertaining hazards.

Hazardous Substances List

Hazardous substances in the sense of *GefStoffV* are hazardous substances and preparations in accordance with s. 3a *ChemG* (chemicals act). This defines hazardous substances as "substances or preparations which (...) 12. are carcinogenic, 13. endanger reproduction, 14. are mutagenic". Carcinogenic substances are defined in greater detail in Appendix 1 No. 1.4.2.1. of the *GefStoffV*. This states for Category 2 that substances should be regarded as carcinogenic for humans if sufficient evidence exists to support the assumption that exposure of a human to the substance can cause cancer. This assumption generally rests on appropriate long-term animal studies and/or other relevant information.

Since neither the *ChemG* in s. 3a nor the *GefStoffV* make an exception for medicines in dealing with hazardous substances (s. 2 (3) *GefStoffV*), it may be concluded that the regulations also apply to the preparation of cytostatics.

The accident prevention decree *VBG* 113 ("Handling carcinogenic hazardous substances") expressly also names carcinogenic drugs as hazardous substances in s. 1 (3). Under special groups of substances, technical rules for hazardous substances (*TRGS*)

905 lists the carcinogenic drugs since these are based on a genotoxic therapeutic mechanism of action.

The cytostatics directive published in September 1998 by the *AOLG* stipulates that the employer must include all cytostatics with CMR properties (carcinogenic, mutagenic or reprotoxic drugs) in a hazardous substances list and classify them appropriately (s. 16 (3a) *GefStoffV*).

With the amendments to the *GefStoffV* of 18 October 1999 the so-called "sliding reference method" was introduced for the classification of hazardous substances and preparations. This means that data concerning hazardous substances and preparations are no longer published in the *Bundesanzeiger* (Federal legal gazette) but in the official journal of the European Union. The same applies for the other legislation concerning the classification and labelling of hazardous substances and preparations. According to s. 4a *GefStoffV* the data in the current EU Substance List are binding in the whole of Europe; deviations from this EU classification are not permissible.

Assistance for the classification is provided in *TRGS* 440 "Ascertainment and evaluation of dangers caused by hazardous substances at the workplace". The information must then be recorded in writing or stored on data carriers. The list must contain at least the following information (15):

1. Name of the hazardous substance
2. EU number
3. Classification of the hazardous substance with R and S phrases
4. Range of quantities of the hazardous substance in the establishment with location
5. Comments

A printed safety data sheet must exist for every hazardous substance in the pharmacy. The Lower Saxony factory inspectorate does not accept out-of-date safety data sheets or those only saved on data carriers.

As an alternative, the hazardous substances list can be integrated in the working rules on condition that the the above information is included (s. 6 (8) *TRGS* 440).

The classification of the cytostatics in the hazardous substances list must be known to all employees handling these directly or indirectly. This requirement derives from

the fact that although drugs with dangerous properties according to s. 2 *ChemG* are excluded from the *GefStoffV* requirements for labelling user packaging, they are still subject to the handling regulations of s. 19 *ChemG* and s. 5 and 6 *GefStoffV*.

The *AOLG* cytostatics directive states that dealing with carcinogenic substances, but also with cytostatics, which are or can be carcinogenic, must be notified to the responsible authorities and the responsible accident insurance provider (s. 37 *GefStoffV*, s. 7 *UVV VBG* 113 (accident insurance provider decree)). Information as to which authorities are responsible is available from local government offices, the relevant department of the administrative district or municipal authorities of towns with their own administration, in particular from the factory inspectorates.

This notification, which must state the names and quantities held of all hazardous substances, must take place no later than 14 days before the first preparation of cytostatics. It must be renewed every 5 years. If further hazardous substances are handled, these must be notified without delay. Notification can be carried out using the *BGW* form "Notification of carcinogenic hazardous substances" (ZH 1/82).

Working Rules

The *GefStoffV* and the *UVV VBG* 113 require written working rules in every area where hazardous substances are handled.

According to s. 20 *GefStoffV* the working rules must contain:

- description of the workplace / activity
- name of hazardous substance
- designation of the hazardous substance at the workplace
- hazards for persons and the environment
- protective measures and rules of behaviour
- action in case of danger
- first aid emergency telephone number / poisons centre telephone number
- organisational rules at the workplace
- restrictions
- proper disposal
- date of posting, signature of the employee.

Sample working rules are available from the *BGW* (M620) or the cytostatics manufacturers.

The general remarks in the *AOLG* directive clearly indicate that the employer is responsible for adapting the organisation and implementation of the cytostatics preparation to the latest safety standards (cf. for example s. 16 (2), 19 (4), 26 (1), 36 (2) and (3) *GefStoffV*, s. 8 (4), 10 (3), 13 (1) *VBG* 113, *TRGS* 525).

Instruction

All persons directly or indirectly handling cytostatics must receive instruction. This includes not only the pharmacy personnel entrusted with the preparation of the cytostatics (see Chapter 1.2. Persons Involved in Preparation) but also non pharmaceutical staff such as pharmacy assistants, pharmacy sales staff and professionals working in the pharmacy who can perform auxiliary work in preparation and in maintaining stocks (see Chapter 1.1. Persons Handling Cytostatics). The instruction process must also include the cleaning personnel responsible for cleaning the rooms of the cytostatics department and the employees of the fetch and deliver service. These employees must in any case be informed verbally about the special hazards and told what action to take in the event of an incident.

The hazardous substances regulations require that before starting work, employees handling hazardous substances be instructed on the basis of the working rules about existing hazards and protective measures. This instruction takes place verbally and in a way appropriate to the particular workplace and is given by the safety officer or the respective supervisor. The instruction must be documented in writing and the following information recorded:

- date
- performed by
- topics instructed, e.g.:

- effects of drugs
- proper handling of cytostatics: acceptance of goods (see Chapter 3.1), store keeping, making ready (see Chapter 3.6), transport (see Chapter 3.7)
- hazards and protective measures
- aseptic procedures (see Chapter 3.4)
- disposal of contaminated materials and equipment and of cytostatic residues (see Chapter 4.1)
- occupational preventive medicine (see Chapter 1.5)
- action in the case of incidents or accidents, not only in theory but also practical exercises of possible exposure to hazardous substances (see Chapter 3.6.2)
- proper use of the personal protective equipment (see Chapter 3.5)

- new methods or substances.

- basis: statutory requirements and working rules
- department, name, date of birth, job title and signature of the person receiving instruction.

BGW leaflet M 620 "Safe handling of cytostatics" and *TRGS* 525 require instruction to take place annually; *UVV VBG* 113 and the *AOLG* cytostatics directive require that the employee be instructed twice a year. Since according to s. 17 *GefStoffV* not only the legal requirements but also the accident prevention regulations (*UVV*) of the accident insurance provider apply, instruction should take place at least twice a year in accordance with s. 5 (2) *UVV VBG* 113. This also applies for hospital pharmacies in public ownership, who must implement the *UVV VBG* 113 as a generally accepted rule because there is no comparable *UVV* of the *GUV* (statutory accident insurance) (14).

In addition, work techniques and the proper use of the protective equipment during the work process must be inspected at regular intervals by the supervisor in this area.

Protection of Working Mothers and Working Young Persons

According to s. 4 (1) of the *MuSchG* (law for the protection of working mothers), pregnant and nursing mothers must not be employed for work in which they are exposed to the damaging effects of substances hazardous to health. In the *MuSchRiV* (guideline directive for the protection of expectant and nursing mothers) issued pursuant to s. 4 (4) *MuSchG* and in the *GefStoffV* there is no unrestricted prohibition of employment of expectant mothers in dealing with carcinogenic, embryotoxic or mutagenic hazardous substances. As long as the pregnant woman is not exposed to these hazardous substances while handling them in the prescribed way, she may continue to be employed (s. 5 (1) *MuSchRiV*, s. 15b (7) *GefStoffV*). Similar wording is used in s. 6 (3) *UVV VBG* 113.

In addition, according to s. 1 *MuSchArvPlVO* (directive on workplaces for working mothers) a hazard re-evaluation must take place **immediately** on notification of an existing pregnancy or intended period of nursing. In order to exclude **all** recognisable risks the following measures must be taken in the order given:
1. Working conditions must be modified to exclude any danger. If this is not possible,

2. transfer must be made to a different workplace. If this is either impossible or unreasonable,
3. the employee must be released from work.

The result of the hazard evaluation and the protective measures must be notified not only to the person affected but also to all female employees (at least those performing similar work) and possibly to the works committee. Furthermore, the factory inspectorate must be informed about the pregnancy and the result of the hazard evaluation, e.g. with the sample in the appendix.

Since an incident during the preparation of cytostatics can never be completely ruled out, a rule must be established in accordance with the *MuSchG* prohibiting the handling of substances dangerous to health (in this case cytostatics) by expectant and nursing mothers.

The Thüringen cytostatics directive recommends in addition that the preparation of cytostatics be performed only by persons who have already completed their family planning (14).

Pursuant to s. 22 (1) 5 in connection with s. 26, the *JArbSchG* (law on protection of working young people) prohibits the employment of young persons with hazardous substances according to s. 15b (4) *GefStoffV*. This does not apply for young persons over the age of 16 years insofar as this work is necessary for attainment of their educational objectives and their protection is guaranteed through supervision by someone with appropriate knowledge (s. 22 (2) *JArbSchG*). In a concern employing a works medical officer or a specialist for safety at work, this person must ensure that the young persons are cared for in respect of occupational medicine and safety. In addition, the *GefStoffV* stipulates that young persons must undergo a medical examination 12 weeks before the start of their employment. Young persons may then only accept the offer of employment if the doctor verifies that there are no health-related reservations against the employment.

A service rule can specify an employment prohibition for employees who must undergo immunosuppressive therapy (e.g. cortisone treatment) or are exposed to an additional risk of cancer as a result of other diseases and their associated therapeutic and diagnostic methods (e.g. X-ray examinations).

Sources:

(1) Chemicals act (*Chemikaliengesetz - ChemG*) of 27 September 1994 (*BGBl.* I, p. 2705)

(2) Regulations for protection from hazardous substances (*Gefahrstoffverordnung - GefStoffV*), last amended 1999

(3) *UVV VBG* 113 "Handling carcinogenic hazardous substances", as at October 1991

(4) Technical rules for hazardous substances *TRGS* 905 "List of carcinogenic, mutagenic or embryotoxic substances", edition of June 1995

(5) Technical rules for hazardous substances *TRGS* 440 "Ascertainment and evaluation of the dangers through hazardous substances at the workplace: procedures", edition of October 1996

(6) Technical rules for hazardous substances *TRGS* 525 "Dealing with hazardous substances in facilities for human medical care", *Bundesarbeitsblatt* (federal worksheet) 5/1998

(7) Law for protection of working mothers (*MuSchG*) of 16 June 2002 (*BGBl.* I, p. 2318)

(8) Decree to the supplementary implementation of the EU directive on protection of working mothers of 15 April 1997 (*BGBl.* I, p. 782)

(9) Law for protection of working young persons (*JArbSchG*) of 12 August 1976, last amended on 21 December 2000

(10) "Production of ready-to-administer cytostatic solutions in pharmacies", decree of the Lower Saxony social ministry of 25 July 1995

(11) Leaflet M 620 "Safe handling of cytostatics", *BGW*, status 2000

(12) *Gifte und gefährliche Stoffe* (Poisons and hazardous substances), text with comments by Dr. H. Gebler, 2nd completely revised edition 1994, published by Govi

(13) Production of ready-to-administer cytostatic solutions in pharmacies (from *Bundesgesundheitsblatt* (federal health paper) No. 9/1998, p. 404), with comments published in Dtsch.Apoth.Ztg., 138, pp 4176-4182 (1998)

(14) Diedrich, R.: "Cytostatics directive of the *Länder*, discussion and comments", Dtsch.Apoth.Ztg., 138, pp 4122-4138 (1998)

(15) Helmut Hörath: *Gefahrstoffverzeichnis* (List of hazardous substances), 5th edition, 2003, pub. Deutscher Apothekerverlag Stuttgart

1.4. Permanent Workplaces

Well trained, permanent employees must be available in adequate numbers for the scope of the preparation.

Permanent workplaces should be avoided in the area of centralised cytostatics production.
Pursuant to s. 36 (6) *GefStoffV*, however, the number of persons potentially exposed should be reduced to a minimum.

Susanne Ruggeberg, Lehrte

In principle only a centralised preparation of cytostatics can guarantee proper implementation using routine procedures (*AGLMB, TRGS* 525).

The applicable requirements formulate contradictory aims: on the one hand, permanent workplaces should be avoided in the area of centralised cytostatics preparation; on the other, the number of employees working in this area should be kept to a minimum. (s. 36 (6) *GefStoffV*).
Although the employer must implement state-of-the-art methods for preventing the release of cytostatics, a release cannot be excluded with 100% certainty. Alternation within the staff performing routine preparations is therefore also essential in order to minimise the potential personal load of each individual.

The number of persons engaged in preparations in the pharmacy is already limited by the necessary specialised knowledge, which must be acquired as a result of training and further training and through continual preparation in practice (see Chapter 1.6. Education, Training and Further Training of Staff). In order to guarantee a proper provision of cytostatics prescriptions, a sufficient number of employees must be instructed and familiarised so as to cover absences caused by training periods, holiday and illness.
It is important to ensure regular changes among the persons performing the preparations, since highly concentrated work carried out in special protective garments is a considerable strain. The rhythm with which such changeovers take place should be mutually agreed among the preparative employees. Models based on a daily or weekly rhythm could be considered, for example. It would be best if those momentarily not involved in preparative tasks could be deployed in documentation or in advising the patients.

1.5. Occupational Preventive Medicine

Employees working in the area of cytostatics preparation are constantly handling CMR drugs. They must be offered regular occupational medical check-ups.
These check-ups should include:

1. Initial examination before taking up employment.

2. Follow-up examinations during their employment at intervals of 12 to 24 months.

3. Examinations at the request of the employee if there is a suspicion of work-related impairment to health.

Despite its limited meaningfulness, it is recommended that biomonitoring be included in the follow-up examinations as a means of performing spot checks on the effectiveness of the existing protective measures.

The employer must document the possible exposure to cytostatics and the preventive measures taken. This includes keeping records of the type and quantity of the cytostatics used and the frequency of the preparations carried out by each employee. Moreover, in the sense of occupational preventive medicine, the application of every technical and personal means of protection must be guaranteed by the implementation of standardised rules focussing on preparation, disposal, cleaning, accident and emergency management.

Prof. Robert Mader, Vienna

The basic issues of occupational preventive medicine for persons exposed to cytostatics derive from the characteristics of these CMR drugs; these substances are expected to remain at least in the next decade as one of the mainstays in the therapy of malignant growths. Despite the impending introduction of new modes of action in haemato-oncology, the quantities of cytostatics used in hospitals will decline only slowly. From the viewpoint of occupational medicine, therefore, prevention is the central element. No matter what measures taken after a CMR drug has exerted an

effect on a human being, there is no way to ensure that the effect of the damage has been neutralised completely. Especially the lack of reliable data on the chronic and subchronic toxicity of cytostatics underlines the necessity for always using the available personal protective equipment, for regular training of the exposed personnel, and for the installation and regular maintenance of technical equipment - as defined for example by the DIN 12980 standard for safety workbenches used in the preparation of cytostatics.

Risk evaluation of cytostatics

The danger presented by cytostatics is based on their genotoxic effect, which cannot be assigned a threshold value. This lack of a scientifically justified limit value derives from the stochastic dose-effect principle of CMR drugs: damage occurs randomly. Moreover, this damage is not an avoidable side-effect of these substances but is the intended therapeutic effect. Consequently, there exists a long tradition of epidemiological and toxicological studies which have attempted to quantify the risk to persons exposed in the course of their employment. After exposure by way of the skin, loss of appetite, nausea, vomiting, diarrhoea, coughing, shortness of breath, cardiac dysrhythmia and hair loss were observed as acute symptoms (Valanis et al, 1993). In addition to these symptoms, which are generally reversible, the literature contains a series of reports on the severe late sequelae of exposure. After many years of exposure to cytostatics, irreversible liver damage occurred in nurses and was classified as occupational (Sotaniemi et al., 1983). The question of an increased rate of spontaneous abortion in nurses was investigated several times and remains the subject of controversial discussion (first reported by Selevan et al., 1985). A further aspect subjected to investigation was menstrual dysfunction (Shortridge et al., 1995). Since in the extreme case this can lead to infertility, the hypothesis of an increased infertility rate as a further late sequela after exposure to cytostatics was investigated and - to a small extent - confirmed (Valanis et al., 1997). For all the work cited there are also studies that failed to reproduce the results claimed. The resulting discussion about the effect of CMR drugs after chronic and subchronic exposure in low concentrations continues today. The questions thrown up cannot be clearly answered retrospectively because the working conditions and the associated exposure are often documented in a very fragmentary way. From today's point of view, new studies in this direction have become necessary because the situation has changed completely and the initial conditions in the past no longer apply to current safety standards. Nevertheless, there is no dispute about the extremely high potential danger presented by cytostatics.

Aim of the prevention

Because of the particularly toxic properties of cytostatics, several aspects are important for occupational preventive medicine:
- ascertaining risks that may lead to diseases in connection with possible loads at the workplace (precancerous stages, disturbances of the immune system, allergies, skin diseases, etc.);
- early detection of loads which in the case of CMR drugs are very probably associated with damage to health;
- early detection of work-related effects which may be triggered by cytostatics (allergies, skin diseases, genotoxic effects, etc.)

Load in this context means exposure of the employed person that can be proved by the analysis of cytostatics or their breakdown products in blood or urine (biological load monitoring). An additional aspect is the effect of the unwanted toxicity of cytostatics associated with their genotoxic effect. This is ascertained by biological effect monitoring - also known as cytogenetic effect monitoring. If occupational medical examination indicates a load or effect arising from cytostatics, biomonitoring is recommended in order to test selectively the effectiveness of the existing protective measures.

Who? When? For what?

Persons employed in the area of CMR drugs must be offered regular preventive occupational medical check-ups.

These check-ups should include:
1. Initial examination before taking up employment.
2. Follow-up examinations during their employment at intervals of 12 to 24 months.
3. Examinations at the request of the employee if there is a suspicion of work-related impairment to health.

It should be stated for the record at this point that these preventive check-ups are mandatory neither in Germany[1] nor in Austria[2]. However, there are recommendations by the *Berufsgenossenschaft fur Gesundheitsdienst und Wohlfahrtspflege* (professional association for the health service and social services) and by the *Bundesverband der Unfallkassen* (federal association of accident insurance bodies) for that group of persons directly involved in the preparation and administration of cytostatics. This recommendation also includes cleaning and disposal personnel. In this connection it may be mentioned that persons exposed to radiation in the course of their employment are subject to much stricter regulations. These persons are continually

monitored by means of dosimetry and must undergo an occupational medical examination at yearly intervals, whereby the employer is responsible for compliance with these requirements.

Nature of the occupational medical check-up

Particular attention should be paid to the following examinations:

- Anamnesis and employment anamnesis taking special account of previous exposure (initial examination); this should include recording the type of work with cytostatics, the quantity and nature of the substances and the protective measures taken.
- Physical status
- Status of the skin and mucous membrane, since damage may occur as a result of direct contact with bleomycin, dactinomycin, dacarbazine, anthracyclines or vinca alkaloids; it is important to note recurrent or therapy resistant eczema, which can present a portal of entry for cytostatics.
- Recording of allergies such as can be triggered by bleomycin and cisplatin.
- Immune status.
- Recording of disturbances of the respiratory organs.
- Recording of disturbances of the liver and kidneys.
- Ascertainment of the lymph node status, e.g. swollen lymph nodes.

Clinical chemical investigations
erythrocyte sedimentation rate
complete blood count including reticulocytes
liver function parameters (gamma-GT, SGOT, SGPT)
creatinine

Circumstances that indirectly make working with cytostatics more difficult should also be taken into account. This includes, for example, allergies towards glove materials such as latex.
The above examinations are not intended to ascertain a specific load or effect, but serve for general orientation. Nonetheless, they are an essential part of the preventive process since problems at the workplace, whether in connection with the administration or preparation of cytostatics, are frequently associated with non-specific symptoms. Often these are manifested as impairment of the sense of taste, headache, nausea, accelerated hair loss and increased susceptibility to infection. If there is a

1 *Technische Regel fur Gefahrenstoffe* (technical rules for hazardous substances) 525 and *Unfallsverhutungsvorschrift* (accident prevention regulation) 100

2 Order of the Federal Chancellory of 13 February 1990 concerning protective measures for dealing with cytostatics

definite suspicion of a load due to cytostatics, biomonitoring must be performed in order to determine the origin of the exposure. In this case the standardised rules for the individual work processes must be used since deviations from standard procedure are frequently the cause of toxic effects.
The employer must document the possible dangers to health as a result of handling cytostatics, and the preventive measures taken. In addition to reporting to the supervisory authorities, this also includes keeping records of the type and quantity of the cytostatics used and the frequency of their preparation, training courses held, and the implementation of the necessary protective measures.

Biomonitoring of load and effect

The technically easiest form of monitoring is environmental monitoring for the detection of contamination at the workplace by means of wipe tests. This type of investigation is very difficult to standardise and the results should therefore be interpreted as semiquantitative evidence. The sampling itself is simple to perform and the analysis can be carried out by a contract laboratory. The cytostatics cyclophosphamide, ifosfamide and 5-fluorouracil are currently available as parameters. These substances are very frequently part of the therapeutic protocol.
Investigations using this method for the above pilot substances have shown that the load in pharmacies where cytostatics are prepared is higher than on the wards where the therapy is administered (Connor et al., 1999). Moreover, contaminations were detected not only on cytostatics workbenches, but also on work surfaces, floors and personal protective equipment. Although these results indicate the problem, they contribute only indirectly to its solution. They can reveal the existence of a load but they do not enable its origin to be localised. Systematic investigations of the load have demonstrated the central role played by the combined effect of personal protective equipment and technical equipment in the hands of well-trained personnel, as reflected in the current state of the discussion. The danger presented by the decentralised preparation of cytostatics and the reduction of the load to quantities below the analytical detection threshold was demonstrated for methotrexate, even using high dose therapy as an example in the course of which dosages of 20 g were administered (Mader et al., 1996). This study documented the massive reduction in load for the pharmacist as a result of applying adequate protective measures. After the introduction of this safety standard everywhere, the situation had improved to such an extent that it was no longer possible to detect any load for the pharmacy personnel. In a long-term study in 21 hospitals with central preparation it was found that accidental contamination during the preparation leads to measurable concentrations of anthracyclines in blood and is also associated with a reversible increase in the effect parameters (Pilger et al., 2000). This increase was characterised

by a statistically significant increase in sister chromatid exchange (SCE), whereas it was possible to detect no more than a trend in the rate of micronuclei (MN). The major conclusion from this study, however, was that it was not possible to prove a systematic increase in load or effect over the representative period of two years. These results were confirmed in subsequent studies (Hessel et al., 2001), which is evidence for the generally high standard of safety within the German speaking region.

For the detection of exposure and genotoxic effect, biomonitoring today has available a set of instruments that is being continually extended. At the same time, however, this search for new methods is also an expression of the inadequacy of existing test systems (for a summary of the methods see Baker and Connor, 1996; Sessink und Bos, 1999). Even the expansion of this spectrum through the addition of molecular biological techniques such as the comet assay or through platinum compound induced DNA adducts can only describe the problem at a moment in time since many types of damage are reversible and can be detected for no more than a few weeks with the existing level of sensitivity. Occupational preventive medicine worthy of the name should therefore involve continuous measurement of individuals, as is performed using dosimetry for persons exposed to radiation in the course of their work. One approach to this would be the method of "personal air monitoring", in which the pharmacist performing preparations wears a small pump for collecting air with the same composition as the air breathed in (immission measurement). This technique involves sucking the ambient air continuously through a filter in order to separate the cytostatics it contains. Approaches of this kind are made more difficult by the fact that cytostatics not only spread through the air in the form of aerosols (as previously believed), but can also occur in the form of gaseous molecular dispersions (Kiffmeyer et al, 2002).

Conclusions

The selection of instruments currently available for occupational medical check-ups can be usefully complemented by the methods of biomonitoring. The possibility of accidental contamination can never be completely excluded even if all the safety rules are observed. Long-term studies have confirmed the effectiveness and the high standard of the existing safety measures as an essential contribution to occupational preventive medicine.

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1.6. Education, Training and Further Training of Staff

Both theoretical knowledge and practical skills are imparted during the education, training and further training of the staff.

Theoretical knowledge:
- **legal principles and directives**
- **correct handling of hazardous substances**
- **dangers and protective measures**
- **accident prevention and action in the case of accident**
- **emergency management**
- **disposal of contaminated materials**
- **active substances and formulations**
- **stabilities, incompatibilities**
- **working in an aseptic work zone**
- **effects of drugs, pharmacology**
- **clinical pharmacy**
- **pathology**
- **departmental and procedural organisation**
- **quality assurance**
- **personal protective equipment.**

Practical training:
- **acceptance of goods**
- **aseptic procedures and inspecting these in connection with simulation of the working steps during the preparation of a formulation**
- **handling single-use articles**
- **simulation of and action in the case of accidents**
- **monitoring the rules**
- **dealing with the documentation system**
- **packaging, delivery, disposal**
- **handling the decontamination set.**

Ruth Hangen, Rotenburg

The aseptic preparation of ready-to-administer cytostatic solutions must be carried out exclusively by trained and instructed personnel (see 1.1. Persons Handling Cytostatics, 1.3. Hazard Evaluation, Working Rules and Instruction).

The guide to quality assurance - "Aseptic preparation and inspection of ready-to-administer agents for parenteral use with toxic potential" issued by the *Bundesapothekerkammer* (federal association of pharmacists) (*BAK-Leitlinie*) lists "possible topics for training courses and instruction" which are connected directly with the preparation (1).

The knowledge to be acquired in order to qualify for the "Cytostatics Preparation" certificate of the Thüringen *Landesapothekenkammer* (association of pharmacists of the *Bundesland*) (2) partly extends beyond the proposed content in the *BAK-Leitlinie.*

In addition to theoretical knowledge connected directly with the work performed, information should also be imparted about the pharmacology, effects, side-effects, interactions and aspects of the clinical pharmacy of the drugs used in order to enable the employees to understand what they are doing and to place it within the overall concept of the cytostatic treatment of patients.

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1.6.1. Training New Employees

Training new employees in the cytostatics preparation sector must be performed very carefully since the workplace involved is potentially very hazardous for person and product.

The content of the training and the time allocated to it must be properly planned (see above) and should take place according to a programme.

Ruth Hangen, Rotenburg

The specialised knowledge demanded by the *AOLG* (association of the highest regional health authorities) guidelines "Preparation of ready-to-administer cytostatic solutions in pharmacies" should be acquired in the course of training events and a safety training course (3). However, this can never be a substitute for systematic training.

The Thuringen guidelines on the preparation of cytostatic solutions (2) require that the personnel performing the preparation must possess the "Cytostatics Preparation" certificate. The award of this certificate requires proof of theoretical knowledge and practical skills. The theoretical knowledge is acquired at two training events, attendance of which is a requirement for participation in the practical part. The subsequent practical training comprises at least three days of working under the guidance of one of the pharmacists authorised by the association. The certificate finally awarded has restricted validity.

Special attention must be paid to the training of employees in the cytostatics preparation sector. The "learning by doing" method, which has been used all too often n the past, is not appropriate for a workplace with such potential hazards for person and product.

It is essential to plan the time and content of training in order not to ask too much of the persons being trained and also to give them the opportunity to acquire in a logical context the necessary preparative skills and the theoretical knowledge needed for understanding.

Different aspects should be emphasised for the different professions. However, it is important to ensure that in an emergency all the pharmaceutical staff in a department must be able to perform every kind of preparation (substance, formulation).

The employee being trained must be allocated a competent contact partner - a "sponsor" - for all the questions that arise during the training period. The "sponsor" should be a member of the same profession as the new employee and must feel responsible for him/her during the training phase. In this way new employees have a means of discussing their anxieties, worries and problems outside any hierarchy and of asking their colleagues about their work.

It is advisable to prepare a programme for the training period.

This training programme should set out the content in modules, which are then imparted to the employee in stages. This makes it possible for familiarity with the complex work area of cytostatics preparation to be acquired in a logical and systematic way.

In addition to planning the content and the time allocated, the programme should also be methodical: how can the syllabus material be conveyed?

The following method can be used, for example, for imparting the necessary knowledge:

1. adequate preparation
2. demonstrate and explain, show and elucidate (what? how? why like this?)
3. imitate and have explained, correct
4. allow to work alone, correct results (methods of working)

A programme in which all the theoretical knowledge is taught first and practical skills afterwards may ask too much of the personnel. A more suitable approach would appear to be combining the theoretical and practical components into logical units in order to associate practical experience with the corresponding theory and therefore improve recall considerably. As far as possible, individual modules should not follow too closely upon each other in order to enable the material learned to be consolidated and to allow time for analysis. Discussions during the course of individual modules represent one possibility for analysis.

All the measures performed must be documented and confirmed by the employee (1).

Knowledge and skills can be imparted using a diversity of methods:
Theoretical knowledge:
- during discussions with the "sponsor" or with colleagues
- by private study of suitable materials: scripts, computer programs[1]
- e-learning as a trend for the future
- by attending lectures/workshops/seminars/beginners' courses[2].

Knowledge of preparation in practice (including aseptic procedures):
- written standard operating procedures
- watching videos
- demonstrations by colleagues.

Practical skills:

The work described or demonstrated is performed using dummy material that should be as realistic as possible; the performance is evaluated (e.g.) using the above methods.

At the beginning of the practical phase it is necessary to decide on the minimum number of sample preparations to be performed of the individual formulations. The number of dummy preparations or the duration of training needed can vary from one person to the next, however, so that more training may prove to be necessary in the individual case.

Practical skills can be learned either in-house or also externally at courses or seminars, or in a pharmacy with an already established cytostatics preparation facility.

Possibilities for "examining" what has been learned:
Theoretical knowledge:
- multiple choice questions
- completion texts
- quiz
- computer program, e-learning program

1. e.g. MARK: Management and awareness of the risk of cytotoxics, ISOPP
2. e.g. Crash-Kurs Zytostatica (cytostatics crash course), *DGOP*

- presentation of the material learned as part of the in-house training.

Practical skills:
- recording all preparation steps on video followed by evaluation and joint discussion; a checklist should be prepared beforehand for checking especially critical points, e.g. in connection with aseptic procedures (4, 5, 6, 7)
- observation of all preparation steps and their documentation by a different person using a checklist, followed by a discussion
- microbiological inspection of "test solutions" prepared and the working environment (e.g. work surface, gloves, containers, safety workbench)
- checking correct hand disinfection by means of fluorescent hand disinfecting agent
- checking for "drip-free" preparation by means of fluorescent solutions or solutions containing dye during the preparation.

Systematic training, examination of the skills learned and the final documentation facilitate the validation of the work process (see Chapter 3.4.1. Validation of Aseptic Procedures). The individual person cannot be validated, but simply the work process [in contrast to (8)]. Nonetheless, the qualification of the employees determines the quality of the work process, which in turn influences the scope of the validation procedures.

"Examination" of what has been learned should take place after completion of every individual training module and at the end of the entire training phase; it must be documented and confirmed by the employee.
The knowledge acquired for award of the "Cytostatics Preparation" certificate (2) of the Thuringen pharmacists association is basic training which, for example, can be completed before a cytostatics department is set up for the first time.

If employees of pharmacy with an established cytostatics preparation facility are trained externally, the particular in-house aspects must be imparted subsequently.
Retraining of employees, e.g. after rotation or a longer absence for other reasons, must also be properly planned in respect of time allocated and content. Practical exercises involving different formulations restore adequate confidence in the employees performing preparations. Innovations must be demonstrated. Revision and imparting new theoretical knowledge can take place during the annual instruction (see Chapter 1.3. Working Rules and Instruction) or by means of in-house or external training events.

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1.6.2. Training and Further Training of Staff

Training and further training is intended to ensure that the knowledge possessed by the employees is kept constantly up to date with the latest scientific and technological developments.

In addition to the annual instruction required by the *Gefahrstoffverordnung* (hazardous substances regulations), persons engaged in preparation must be given sufficient opportunity to take part in both in-house and external training events.

Documentary proof of such participation must be provided.

Where offered, opportunities should also be grasped to take part in specialist further training in the field of oncology.

Ruth Hangen, Rotenburg

In times of rapid medical and scientific progress it is absolutely essential that employees engaged in the preparation of cytostatics take part in continual training and further training.

The hazardous substances regulations and *TRGS* 525 (9) require that instruction be given before starting work and subsequently at annual intervals (see Chapter 1.3. Risk Evaluation, Working Rules and Instruction). The content and scope of this instruction are oriented on the potential dangers associated with the substances used and with handling them. Practical exercises should also be carried out.

The *BAK* guidelines (1) specify that employees must receive training at regular intervals of no less than one year by means of internal training courses and external training if necessary.

Internal training can be organised as practice days or the presentation of innovations in the form of talks and demonstrations by the employees themselves.

In addition to the events already mentioned, external training also includes visiting other pharmacies in order to learn about their methods of working. Employees can

also train themselves by means of studying the literature or using computer programs. Particular importance should be attached to practical work and the exchange of experience with colleagues; this is the only way that automatisms and blindness to the shortcomings of one's own company - which always creep in where routine work is performed - can be recognised and countered. Although this is relevant for pharmacists, it applies much more for pharmaceutical technicians who are generally the persons carrying out the preparations.

Training events focusing on innovations in cytostatics therapy are available at the national level, organised and/or supported by the pharmacists associations, professional bodies or by the pharmaceutical industry.

For pharmacists, the federal pharmacists association in collaboration with the pharmacists associations of all the *Länder* except Hamburg offers a "certified training course in oncological pharmacy", which deals with the entire topic in depth (10, 11). The Hamburg pharmacists association offers "further training as pharmacist for oncological pharmacy" with similar content but which includes a far wider scope of practical exercises and lasts a minimum of 24 months; completion of this course entitles the participant to the corresponding additional title (12, 13). The *DGOP* ("German association for oncological pharmacy") offers the *"Onkologischen Pharmazeuten DGOP"* with identical curriculum to the Hamburg pharmacists association for members of other sections of the association.

The title can also be used as an independent qualification.

The IFAHS is commissioned by the *DGOP* to offer a training course in cytostatics preparation (14). The possibility for pharmaceutical technicians also to acquire training points is currently under discussion and has already been implemented by the Thüringen pharmacists association. Events recognised as belonging to continual training are inspected and evaluated.

All training measures must be documented and the employees must confirm their participation (1).

There are currently no regulations as to how often training events on the topic of cytostatics should be attended. Defining this is made more difficult by the considerable differences in the quality of the individual events.

Opportunities offered for training and further training should be taken advantage of since this is the only way in which the qualification of the employees can be maintained at a consistently high standard. Moreover, the pharmacy regulations (15) require that cytostatic solutions be prepared in accordance with recognised pharmaceutical practice and the start of the art. This automatically generates a duty to undergo continual training and further training.

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2.1. Rooms and Equipment

Preparation takes place in a segregated, clearly labelled clean-room work area. The general requirements of work rooms must be met. In addition, a separate room must be provided for street clothing and work clothing, which ideally should be an air lock. The work room must be accessible only through the air lock.

The rooms used must not form a spatial unity with the remaining rooms of the pharmacy.

In addition to a suitable safety workbench (see. Chapter 2.2. Ventilation and Air Conditioning Systems), the work area is equipped with furniture and fittings associated with making ready, preparation and documentation. The entire equipment of the preparation room must be defined in an installation plan and be reduced to the necessary minimum.

Ruth Hangen, Giessen

Work Area

In addition to a preparation room, the "Cytostatics Directive of the Länder" requires the provision of a room for storing street clothing and work clothing, which should function as an air-lock (Commentary to the Directive; EU Guide to Good Manufacturing Practice, Annex 1, Manufacture of Sterile Medicinal Products). At least one further room is also necessary, in which the make ready and documentation unit can be housed. If there is sufficient space available, it is recommended that a make ready room be provided with air lock connection to the preparation room, and a separate documentation room. This will ensure that persons working in the documentation room will not be exposed to CMR drugs at any time.

The work area must be used solely for the preparation of ready-to-administer cytostatics (EU Guide to Good Manufacturing Practice, 3.6.) In exceptional cases the work area may also be used for the preparation of other drugs. In such a case, organisational steps must be taken to ensure a strict chronological separation of the different drug preparations, including make ready activities.

In addition, adequately large work and storage areas are demanded (EU Guide to Good Manufacturing Practice, 3.8.) The strict separation of making ready from preparation and the provision of adequately large areas create a situation where mistakes are unlikely. The measures serve to prevent the danger of contamination for different personnel, and to ensure product integrity through the avoidance of cross-contamination.

For the cytostatics preparation work area, the ApBetrO (pharmacy regulations) permit exceptions from the required spatial unity of the pharmacy rooms. However, the rooms must be located on the same or an immediately adjacent site.

Communications within the Work Area

By means of a two-way intercom, communication is always possible between persons inside and outside the preparation room. The necessity for a two-way intercom system is underlined by the requirement that doors to the preparation room must not be opened during preparation (Directive; BuBaV (procedure recognised officially and by the professional association)).

For safety reasons (e.g. a work accident, failure of the two-way intercom) there should always be visual contact between all the rooms of the work area. Visual contact can be achieved either through broad window frontages or, more simply, through window panes in doors to the rooms and air lock.

Preparation Room

According to the Directive, the preparation room is a separated room, which must be clearly labelled through suitable warning and danger signs. The general requirements of work rooms must be met, e.g. ventilation in compliance with the ArbStätt-VO (workplace regulations) (cf. Chapter 2.2. Ventilation and Air Conditioning Systems).
The access of daylight must be ensured (Arbeitnehmerschutzgesetz (law on employee protection)), but it must not be possible to open any windows present.
Doors to the preparation room must not be opened while preparation is taking place. The only possible access of persons and materials must be through an air lock into the preparation room.

There are no statutory requirements concerning the cleanness class of the room, though diverse guidelines and directives make statements regarding this. [**updated by A.Heiny and H.Vaitiekunas, Braunschweig**] Ideally, a room conforming with

GMP should be realised (this requirement was also put in the Thüringen directive of 11/96):

For aseptic preparations the EU Guide to Good Manufacturing Practice, Annex 1 requires that these be prepared under the conditions of cleanness Class A (corresponds, for example, to a safety workbench with laminar air flow = critical area) in a room of cleanness Class B (= controlled area), insofar as the preparations are not subjected to sterile filtration. Up to now, it has not been conclusively clarified whether these conditions, which apply for the large-scale industrial production of drugs, must be applied without restriction to the aseptic preparation of ready-to-administer parenteral preparations in the pharmacy.

In some countries national GMP guidelines already exist for the aseptic preparation in pharmacies of preparations for parenteral use, for example in the USA, the Netherlands and the United Kingdom, where the risk areas are to some extent more generously delineated than in the EU GMP guide.

In the American pharmacopoeia USP XXIII currently in force, the following criteria are listed for a "low-risk" preparation of aseptic preparations for parenteral use in the ambulant sector: preparation is performed in a laminar flow bench of Class 100, which must be installed for "low-risk" preparations in a room of cleanness Class 100,000.

In the EU GMP guide, classes A and B are allocated to Class 100 (USP), Class C is allocated to Class 10,000 (USP) and Class D is allocated to Class 100,000 (USP). Classes A and B (GMP) are distinguished by the maximum count of viable microorganisms (Table 2). It is clearly apparent that the requirements on the cleanness classes of the rooms for preparing aseptic preparations for parenteral use are less demanding in USP 23. The installation of a suitable safety workbench (Class A) in a room of Class B fulfils the requirements for an aseptic preparation. The decisive factor is that the room used is cleaner than the remaining rooms in the pharmacy (cf. Commentary to the Cytostatics Directive). *The BAK* (federal pharmacists association) guidelines follow the USP 23 and allow the installation of a safety workbench in a room of Class D for preparation in the closed system. If the preparation extends beyond the "low-risk" conditions (e.g. through the use of already opened packs or preparation of materials in advance), the space around the workbench must comply with clean room Class C standards. [**updated by A.Heiny and H.Vaitiekunas, Braunschweig**]

The Dutch directive specifies a clean room of Class A for the critical area and a clean room of Class D for the controlled area, whereas the directive in the United Kingdom takes over the EC GMP requirements for Class A into Class B.

Table 1: Cleanness Classes

GMP Particle count/m³				**USP XXIII** Particle count/cubic foot*		
Class		≥ 0,5µm	≥ 5µm	Class	≥ 0,5µm	≥ 5µm
				1	1	0
				10	10	0
A (LAF)	not operat.	3,500	0	100 (LAF)	100	0
	operational	3,500	0			
B	not operat.	3,500	0	1,000	1,000	7
	operational	350,000	2,000			
C	not operat.	350,000	2,000	10,000	10,000	70
	operational	3,500,000	20,000			
D	not operat.	3,500,000	20,000	100,000	100,000	700
	operational	not given	not given			

* 1 foot = approx. 0.3 m, 1 cubic foot = approx. 0.027m³

Table 2: Max. count of viable microorganisms/m³

Class	**GMP**	**USP XXIII**
A	less than 1	less than 1
B	(5*) 10	18
C	100	88
D	200 (500*)	not given

(*) = Revision of Annex 1 to the EU Guide to Good Manufacturing Practice, September 1996

The room size must be such as to guarantee unimpaired functioning of the safety workbench. Planning should therefore be carried out on the basis of appropriate room air calculations (see Chapter 2.2. Ventilation and Air Conditioning Systems). Conclusive proof of proper functioning must be obtained before using, and also after every modification within the room (e.g. a change in the number of pieces of furniture).

There are minimum requirements for room size, room height and freedom of movement (Directive; *BuBaV; ArbStättVO*).

- Area of the work room: min. 10 m2
- Height of the work room: min. 2.50 m
- Area of free movement at the workplace must not be less than 1.5 m2 and must nowhere be narrower than 1 m
- Minimum separations: Neither furniture nor equipment nor walls may be positioned less than 1.2 m in front of or 0.3 m to the side of the workbench.

Extensive information on minimal separations is given in British Standard BS 5726 Part 2, 1991:

Separation

• in front of the workbench (= disturbance-free zone):	1.0 m	
• to side walls, pillars:	0.3 m	
• to work areas at the side:		1.0 m
• to a door at the side:	1.0 m	
• to an opposing work area:		1.5 m
• to an opposing wall:	2.0 m	
• to an opposing workbench:	3.0 m	
• to an opposite door at the side:		1.5 m

A disturbance-free zone of 1.0 m should also be maintained at the sides of the workbench.

Installed objects should be arranged so as to maintain the minimum separations to the workbench. Paths within the room should be defined so that the functions for protecting persons and products at the workbench are not impaired through movements by the persons present in the room. In this sense, the number of persons present in the room must be restricted to a minimum.

The walls, ceilings and floors of the preparation room must be such that they are easy to clean and disinfect. Tiles are not an acceptable material for a room complying with GMP since their use results in inhomogeneous surfaces which do not allow a simple cleaning process (see Chapter 3.3.1. Validation). For rooms being subsequently converted to preparation rooms, it is recommended that the walls be covered with an abrasion resistant coat of a latex paint complying with DIN 53778 SG or SM, whose surface meets the requirements.

In addition to the safety workbench, the preparation room contains the following:
- two-way intercom
- enclosed storage facilities for limited quantities of drugs, disposable articles and auxiliary materials
- ergonomic, easily cleaned seating
- waste containers
- an adequately sized work and storage area with plastic-film welding machine
- a possibility for direct documentation of the preparation process
- decontamination kit for cytostatics accidents (see Chapter 4.2. Decontamination after inadvertent release)

An installation plan must be prepared and updated when changes are made.

Air lock

Whereas the Directive, following the GefStoffV, simply specifies that a room be set up for separately storing street clothing and work clothing, the Commentary to Directive 3.1. defines the function of this room more precisely. Thus it must ideally function as an air lock. The requirement for an air lock also corresponds with the EU Guide to GMP, Annex 1.

If there is adequate space available, separate air locks for materials and personnel are recommended in front of the preparation room. In the materials air lock, all the materials to be brought in can be disinfected (e.g. through spraying beneath a fume hood installed for this purpose or by wipe disinfection) and placed ready for transfer into the preparation room. Visual contact to the preparation room should be possible through both air locks. Since the two air locks are independent, one of these can be used if necessary without affecting the other. This higher level of safety would also be of advantage, for example, in the event of inadvertent release inside the materials air lock; the non contaminated personnel air lock could still be used.
The air lock can also be placed in front of the preparation room as a combined air lock for materials and personnel. Window frontages integrated in the doors could maintain visual contact in both directions. It must be possible to open the window frontage to the preparation room through a sliding mechanism in order to hand in working material. For safety purposes, a surface for placing objects on must be provided in the vicinity of the window frontage; this, however, is a potential source of accidents, for example if material to be passed in is still on the surface as somebody enters the preparation room.
If such a surface is not provided at all, however, the possibility exists of materials falling to the floor while being handed through.

Contrary to earlier statements, there should be neither wash basins nor drains in the controlled area (BAK guidelines). [**updated by A.Heiny and H.Vaitiekunas, Braunschweig**]

Before entering the preparation room, work clothing or protective clothing must be put on inside the air lock, and also work footwear, which should be capable of being sterilised/disinfected.
The air lock door to the preparation room must not be opened during preparation. Moreover, care must be taken that the two air lock doors are never opened simultaneously.

Make Ready Room

In the make ready room the materials needed for the preparation of finished drugs are properly stored and brought into the preparation room through an air lock.
Solutions ready for dispatch are packaged here for transport in unbreakable, liquid-tight closeable containers. The containers should be labelled as containing cytostatics (*TRGS* 525 5.6.)
An adequately large work surface must be provided for collecting together the substances and materials.
Verbal and visual contact with the preparation room must be ensured.
The refrigerator for storing finished drugs, partly used bottles and items to be returned to the ward is located in the make ready room. If the air conditioning and ventilation system is appropriate (e.g. individual extraction) it can also be placed in the clean room.

Documentation Room

The equipment in the documentation room includes writing desk, telephone and two-way intercom, computer, printer and a system of shelves or cabinets for holding literature and documentary materials.

Documentation System (cf. Chapter 3.6.2. Documentation)

It is urgently recommended that the preparation of ready-to-administer cytostatics be computer-aided since the expressly stipulated extensive records to be kept of the preparation extend beyond the documentation of individual prescriptions specified in the *ApBetrO* (Directive 6.1., 6.2.)
Two differently functioning computer systems are currently available:
- mass-oriented computer aided working (CYPRO, CATO)
- volume-oriented computer aided working (CYTOS; ZENZY, ZYTO...)

When setting up a computer system for the preparation of cytostatics, efforts should be made to network the making ready, preparation and documentation units in order to guarantee rapid processing of the diverse tasks:
In the documentation area, therapeutic regimens are recorded and prescriptions corrected if necessary. After completion of the preparation process, this is documented. In the preparation area, all prescriptions and regimens can be called up and processed. For precise calculation of the materials to be used, it is recommended that the preparation room also be linked to the network, if this is spatially separated from the documentation area. The ideal situation would be networking with the computers of the departments submitting requisitions, since prescriptions and therapy changes or discontinuations could then be called up directly. Further possibilities for monitoring therapies can arise through access to the patient data (see Chapter 3.5. Requisition of Ready-to-Administer Cytostatic Solutions).

Authorised Persons (see Chapter 1. Personnel)

Access to the work area of central cytostatics preparation is permitted only to authorised persons, whose number should be restricted to the absolute minimum. Authorised persons are:
1. Pharmaceutical personnel trained or being trained in dealing with cytostatics (Group 1: pharmacists, pharmacy technicians, trainee pharmacists, etc.)
2. Cleaning staff (Group 2)
3. Personnel responsible for materials supply and transport (Group 3)

Persons belonging to Groups 1 and 2 have access to the entire work area while persons from Group 3 are only permitted to enter the make ready area.

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Directive: Cytostatics Directive of the AOLG, "Preparation of ready-to-administer cytostatics solutions in pharmacies, Federal Health Paper 9/1998, Dtsch. Apoth. Ztg. 1998, 138: 4176-82

Commentary to the Directive: Commentary to the Cytostatics Directive of the *AOLG* , "Preparation of ready-to administer cytostatics solutions in pharmacies", Federal Health Paper 9/1998, Dtsch. Apoth. Ztg. 1998, 138: 4176-82

BuBaV: Directive, procedure recognised officially and by the professional association: "Standards for the operation of safety workbenches with recirculated air for work with carcinogenic or mutagenic cytostatics", Federal Health Paper 7-8/1998, Dtsch. Apoth. Ztg. 1998, 138: 76-7

ArbStättVO: Arbeitsstätten Verordnung (workplace regulations)

Arbeitneherschutzgesetz (law on employee protection)

Gefahrstoffverordnung (hazardous substances regulations)

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EU GMP guide: EU Guide to Good Manufacturing Practice for Medicinal Products, European Commission, Directorate General III, Industry (III/2244/87-EN, Rev. 3; January 1989)

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BAK-Leitliniek (Federal pharmacists association guidelines): *Leitlinie zur Qualitätssicherung: Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia mit toxischem Potential* (Guidelines on quality assurance: aseptic preparation and inspection of ready-to-administer potentially toxic agents for parenteral use) (2003, see www.abda.de)

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M 620: Professional association for the health service and social services, "Safe handling of cytostatics", Leaflet 620, 1998

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II. Literature on the Topic:

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Seyfarth H., "Microbiological monitoring for controlling the hygiene standards of the EU GMP guide for medical products", Part 1; Standards. Pharm Ind 1993; 55: 503-8

Steinlen S. "Preparation of medical products according to GMP guidelines". Krankenhauspharmazie 1998; 19:521-5

2.2 Ventilation and Air Conditioning Systems

A cytostatics workbench of type H must be used, type tested in accordance with DIN12980 as laminar air flow (LAF). Cytostatics workbenches with an additional HEPA cassette filter stage beneath the work surface are to be preferred.

An exhaust air system should be installed as an additional safety measure.

If realization of an exhaust air system is not possible for technical reasons, it is mandatory to use an LAF with two HEPA filter stages before the air is returned to the preparation room. If a workbench is operated using recirculated air, the air changes must not exceed 8; all the other requirements of the *BuBaV* (procedure recognized officially and by the professional association) must be fulfilled.

In every case, a ventilation system must be installed that leads adequately conditioned and purified fresh air complying with DIN 1946 into the room for compensating the flow of exhaust air in accordance with *TRGS* ("technical rules for hazardous substances") 560 and *ArbStättV* ("workplace regulations"), without impairing the protective function of the cytostatics workbench. The velocity of the input air must not exceed 0.2 m/s.

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1. In August 2002, after a period of exactly six years, DIN12980 "Cytostatic Workbenches" was completely revised. The manuscript is ready for publication, which is expected to take place at the end of 2003. Type V (for the preparation for use) was deleted as were the "other designs". DIN 12980 now applies exclusively for workbenches of type H (for the production of ready-to-administer preparations) with one or more work openings beneath the window. In future all workbenches conforming to DIN12980 must be tested for their ability to prevent cross-contamination. This essentially corresponds with a Class II workbench in accordance with DIN-EN 12469:2000 "Performance criteria for microbiological safety cabinets". Although the last DIN Commission meeting included a lively discussion about abolishing the separate cytostatics workbench standard, the advantages of an independent standard for a cytostatics safety workbench are obvious. As an example, the

contamination free filter replacement of contaminated filters was included as a requirement in DIN12980. The topic of connection to an exhaust air system as an additional safety measure will now be attributed greater importance. In future, Chapter 4 will be called "Designs and Connection to Exhaust Air Systems". The comments in the application sector urgently advise that a cytostatics safety workbench is intended to retain airborne particulate contaminants, **but is not suitable** for removing gaseous substances.

Contamination free filter replacement is generally realized by means of an additional modular HEPA filter stage beneath the work surface, which consists of cassette filters and can therefore be changed easily and safely. The cassettes fit into the normal cytostatics waste containers so that disposal also poses no problems. At the same time, this first HEPA filter stage (assuming its integrity is unimpaired) protects the whole of the inside of the workbench from particulate contamination. Interventions in the motor room can therefore be made without contamination and this is also possible at the main and exhaust filter stages. In benches conforming to DIN12980 these are mostly of modular construction and therefore also easier to dispose of. In *TRGS* 525 ("Handling hazardous substances in facilities for human medical care") and in the leaflet M620 "Safe handling of cytostatics" from the *BGW*, the requirement is simply a safety workbench that provides an equivalent level of safety to that of workbenches conforming to DIN 12980. The cytostatics directive of the working group of the highest regional health authority *(AOLG)*, however, stipulates unambiguously that a workbench in a new facility must be type tested in accordance with DIN 12980. This official requirement corresponds exactly with the standard we already proposed at the beginning of 1996 in the first edition of the QuaPOS. It should be possible to continue operating already installed workbenches with equivalent safety technology (e.g. in accordance with DIN 12950 Part 10) with a transition time limit of five years after DIN 12980 comes into force - i.e. until no later than August 2001. The requirement to allow only DIN 12980 type tested workbenches to be operated from August 2001 was (unfortunately) cancelled by order of the federal ministry of employment on 15 January 2000.

With the abolition of the "other designs" according to DIN 12980 a workbench with an isolated work area no longer complies with the DIN standard. No test for product protection or cross-contamination is stipulated for Class III microbiological safety workbenches (isolators) conforming to DIN EN 12469. There is no requirement for displacement laminar flow. It is common knowledge that the apparently greater safety provided by an isolator is achieved at the expense of considerable handling difficulties during operation. Apart from the solved "work opening safety

problem", all the other safety aspects - such as retention performance at the extracted air filter, exhaust air system and the replacement and disposal of filters - must be evaluated in the same way as for a bench of type H. If the flow and pressure relationships in the cytostatics laboratory are properly controlled, the safety air stream of a properly operated Type H workbench will also prevent the release of hazardous substances through its work opening. However, the handling, and the bringing in and out of materials is much simpler for Type H benches. Under these circumstances hardly any user will still opt for an isolator. The topic of isolators therefore appears to be no longer relevant.

For safety reasons, cytostatics workbenches with work opening should either run continuously (in standby mode) or the work opening should be closed during longer periods of non-use. In this way it is possible to prevent deposited particles escaping as a result of air movements in the vicinity of the work opening of the bench and contaminating the laboratory.

2. Not least through the efforts of the participating hospital pharmacists, the requirement was included in DIN 12980 that an exhaust air system and an additional upstream HEPA filter stage are useful additional safety measures. The latter applies particularly if, as a result, the first filter stage (cassette filter) can be changed and disposed of without contamination. The requirement for an exhaust air system for the air extracted from the workbench is supported by the principle that returning the extracted air is generally not permissible when dealing with carcinogenic hazardous substances. A functioning exhaust air system and an appropriately dimensioned and adapted input air supply, which exerts no negative effects on the safety of the cytostatics workbench, must be regarded as the standard. Since it is hardly possible to realize a closed exhaust air system free of reactions and disturbances, the extracted air must be led into the open (e.g. through a chimney stack). In the case of open extraction, the volume of room air sucked in must be approximately 20% greater than the extraction volume of the bench in order to guarantee complete removal of the extracted air. An exhaust air system is also on the safe side in respect of the discussion about gaseous impurities resulting from cytostatics with appropriate vapour pressures, which may pass through the HEPA filter. The installation of active filter stages that also guarantee the separation of gaseous impurities is only necessary and useful if operating in recirculation mode cannot be avoided.

3. An exception to the exhaust air system is possible only if this is unreasonable or, better, not technically feasible, and the returned air is purified from carcinogenic substances using methods approved by the professional association or the authorities. However, in the case of air being returned into the preparation room (recirculated air mode) without an exhaust air system, the standard stipulates a greater size and volume for the preparation room. In the case of recirculating air operation of a workbench, the *AOLG* Cytostatics Directive requires that the air change rate (quotient of [extracted air volume of the bench(es) per hour]/[net room air volume]) does not exceed a value of 8.

Thus, for example, a bench with a width of 1.80 m and an extracted air volume of approx. 800 m3/h may be used in recirculating mode only in a room of at least 100 m3 net room air volume (6m x 7m x 2.5m = 105 m3 - 5 m3 furniture). If the only available room is smaller, a correspondingly smaller bench with a lower extracted air volume must be used (or an exhaust air system installed).

As a duty towards our pharmaceutical personnel, at least one additional safety stage must be demanded: either an exhaust air system for air extracted from the workbench or an additional HEPA cassette filter stage, which should in any case be present in every cytostatics workbench and whose advantages during filter replacement and disposal are obvious. When using a bench with additional HEPA filter stages, it is important during routine measurements that the retention capacity of each filter stage is determined separately - in the case of modular construction also every individual filter cassette. Otherwise, a leak will not become apparent until both filter stages (in front of the exhaust air and in front of the downflow) become defective. Thus simply purchasing a bench with an additional filter stage is not sufficient; the double safety through the additional filter stage must be regularly verified by means of separate tests.

4. Open ventilation, e.g. through a window, would already be forbidden in a cytostatics laboratory by the requirements of GMP; when operating a safety workbench of Type H, this would be classed as negligent. Therefore, a ventilation and air conditioning system must always include an inlet air unit which brings sufficiently conditioned and purified fresh air into the room without impairing the retention capacity of the safety workbench. The air velocity must not exceed 0.2 m/s. If an exhaust air plant is being operated, approximately the same volume of air must be brought into the room as is extracted from it. (Example: 1.80 m bench: 800 m3/h. Air extracted from the bench + 20% = 960 m3/h). Pursuant to the *Arbeitsstättenverordnung* (workplace regulations) the inlet air must contain at least 40 m3 of fresh air (outdoor air) per person per hour.

At this point the erroneous belief must be corrected that in a laboratory in which a cytostatics workbench is being operated in recirculating mode it is only necessary to introduce approximately 40 m3 of fresh air per person per hour, as specified by s. 5 *ArbStättV*. *TRGS* 560 ("Air recirculation when handling carcinogenic hazardous substances") only allows an exception from the prohibition of air recirculation in the individual case if, firstly, the recirculated air is purified from carcinogenic substances and, secondly, the air recirculation constantly meets the requirements in No. 5 of the *TRGS* 560. This states in para. 3: „The proportion of recirculating air in the inlet air must not exceed 50 %". This also means, however, that the volume of inlet air brought into the room must be at least as high as the volume of extracted air the safety workbench removes from the room. Workbenches must therefore not be operated in rooms with lower rates of inlet air. For a bench in recirculation mode with an extracted air volume of 800 m3/h, at least 800 m3/h of inlet air must also be brought into the room, compared with 960 m3/h for exhaust air mode. Thus the outlay for inlet airflow is approximately equal for recirculation and exhaust air operation. **Viewed more closely, therefore, dispensing with an exhaust air system provides no great financial advantage, but simply generates a considerable safety disadvantage.** In the individual case it is essential that the recirculated air mode be approved by the responsible authorities after a hearing by the professional association.

The flow relationships of the ventilation system and the safety workbench must be matched to one another and already accounted for in the conception of the room. The inlet air must be purified in accordance with DIN 1946 „Ventilation and air conditioning systems in hospitals". A prefilter (at least EU4) at the outside air inlet, a filter (at least EU 7) on the pressure side before distribution into the ventilation network and a HEPA filter (Class S or R, separation min. 99.9%) as close to the room as possible should be provided for purifying the inlet air of a cytostatics sterile laboratory. These standards must be raised for a sterile room in a hospital pharmacy (Room Class I). The final particulate filter stage can be dispensed with in laboratories in which relatively few cytostatics preparations take place. This corresponds to the standards for Room Class II. However, the higher particulate loading of the air in rooms of Class II results in a comparably short service life for the HEPA filters of a workbench in continuous operation.

DIN 1946 Part 4 also describes exactly the air flow conditions for a sterile laboratory. From a hygienic point of view, the air should flow from the sterile area into the less sterile areas in order to keep back microorganisms. In practice, this means an

overpressure in the sterile laboratory, which is achieved through the quantity of inlet air exceeding that of the extracted air.

DIN 1946 Part 7 stipulates a partial vacuum for laboratories working with hazardous substances in order to protect the environment from contamination escaping from the laboratory.

Ideally, both requirements should be demanded for a cytostatics laboratory; and this is, in fact, even possible by means of an air lock. The air lock between the laboratory and the other rooms must be at a significantly higher pressure than the production room and a slightly higher pressure than the remaining rooms. This will prevent hazardous substances from the cytostatics laboratory penetrating the air lock and, in particular, the other rooms. At the same time, the higher pressure in the air lock will prevent the penetration of pathogenic microorganisms from the adjacent rooms.
Inlet air and extracted or exhaust air must be matched exactly to each other and designed in such a way that they do not negatively influence the containment capacity of the safety workbench even in the worst-case situation. A ventilation and air conditioning system of this kind must be planned and realized only by experienced ventilation engineers.

After installation or modification of the ventilation and/or exhaust air system, the containment capacity (personal protection) of the workbench must be re-tested on site under the changed conditions.
Even the rearrangement of furniture or the redesign of the room requires a re-inspection on site.

Literature:

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3. DIN EN 12469, "Performance criteria for microbiological safety cabinets", German version EN 12469:2000, September 2000

4. *TRGS* 525 „Handling hazardous substances in facilities for human medical care", Federal Worksheet 5/1998, DAZ, 138, 28 2654-2661

5. M 620: „Safe handling of cytostatics", *BGW* Leaflet, October 1998

6. "Standards for the operation of safety workbenches with recirculated air for working with carcinogenic or mutagenic cytostatics - procedure recognized officially and by the professional association (*BuBaV)* pursuant to s.36(2) *GefStoffV*, Federal Work Sheet 7-8/1998 p.69

7. Cytostatics Directive of the *AOLG*, Production of ready-to-administer cytostatics solutions in pharmacies", DAC 1999 / NRF 16. supplementary material, 1999 or Federal Health Paper 9/1998 or DAZ, 138, 43: 4176-82

8. *TRGS* 560, „Air recirculation in handling carcinogenic hazardous substances", Federal Worksheet 5/1996

9. DIN 1946 Part 2, Ventilation and Air Conditioning: technical healthrequirements", January 1983

10. DIN 1946 Part 4, Ventilation and Air Conditioning: ventilation in hospitals, December 1989
11. DIN 1946 Part 7, Ventilation and Air Conditioning: ventilation in laboratories, June 1992

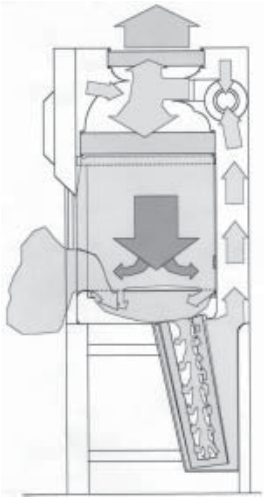
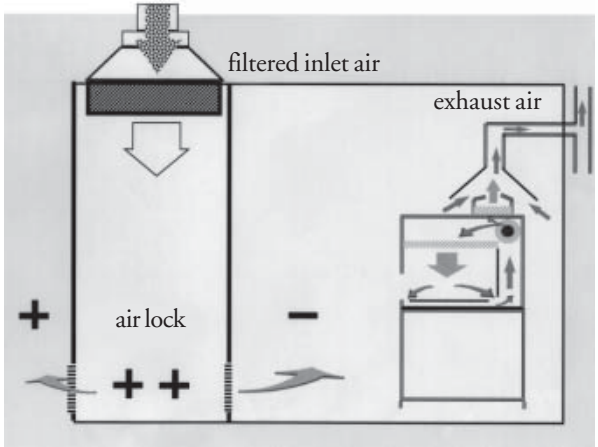


Diagram of a safety workbench complying with DIN 12980 with segmented filter stage beneath the work surface.



Drawing of an ideal air lock.

3. Cytostatics Preparation

3.1. Acceptance of Drug Deliveries

Taking delivery of goods when these are cytostatics may only be performed by trained pharmacy personnel.

Opening the packages and the sealed-in cytostatics is done at a different place. The personnel wear appropriate safety equipment.

Unusual circumstances such as breakage, contamination, etc. must be documented and reported to the manufacturer and to the specialist responsible for work safety. The cause must be ascertained as quickly as possible and remedied.

Dr. Elisabeth Kretschmer, Baden

Outside contamination of cytostatics packages can arise during industrial filling or as a result of damage during transport or storage. Investigations [1] carried out in European countries with comparable safety standards on the topic of outside contamination of cytostatics packaging were able to prove this in every case. Ignoring safety rules while handling cytostatics when accepting goods may result in cytostatics being carried over in an uncontrolled way either as pure substances or in highly concentrated form. This can be largely avoided, however, by observing safety rules and by obligatory cleaning.

Acceptance of Goods

Cytostatics deliveries are transported unopened to the place where cytostatics are unpacked.

Unpacking Place

This is a specially designated and secured place. The cytostatics deliveries are opened only by appropriately trained personnel.

1. Donning of personal protective garments (cytostatics gloves, cytostatics gown)
2. Provision of a liquid-tight work underlay and the emergency kit.

3. Opening the outside packaging, removing the seal packaging film.
4. Opening the secondary packaging (collapsible cardboard box).
5. Visual inspection of the secondary packaging for breakage, cracks, outside contamination.

If this is in order:

6. 1st cleaning step: primary packaging with 0.01 M NaOH (wiping method) [2].
   2nd cleaning step: with 98% isopropanol (wiping method).
7. Transfer of the cytostatic in the primary packaging into the closed cytostatics cabinet or closed cytostatics refrigerator, depending on the respective storage conditions.
8. Proper disposal of the packaging materials.
9. Cleaning the work surface with 0.01 M NaOH and then with 98% isopropanol.

If this (Point 5) is not in order:

6. Donning of the personal protective equipment for special cases (additional respiratory protection equipment, protective eyewear, overshoes).
7. Proper disposal according to the "technical rules for hazardous substances" (*TRGS* 525) and the hazardous substances regulations.
8. Documentation and sending this to the manufacturer and the responsible safety officer.

Place of Storage

Cytostatics must be stored separately from other stock items in appropriately labelled storage places (closed cytostatics cabinet, refrigerator). Because of the preceding cleaning process the materials are stored in the primary packaging.

In-house transport of cytostatics must take place in suitable unbreakable and leak-tight containers.

References

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2. Dr.T.Kiffmeyer: *"Vorkommen und Beseitigung von Aussenkontamination bei Primärpackmitteln"* (Occurrence and removal of outside contamination of primary packaging materials), 6th further training event *"Sicherer Umgang mit Zytostatika"* (Safer handling of cytostatics), *IUTA* ("Institute for energy and environmental technology"), Duisberg 2002.

3. Technical rules for hazardous substances *TRGS* 525 „Dealing with hazardous substances in facilities for human medical care"

Acceptance of cytostatics deliveries in the pharmacy

(Appendix for posting)

Only appropriately trained pharmacy personnel may accept deliveries of cytostatics in the pharmacy. Cytostatics deliveries are opened in a secured, specially designated place, cleaned and stored.

1. Delivered goods labelled as cytostatics are transported unopened to the cytostatics unpacking place.

2. Put on personal protective equipment (protective gown, cytostatics gloves).

3. On a liquid-tight work underlay remove the secondary packaging and dispose of it properly.

4. Carefully inspect primary packaging for damage and contamination*.

5. Clean the primary packaging using the 2-stage wiping method:
   first with 0.01 M NaOH and then with 98% isopropanol.

6. Transport to the place of storage (cytostatics cabinet, refrigerator).

7. Proper disposal of the work underlay and the packaging material.

8. Cleaning the work surface with NaOH and isopropanol.

* If the packaging is visibly damaged (crack, breakage, contamination) the cytostatic is disposed of properly observing the appropriate rules for protection and disposal. This incident is documented and copies sent to the manufacturer and to the safety officer.

3.2. Personal Protective Equipment

The directives, regulations and guidelines currently in force (*GefStoffV* (hazardous substances regulations), *TRGS* (technical rules for hazardous substances) 525, Cytostatics Directive of the *Länder*, regulations and leaflets of the *BGW / GUV*) stipulate the use of protective equipment by every employee of a cytostatics department deriving from evaluation of the hazards involved. The personal protective equipment must carry the CE mark and must be specified in writing in the hazard evaluation.

In the case of cytostatics preparation, this also applies to those employees who put together the finished drugs for the preparation and package the ready-to-administer solutions.

Personal protective equipment includes:

- **overall or protective gown (possibly in combination with cuffs)**
- **protective gloves**

and in special cases

- **respiratory protective equipment**
- **protective eyewear**
- **overshoes.**

Special cases include:

- **cleaning tasks inside the safety workbench which extend beyond simply wiping the work surface**
- **clearing up spilled cytostatic materials**
- **filter replacement in the safety workbench.**

The personal protective equipment must be adapted to the different requirements and derives from the hazard evaluation.

Gerhard Carstens, Hannover

In order to prevent employees being contaminated with cytostatics, the use of personal protective equipment is the third measure to be taken in addition to organisational measures and the technical equipment.

It must be stressed that organisational measures and technical equipment take priority over personal protective equipment. Thus the technical equipment must be adapted to the state of the art since personal protective equipment, no matter how good, can never compensate for the weak points of obsolete technical equipment. (see Chapter 2.1. Rooms and Equipment).

According to studies by different authors [1 - 3], however, there exists the possibility of contamination in the area outside the workbench despite proper technical equipment. In this connection note must also be taken of works dealing with the outside contamination of primary packaging for cytostatics [4 - 6].

Because of the hazards listed (see Chapter 1.3. Hazard Evaluation), personal protective equipment represents a mandatory measure in respect of minimising the risk of contamination.

Needless to say, this also includes employees who put together the finished drugs for the preparation and package the ready-to-administer solutions, and employees from the sectors cleaning, disposal and transport to the extent that they handle cytostatics. This derives from the definition of the term *"Umgang"* (handling) according to *TRGS* 525: handling means preparation including extraction or using. Using includes applying, consuming, storing, keeping, processing and refining, filling, transferring, mixing, removing, destroying and conveying. Handling hazardous substances includes all activities within their danger zone.

When responsibilities of facilities for human healthcare (hospitals, medical practices, pharmacies, etc.) are assigned to outside firms (outsourcing), which is especially common in the transport and cleaning sectors, the safety regulations also apply for the external contractor. The client (e.g. the hospital provider, doctor, pharmacy manager) must inform the contractor (managing director of the external firm) that CMR drugs are being handled in order that it can carry out the instructions properly, with assistance from the client where necessary (see Chapter 1.3. Instruction).

Before the selection and use of personal protective equipment a hazard determination procedure must take place in which not only the kind and scope of the risks at

the workplace are ascertained, but also the working conditions and the personal constitution of the person wearing the equipment (*TRGS* 440, ZH 1/700).

In evaluating and selecting personal protective equipment for the aseptic preparation of ready-to-administer cytostatics it is essential that not only aspects of personal protection and wearing comfort are taken into account, but also the requirements of product integrity. The principles of aseptic procedures and the GMP guidelines bear the same weight as the requirements of personal protection.

For the development, production and marketing of personal protective equipment the EU Commission has formulated basic requirements for health protection and safety. Knowledge of the requirements relevant for the oncological sector can be of assistance in selection and use:

Ergonomics
Personal protective equipment must allow the user to perform the work normally and offer the maximum protection appropriate to the risk.

Maximum level of protection
The optimal level of protection is such that to increase it would lead to problems in use and/or to rejection by the user. Personal protective equipment can only fulfil its intended function if it is accepted and used.

Protection classes according to the level of risk
If different levels of intensity of the same risk are to be expected, corresponding protection classes must be defined. Different levels of intensity can refer both to the cytostatics used and to the methods or types of work and duration of exposure.

Suitable starting materials
The starting materials must not exert any harmful influence on the health of the user. This may be relevant in the case of latex gloves.

Appropriate condition of the surface
Parts of an item of personal protective equipment that may come into contact with the user while being worn must not have any sharp edges or points that can cause excessive irritation or injuries. An example would be badly positioned Velcro closures on single-use gowns.

Adaptation to the figure of the user

Personal protective equipment must fit the figure of the user, either by means of suitable adjusting and retaining systems, or by the availability of an adequate range of sizes and/or shapes.

Manufacturer's information brochures
In addition to other information, the brochures must contain instructions for storage, use, cleaning, maintenance, inspection and disinfection. Notes on storage and disinfecting, or the prohibition of disinfection, can, for example, exert a considerable influence on the protective efficacy of single-use gloves.

Personal protective equipment that "wraps in" the body parts to be protected
"Wrapping" personal protective equipment must be adequately ventilated as far as possible, or include a method for absorbing perspiration.

Personal protective equipment subject to ageing
If effectiveness can be noticeably impaired as a result of ageing, every individual item of such personal protective equipment must bear the date of manufacture and, if possible, the expiry date. If the manufacturer is unable to provide precise information, it must list all useful information that will enable the user to determine a plausible shelf life based on the actual situation. As an example, it may be assumed that single-use gloves are subject to ageing of this kind.

If modified performance is a result of ageing caused by a cleaning method recommended by the manufacturer, the maximum number of times the personal protective equipment may be cleaned must be stated if possible on every individual item. This may be applicable to multi-use overalls and gowns.

The EU directive is implemented at national level by application of the regulations on safety and health protection in the use of personal protective equipment at work (*PSA-BV*), which in addition to the definition of the area of applicability, also contains basic regulations for provision, use and instruction.

References:

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General legal principles:

- *TRGS* 525: "Handling hazardous substances in facilities for human medical care", May 1998, *BArBl.* No. 5/98: 99-105
- *TRGS* 440: "Ascertainment and evaluation of the danger presented by hazardous substances at the workplace: procedure (ascertainment duty)", March 1999, *BArBl.* No. 3/99
- ZH 1/700: "Rules for the use of protective garments", *Hauptverband der gewerblichen Berufsgenossenschaften* (main association of professional bodies) April 1994
- Council directive on the harmonization of legal requirements of the member states for personal protective equipment (9/686/EEC) September 1996
- *Verord*nung über Sicherheit und Gesundheitsschutz bei der Benutzung persönlicher Schutzausrüstungen bei der Arbeit (regulations on safety and health protection in the use of personal protective equipment at work (PSA-Benutzungsverordnung – P*SA-BV*) December 1996, *BGBl.* I 1996: 1841

3.2.1. Overall / Protective Gown

The personal protective equipment covering the body (overall/ protective gown) must be closed up to the neck. It has long sleeves with close-fitting cuffs. It should repel liquids at especially exposed positions. For reasons of product integrity it should be as near sterile as possible and give off as few particles as possible.

Gerhard Carstens, Hanover

"Technical rules for hazardous substances" *TRGS* 525 recommends the wearing of a high-closing gown with long sleeves and close-fitting cuffs during the preparation of cytostatics. For cleaning tasks in the safety workbench which extend beyond simply wiping the work surface, a liquid-tight protective gown with long sleeves and close-fitting cuffs is required; the same applies for the removal of inadvertent contamination arising during preparation or administration (see 4.2. Action after Inadvertent Release of Cytostatics). During filter replacement in a safety workbench the use of protective gowns is stipulated but these need not be liquid-tight.

The cytostatics directive of the *Länder* published in 1998, which is part of the *NRF* (new prescription formulary) as No. I.7. "Cytostatics", demands - cautiously - "suitable protective clothing" as protection covering the body. The associated commentary states that a combination of a long-sleeved liquid-tight gown closed high at the front and with close-fitting cuffs may be regarded as suitable protective clothing for personal protection and product integrity.

Discussion: Gown or Overall

Leaflet M 620 ("Safe handling of cytostatics") of the *BGW* (professional association for the health service and social services) takes over the exact wording of *TRGS* 525 in respect of the gown to be worn during preparation, cleaning and the removal of inadvertent contamination.

The immediate reaction is to think of a gown as protective clothing for covering the body. This is a common garment within the health system, has different protective functions, is available in diverse qualities and is relatively simple to put on. However, there are also areas of activity and types of hazard for which alternatives must be considered. The first case to consider is the actual preparation: if the requirements

must be met for a clean room of Class A (workbench) in a clean room of Class B (preparation room), this standard is easier to fulfil by means of a combination of overall, boots and cap than with a gown, hood and clean-room shoes.

Whereas it is possible to achieve acceptable results in the preparation area with either alternative, a gown is not a suitable protective garment in the danger zone during the removal of inadvertent contamination - at least when larger quantities of liquid or solids are involved. A long gown that protects the legs of a person standing can become the equivalent of a feather duster or floor mop when the wearer squats down or bends forward to remove broken material and contamination. A sufficiently large overall must therefore be demanded at least for spill kits, and is worth considering in general as protective clothing for the cytostatics area (see 4.2. Action after Inadvertent Release of Cytostatics).

Discussion: Use of Single-use Material or Multi-use Products

Protective garments are available both for single and for multiple use. When deciding this basic question it is first of all necessary to consider the aspects of personal protection and product integrity.

If collecting potentially contaminated multi-use garments is organised safely, the cleaning procedures remove any contamination completely without impairing the protective properties of the material and any danger to the laundry personnel can be excluded, multi-use protective garments are equivalent to single-use garments from the point of view of personal protection.

Product integrity can be guaranteed independent of reusability. The EU GMP Guide requires that the room in which the cytostatics workbench is installed be a clean room of Class B and that protective and work garments must be sterilised (see 2.1. Rooms and Equipment). Nevertheless, cytostatics preparation areas are being operated in Germany which do not meet these standards. In rooms of Class C and poorer the question of product integrity as a result of protective garments is not so important. However, in these facilities it should at least be ensured that body parts reaching into the workbench (clean room Class A) are covered by sterilised and low-particle protective clothing. Under appropriate circumstances this may be possible using suitable gauntlets.

In addition to the aspects of personal protection and product integrity, selection should also take aspects of wearing comfort, economics and environmental impact into account.

Harrison and Kloos put their finger on the importance of wearing comfort: “Selecting the best protective clothing materials from this group” (materials tested) “cannot guarantee protection if the persons carrying out the preparation do not wear the protective garments properly” [1]. Economical considerations must, of course, take the total costs into account, which may also include control and instruction measures in the case of multi-use protective garments. Evaluation of environmental impact will probably prove more difficult since this must take account of cleaning and disposal in addition to the impact of the preparation itself. The evaluation requires exact knowledge of the processes involved. The price is of limited help since this rather reflects the market situation than the environmental costs.

Discussion: Wearing Duration

In contrast to the situation for protective gloves, there exist only very limited recommendations for the wearing duration of protective garments. *TRGS* 525 stipulates that the protective equipment to be worn during the preparation of CMR drugs must be changed immediately if it becomes contaminated or damaged. The guidelines of the *AOLG* (working group of the highest regional health authorities) adds that the locally used personal protective equipment must be removed on leaving the cytostatics work area. This may possibly mean wearing times of several hours.

A potential risk for persons is the unnoticed contamination of the protective clothing that as a result of penetration may lead to direct danger for the person wearing the protective clothing. In addition, other persons are at risk through carry-over of the contamination. The problem of carry-over is also relevant if the work in the preparation area is interrupted for a shorter (minutes to hours) or longer period (hours to days). The gowns or overalls - unwittingly contaminated - can result in persons being contaminated directly during removal, donning and storage, and also in the carry-over of the contamination to other objects and surfaces. In the context of product integrity the GMP guidelines preclude multiple use without intervening treatment (cleaning and sterilisation). When evaluating the costs, not only the number of gowns or treatment processes should be considered, but also the costs that may be incurred as a result of contamination being carried over or of inadequate asepsis. Procedural deviations from the state of the art are only permissible if the equivalent quality can be provenly guaranteed (see 3.3.1. Validation of Aseptic Procedures). Provision of such proof is also a cost factor that must not be ignored.

The question “liquid-tight or not” is closely connected with the wearing duration. Even when working in a workbench it is conceivable that aerosols or drops could

cause contamination in the region of the arms, the chest, the stomach and the thigh. While cytostatics are being unpacked and reached into the workbench there is the possible risk of the protective clothing being contaminated by material on the primary packaging which - for example - could be dissolved or suspended by splashes during hand washing. In cases of breakage, any amount of contamination is conceivable. The wish for liquid-tight protective clothing also to be worn in the preparation area is understandable in the light of the above considerations. However, it must be borne in mind that a liquid-tight, possibly smooth, outer surface of the personal protective equipment may lead to liquid contaminants dripping off and causing further carry-over. Published investigations of common commercially available products have revealed widely different levels of protection against penetration and permeation by cytostatic solutions [1, 2, 3]. Unfortunately it appears that wearing comfort and protective effect are inversely proportional to one another [1]. The ideal material for protective clothing has an absorbent outer layer and a liquid-tight inner layer and combines protection against penetration and permeation with high wearing comfort and breathability. The impossibility of such a combination forces compromises to be made according to the local situation.

Textile Materials

It is possible to use long-sleeved, high-closing gowns of the kind used in hospital operating theatres, or overalls of appropriate material. Accordance to EEC Directive 93/42 these operating gowns are medical devices [4] which must satisfy the requirements of EN 13795 [5]. Although the actual purpose of this standard is to prevent the transmission of an infectious organism during an operation, the properties it guarantees are also useful in the preparation area in respect of personal protection and product integrity. Among other requirements, this standard defines levels of microorganism penetration, liquid penetration and particle emission.

The following fabrics or laminates are available today as textile barrier materials:

Mixed fabrics of polyester and cotton

An intimate yarn mixture of polyester and long-stapled cotton, which is processed into a dense fabric and then treated with fluorocarbons, is able to achieve a barrier effect that satisfies the requirements of the standard.

Microfilament fabric

The yarns for the microfilament fabric are woven from very fine, continuous polyester filaments. They are essentially free of particles and very hard-wearing. When

made liquid-repelling by treatment with fluorocarbons these fabrics also satisfy the requirements of the standard.

Textile laminates

A trilaminate consists of a microporous membrane embedded between an upper and a lower layer. The pore size of the membrane can be chosen such that an effective barrier is formed against the penetration of bacteria and viruses in combination with liquid. This microporous membrane does not impede the passage of water vapour so that natural thermoregulation is ensured. In contrast to the barrier fabrics based on fluorocarbon treatment, a trilaminate is also absolutely impenetrable to microbiological organisms under high pressure. Since the upper and lower layers consist of polyester filaments, there is practically no emission of particles.

If the safety workbench used for the preparation of cytostatics is not installed in a clean room of Class B, there is no need for final sterilisation of the gowns since, depending on the cleaning and drying process, the gowns are essentially sterile as a result of heat treatment. They must be supplemented with sterile (sterilised) gauntlets of liquid-repelling material. In doing this, the glove gauntlets should be pulled over the cuffs of the sleeve gauntlets in order to ensure the best possible protection at the transition from gloves to sleeve gauntlets.

When using multi-use materials the manufacturer's instructions for use should be followed regarding methods of cleaning and treatment, disinfection and impregnation [6].

There are currently no data available on the possible permeation of cytostatics into the textile barrier materials.

Single-use gown of liquid-repelling material

Sterile (sterilised) gowns and gauntlets are offered as single-use articles for cytostatics preparation; these are manufactured from polypropylene, with or without a polyethylene coating. They are also available non-sterile. The wearing comfort is significantly lower than that of the textile materials.

A limited amount of data is available on the possible permeation of cytostatic [1, 2, 3] and if needed can be acquired from the manufacturer or supplier.

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3.2.2. Single-Use Gloves for Protection During the Preparation of Cytostatic Solutions

Suitable gloves or glove combinations must be worn; these must be changed at regular intervals and also in the event of contamination.

Dr. Renate Hepp, Giessen

Single-Use Gloves for Protection During Preparation

During the preparation of cytostatics, sterile single-use gloves are used which support aseptic procedures in the sense of product integrity, but simultaneously perform the function of personal protective equipment (PPE).

Sterile, powder-free single-use gloves must be used during the preparation of cytostatics. They must be sterile in order not to endanger the aseptic procedures for preparing cytostatics solutions and they must be powder-free in order not to increase the particle loading in the preparation area. According to *TRGS* (technical rules for hazardous substances) 540 latex gloves must be powder-free and low in allergens [1].

In order to meet standards of personal protection and product integrity during the preparation of cytostatics the gloves must be tear resistant, must fit well with tightly sealing sleeve bands and must provide a good grip.

A further requirement is that damage (faults, holes, tears) must be detectable before, during and after using the gloves. The use of coloured gloves or glove combinations ensures that damage can be detected more quickly and with greater certainty [2, 3]. Gloves must meet standards that guarantee a specific imperviousness [4, 5, 6].

Before using the gloves the wearer must make certain that their macroscopic properties reliably protect person and product from contamination.

The protective function of the glove against the cytostatics used in the preparation (commercial preparations) must be tested. When selecting gloves account should be taken of the quality standards set by DIN EN 374 [3].

Gloves must be stored in a way that does not impair their quality.

Gloves as Barriers against Cytostatics

Protective Aim and Impairing Influences

Gloves used in the area of cytostatics preparation are an important part of the personal protective equipment (PPE) and in the majority of cases also serve to protect the integrity of the product being prepared. The ideal protective glove is impervious to harmful substances. In reality this ideal is not achieved completely.

The harmful substance can pass through the material of the glove by penetration or permeation. These processes are defined as follows (DIN EN 374-1):

Penetration: The movement of a chemical or a microorganism through porous material, seams, pinholes or other defects in the material of the protective glove at a non-molecular level.

Permeation: The process by which a chemical passes through the material of a protective glove at the molecular level. Permeation involves the following steps:

1. Molecules of the chemical applied are taken up by the (outer) surface of the material.
2. These molecules diffuse in the material.
3. The molecules are given off by the opposite (inner) surface of the material.

What methods are used to test the retaining power of the gloves used?

Single-use gloves are normally used during work with cytostatics. These are, for example, surgical gloves and nursing gloves that have been tested in accordance with the standard DIN EN 455 "Medical gloves for single use". The intended use of these gloves is in the medical sector for protecting patient and wearer from contamination [4].

Gloves tested in accordance with DIN EN 374 are also used for handling cytostatics. Gloves complying with this standard serve for "Protection against chemicals and microorganisms" and are only intended to protect the wearer from these influences.

Test for freedom from holes in accordance with DIN EN 455

"Medical gloves for single use" are tested for freedom from holes.

The method used is a water retention test for ascertaining the existence of holes. Single-use gloves tested according to Point 5.1 must fulfil the required standard for freedom from holes with an AQL of 1.5.

The AQL (acceptable quality level) is part of a statistical inspection system that was developed by standards authorities, manufacturers and users for testing the quality standard of a product. One important factor is the number of samples to be tested, which decisively influences the evaluation of product quality. That means: the lower the AQL value, the "better" the product, and the higher the number of random samples, the "greater" the probability of finding batch sizes from production that do not meet the standard [7].

For further information on AQL (Use, applicability, definition of AQL values) see DIN ISO 28590-1 [8].

Test for penetration in accordance with DIN EN 374

"Protective gloves against chemicals and microorganisms" (DIN EN 374) are subjected to a penetration test in order to determine their freedom from holes.

The inspection method to be used for resistance against penetration is the air leak test Point 5.2 or the water leak test Point 5.3.

In respect of the required standard for resistance against penetration by this type of glove, DIN EN 374-1 differentiates between three performance levels (Class 1 - 3) with corresponding AQLs (0.65 / 1.5 / 4.0).

DIN EN 420 "General standards for gloves", Point 7.3 "Information and instructions for use" requires the glove manufacturer to state the performance class achieved [9].

Test for permeation of the test chemicals in accordance with DIN EN 374

"Protective gloves against chemicals and microorganisms" (DIN EN 374) are also subjected to a permeation test.

For each test chemical the protective glove/test chemical combinations are classified according to the breakthrough time during which the glove prevents permeation. The protection index below is based on the breakthrough time (Table 1) measured during constant contact with the test chemical under normal laboratory conditions,

as described in DIN EN 374-3. The actual duration of protection at the workplace can deviate considerably from this protection index.

Table 1: Protection index against permeation

Measured breakthrough time	Protection index
> 10 min	Class 1
> 30 min	Class 2
> 60 min	Class 3
> 120 min	Class 4
> 240 min	Class 5
> 480 min	Class 6

The breakthrough time is defined as the time that elapses between the first application of the test chemical on the surface of the material of a protective glove material and the subsequent appearance on the other side of the material, measured as described in the standard (DIN 374-3).

It is important to point out that the breakthrough is regarded as having occurred as soon as the permeation rate of the test chemical through the glove material amounts to 1 µg min^{-1} cm^{-2} . As long as the permeation rate is lower than this, the glove is regarded as safe for handling the (liquid) test chemical. The tests are performed at a standard test temperature of (23 ± 1) °C.

Studies on the Permeation of Cytostatics through Protective Gloves

Gloves used in the preparation of cytostatics should in addition be tested for their resistance to permeation of the cytostatics being handled (commercial preparations) to the extent that this is not included in the tests performed on the basis of their intended use (e.g. surgical gloves).

Most of the studies in this connection were carried out by interested work groups using non standardised methods.

Permeability experiments on surgical gloves of latex and polyvinyl chloride (PVC) have shown that latex gloves provide better protection than PVC gloves against most cytostatics [10]. Because of these results, its wearing comfort and its material properties, the latex glove has been preferred in the preparation of cytostatics. However, since the latex proteins contained in the glove can lead to allergies in some users,

gloves made from other materials also had to be tested with regard to their suitability for handling cytostatics.

Numerous permeation experiments were performed on commercially available latex gloves (material thickness approximately 0.2 - 0.4 mm) and also on glove combinations (two thinner latex surgical gloves worn one over the other) [2, 11, 12, 13, 14]. Rapid permeation of carmustine and/or thiopeta is frequently reported for single-layer latex protective gloves. Mitoxantron is mentioned in this connection to a lesser extent [2, 10, 11, 12, 13, 15]. In experiments using the model substance carmustine and four other cytostatic agents, combinations of two latex surgical gloves proved to be better barriers, or even completely reliable, in their retention power [6, 12].

In a study using ifosfamide, latex gloves with a lower wall thickness (approx. 0.24 mm) provided better protection against the cytostatic than latex gloves of thicker material (0.33 mm) [16]. Compared with the protective gloves commercially available in Germany, a double surgical glove system (two thin hydrogel polymer-coated latex gloves worn one over the other) even provided very good protection against carmustine and proved to be superior to a single glove of the same kind in the test with further cytostatics [17, 18, 19]. Permeation of thiopeta through the material of hydrogel polymer coated latex gloves was also faster than for other cytostatics. A double glove provided the best protection [19].

In tests over three hours with 5 cytostatics, neoprene gloves fulfilled the breakthrough criteria of DIN EN 374-3; the cyclophosphamide measurements were sensitive to interference by the glove material [20, 21, 22]. With regard to their retaining power against the cytostatics tested, neoprene gloves performed as well or better than non powdered single and double surgical gloves containing latex (referred to thiopeta) [19].

No permeation through nitrile gloves was detected for the 11 cytostatics tested using a conductometric method under the experimental conditions of the ASTM American standard. Although alcohol was detected in the acceptor medium during the test with carmustine, there was no increase in conductivity. Since it is possible, however, that the substance dissolved in ethanol permeated together with the ethanol, the authors recommend that this be subjected to further investigation [23, 24]. Recent studies have been performed using methods analogous to those of DIN EN 374. In an investigation of 15 cytostatics the resistance of selected gloves against these cytostatics was tested over a period of 3 hours. The cytostatics selected were either new or known to be critical. Most of the cytostatics showed no or only slight

permeation. The measured permeation rate over 3 h lay at £ 0.2 nmol min^{-1} cm^{-2} . The carmustine permeation rate for single layer latex gloves was up to 11 times this value [15].

In a second investigation the commercial cytostatics preparations of one drug manufacturer were tested for permeability through different single-use protective gloves of diverse materials. Here too, the measured permeation rates over a period of 3 h were below 1 µg min^{-1} cm^{-2} [25].

Special Notes on Latex Gloves

Latex Allergy

During the years between 1980 and 1990 there was a dramatic increase in early reaction type allergies towards natural latex products, mostly caused by gloves. Health service employees are one of the groups at risk [26]. One theory for the increase in the allergy rate is the rapid rise in the use of gloves since 1987 [27]. In addition, the increased demand and the cost pressure in the past has resulted in cheaper production methods and therefore to products with a higher protein fraction being launched on the market [27, 28]. In the meantime the frequency of latex allergies among employees in the medical sector has risen to 17% [29]. The immediate or Type 1 allergies, which represent the majority, are triggered by latex proteins. However, late or Type 4 allergies (6 - 48 hours after allergen contact) also occur, triggered by additives used in the manufacturing process as vulcanisation accelerators, especially substances of the thiuram group [30].

Powdered gloves present a particular allergy risk since the latex proteins bound to the powder enter the air as soon as a package is torn open and can result in irritation of the eyes and the respiratory passages. This may cause conjunctival reddening, running nose, coughing and bronchial asthma. Severe general symptoms - even as far as anaphylactic shock - are possible. The first fatalities have already been reported [30].

Avoidance of Latex Allergies

Primary prevention: The following recommendations are among the protective measures suggested [30, 31, 32, 33]:

- Use of non powdered latex gloves with low protein concentration (if possible < 30 µg per g glove)
- Use of thiuram free gloves in order to reduce the risk of allergic contact eczema

- Consistent skin protection scheme (a skin protection plan must be prepared: *TRGS* 525 3.6 (4), *TRGS* 540 4.4 (3)).

Secondary prevention: Persons allergic to latex may only use latex free gloves. They must avoid any contact with products containing latex.

Statutory Requirements for Handling Latex Gloves

The handling of latex gloves is covered by the *Gefahrstoffverordnung* (hazardous substances regulations) [34] (which were issued on the basis of the *Chemikaliengesetz* (chemicals act) [35]) since they belong to those products from which hazardous substances may be released during use [36]. Because of their sensitizing properties, latex proteins are hazardous substances in the sense of the chemicals act.

In the USA labelling of medical devices containing latex has been compulsory since 1997 [30]. In the course of harmonisation of international standards, based on the biological evaluation of gloves made from natural rubber latex, mandatory labelling was also included in EN 455-3 [4]. This requires that latex gloves be declared with the statement: "(This product) contains natural rubber latex which may trigger allergies".

Pursuant to the handling requirements of the hazardous substances regulations the employer has a duty to determine whether hazardous substances are being handled in its enterprise (duty to investigate [37]). The manufacturer or supplier must pass on product information if this is requested by the employer [38] (e.g. the protein content of the gloves). The employer is subject to the so-called duty to substitute [39]. This means that it must determine whether products with a lower risk are available, whether it may be reasonably demanded of it that it use these products, and whether substitution with these products is necessary for the life and health of the employees. (If this applies, it may provide only such gloves as are appropriate) [30].

Since the use of latex gloves is regarded as handling hazardous substances, the gloves must be included in the hazardous substances list which the employee must maintain in accordance with the hazardous substances regulations [40]. The working rules prepared for the preparation area must also cover latex gloves. The employees must be given instruction on handling these products at least once a year [41], See also Chapter 1.3. "Hazard Evaluation, Working Rules and Instruction".

Handling Gloves During Preparation

Is it reasonable to disinfect gloves that are not or no longer sterile?

In permeation tests different formulations of the cytostatic vincristine demonstrated very diverse permeation properties. One commercial preparation contained benzyl alcohol, which caused the cytostatic to penetrate through the glove material very rapidly. In contrast, no permeation was observed for an aqueous solution with the same concentration [19].

The safety of protective gloves is tested according to the conditions defined in studies. These do not take into account the use of disinfecting agents.

The disinfecting agent (e.g. alcohol, tenside, aldehyde) can interact both with the glove material and with the cytostatic. This can lead to unpredictable influences on the protective efficacy of the glove.

For these reasons the use of disinfecting agents for disinfecting gloves used during cytostatics preparation does not appear to be sensible at the present time.

When must protective gloves be worn?

Protective gloves must basically be worn for all types of work during which a contamination by active substances cannot be excluded, e.g. already while unpacking and when preparing infusion bottles with dry substances and cytostatic solutions from ready drugs [42, 43, 44, 45]. It is not necessary to wear sterile, single-use gloves in every case.

In this connection the fact should be considered that examination gloves, which are frequently worn for unpacking the preparations, have been the subject of far fewer permeation tests than surgical gloves. Examination gloves, however, are generally made of thinner material.

Intervals for Changing Gloves

According to leaflet M 620 protective gloves should be changed every 30 minutes, regardless of visible contamination or damage, in order to avoid invisible damage or taking up invisible contamination [3].

Rapid penetration of carmustine and thiopeta has been demonstrated for single layer protective gloves made of latex [2, 10, 11, 12, 13, 15]. Changing soon after the preparation (e.g. performed towards the end of a changing interval), the use of

more suitable gloves, or a double glove system is advisable. For thiopeta neoprene gloves are better than latex gloves [19]. A breakthrough time of < 10 minutes through latex gloves has also been described for mitoxantrone [13], though more recent findings report that no permeation through different glove materials was observed for up to 3 hours [15, 46].

Double glove systems are strongly recommended because of their more than additive protective effect and their "double floor", whereby the outer glove must be changed regularly (and the entire combination when handling critical substances).

In respect of cross-contamination in the working surroundings, a changing interval of 30 minutes also means an interruption in the distribution of cytostatics in the work room. Investigations from the field of occupational medicine reveal that it is still always possible for primary packaging to be contaminated with commercial preparations [45]. Unfortunately commercial preparations with low-contamination or contamination free packaging are not universally available.

As soon as this situation improves and the user is provided experimental results with appropriately low detection thresholds proving that gloves guarantee reliable protection against the commercial preparations being handled, it will be possible to consider longer wearing times for gloves.

Storing Gloves

Gloves must be stored in accordance with the manufacturer's recommendations. These are generally: cool and dry (between 5 and 30 °C). No weight should rest on the gloves during storage as this can result in cracks forming at the folds. The requirements of DIN 58 953 Part 7 (8.2 "Storage duration of sterile goods") must be met [47].

Discussion

Numerous requirements are set for single-use gloves worn during the preparation of cytostatics solutions; these requirements may differ depending on the preparation facility and the user. The employer is legally obligated to provide "effective protective garments with appropriate wearing properties" [1, 48, 49].

The following criteria should be taken into account when selecting gloves:

- material properties (tear resistance, thickness, uniform thickness)
- size and fit

- safety during use (grip)
- retaining power for cytostatics
- tested for freedom from holes (in accordance with DIN EN 455 or DIN EN 374)
- detectability of any damage
- health of the personnel (including low allergenic potential in the case of latex gloves, alternative material for allergic persons).

Many commercially available (single-use) protective gloves are tested for freedom from holes (penetration) according to DIN EN 455 or DIN EN 374 and guarantee high quality in respect of the perfection of their material (defects, holes). However, hardly any gloves are available that have been tested for permeation of cytostatics according to DIN EN 374-3 [50].

Investigations of the permeation of cytostatics through glove materials are predominantly the result of the initiative of different work groups.

Up to now there has been no standard against which "cytostatics protective gloves" could be tested. In this respect the following aspects would need to be considered:

Cytostatics form a heterogeneous group of substances and even different formulations of the same substance can have very different permeation characteristics [19]. A single molecule of a cytostatic agent may damage the genome of an individual. As the actual acceptor medium, the skin has lipophilic properties. Especially the wearing of gloves for long periods results in occlusion, warming and perspiring, leading to many substances being taken up more readily by the skin. The body temperature is approximately 37 °C.

It is a fact that most of the investigations to date were not carried out using standardised methods; they have in common that the chemicals being tested (normally stock solutions of commercial preparations) are applied to one side (outside) of a sample of glove material and an acceptor medium on the other side (inside) of the glove material takes up the permeated substance. The cytostatics are quantitatively analysed using a variety of analytical procedures. Generally, the time is given after which the first detectable quantities of the cytostatic appear in the acceptor medium, or periods of time are measured during which no substance is detectable. In recent years more and more studies have been performed based on the permeation test of DIN EN 374 [15, 19, 20, 25].

The detection threshold of the analytical method used in the test is of decisive importance for evaluating the protective efficacy of gloves. In every publication up to now, it has only been possible to make statements within the context of the experimental conditions used and the detection threshold achieved for the cytostatics. More sensitive analytical methods could result in shorter breakthrough times for cytostatics in the future.

Studies performed up to now have delivered significant information for the evaluation of single-use gloves for the preparation of cytostatics. The retaining power of gloves does not depend on the material thickness alone [16]. The double glove provides particularly effective protection [51]. Results gathered for one type of glove cannot be transferred to a different type of glove made of the same material. This applies not only for products from the same manufacturer (e.g. examination gloves and surgical gloves) but also for products from different manufacturers (e.g. surgical gloves from different firms). Stretching does not in every case affect the resistance of a glove against permeation [52].

In recent years one work group has methodically carried out a wide range of glove tests using the same methods with the result that directly comparable data are now available concerning the permeation of commercial cytostatic preparations through the materials of different brands of glove.

These were obtained analogously to the methods of DIN EN 374 and must also be evaluated from the aspect of the respective definition of breakthrough [15, 19, 20, 21, 25]. In every case the permeation rates of the cytostatics through the glove material over a period of 3 hours were below 1 $\mu g\ min^{-1}\ cm^{-2}$ so that, in the sense of this standard, they are regarded as safe for handling the (liquid) test chemical. In some cases, however, cytostatics were detected in different concentrations in the acceptor medium. Users must interpret the studies exactly and take such results into account when selecting the glove "suitable" for their purpose.

A welcome development is the initiative of one manufacturer in having the suitability of different single-use gloves tested for handling its cytostatic preparations [25]. Other manufacturers are urged to follow this lead and provide such test data for their products in order to facilitate the user's search for a single-use glove suitable for the preparation of cytostatics.

When searching, it is important to realise that a glove manufacturer may only declare its product in accordance with one standard, even if it has been tested in

accordance with two standards (e.g. according to DIN EN 455 and DIN EN 374). It is therefore always worth asking whether the gloves have been subjected to tests extending beyond the declared standard.

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3.2.3. Respiratory Protection, Protective Eyewear, Overshoes

In special cases the avoidance of contamination when dealing with cytostatics requires the wearing of respiratory protection, protective eyewear and overshoes in addition to a protective gown and protective gloves. These additional measures are mandatory for certain tasks, including cleaning the safety workbench, clearing up spillages of cytostatics and during filter replacement at the safety workbench.

Respiratory protection must consist of a particle filtering half-mask complying with DIN EN 149.

The protective eyewear must provide protection at the side and be capable of being worn over any personal aids to vision.

Overshoes must be liquid repelling and cover the entire foot as far as possible.

Gerhard Carstens, Hannover

Respiratory protection for avoiding the risk of inhaling cytostatics and the wearing of protective eyewear to protect the eyes play only a minor role in cytostatics preparation since the directives currently in force require that cytostatics be prepared in a safety workbench (see 2.1. Rooms and Equipment).

During cleaning tasks in the safety workbench which extend beyond simply wiping the work surface, when removing cytostatics contamination outside the workbench, and while replacing the workbench filters, a liquid repelling gown, protective gloves, protective eyewear with side protection and a respiratory protective mask of at least Class P2 [1] must be worn. When cleaning up inadvertent contamination occurring during the preparation of cytostatics the wearing of overshoes is specified in addition (see Section 4.2. Action after Inadvertent Release of Cytostatics) [2]. The employer must instruct the employees in the proper and safe use of the personal protective equipment and organise training courses and provide informational material as necessary [3].

Particle Filtering Half-Masks

Particle filtering half-masks are divided according to DIN EN 149 into the classes FFP1, FFP2 and FFP3. These are complete respiratory protection devices consisting wholly or partly of the filter material [1]. The filter materials are divided according to DIN EN 143 into 3 classes according to their filtering efficiency (corresponding to the pore size): P1 low filtering efficiency, P2 medium filtering efficiency, P3 high filtering efficiency. They differ in their thickness and tightness. In comparison to a P3 mask, a P1 mask is much thinner, sits lightly on account of its construction and is accordingly less tight. P1 masks may not be used for handling cytostatics. A minimum of a P2 mask is required for handling cytostatics. P2 masks may be used at concentrations up to 10 times the MAC value (maximum admissible concentration). Since no MAC values exist for cytostatics, the decision to specify the use of P2 masks for the hazardous substances sector CMR drugs was taken arbitrarily. The performance of the P3 masks, which are approved for radioactive substances, viruses and enzymes, is three times that of the P2 masks.

P2 and P3 masks are available as "S" (solids only) and "SL" (solid and liquid substances) types. The greater the filtering efficiency of a particle mask, the greater the breathing resistance, which restricts the wearing comfort of the mask. This is a relevant criterion when selecting the mask since a mask that is worn improperly or not at all increases the risk.

Particle filtering half-masks cover the nose, mouth and chin and have a soft fleece inner lining, which makes them comfortable to wear. The use of efficient expiration valves prevents the build-up of heat and facilitates breathing.

P2 and P3 masks are fastened to the head with straps such as to guarantee a firm seat. If the straps are adjustable they must be constructed in such a way that the adjustment cannot change accidentally during use.

When donning the mask the manufacturer's information for the user should be followed to ensure that the seat is as airtight as possible. In the case of persons who wear glasses, a poor seal at the root of the nose can lead to additional impairment through the glasses misting over. The wearing of a protective mask must restrict neither the field of view nor the sight [4].

As a general rule the mask must be changed as soon as resistance to breathing is too great. This also applies for replaceable particle filters in half-masks.

Particle filtering half-masks without replaceable filters are not intended to be be cleaned or disinfected [1]. Such masks must not be used by several persons and must normally not be used for longer than eight hours. Half-masks removed temporarily must be protected against contamination, moisture and other impairing influences.

Protective Eyewear

Protective eyewear must comply with the requirements of DIN EN 166 "Personal eye protection; standards". So-called *Korbbrillen* (mask goggles) provide a very high level of safety. According to the rules for the use of eye and face protection, mask goggles are defined as protective eyewear in which the supporting body is basket-shaped and of soft, flexible material so that the basket of the spectacles encloses the region of the eyes and fits gently to the contours of the face [5].

Protective eyewear must be sufficiently optically neutral that more or less fine precision work and/or boring tasks are possible. They must be resistant to misting over and must allow the simultaneous wearing of spectacles or contact lenses [4].

Mask goggles are available from the usual manufacturers of laboratory equipment.

Overshoes

Overshoes are required as part of the protective equipment if cytostatic contamination must be removed [2]. They must therefore be included in the "spill kit" used when spillages must be cleared up (see 4.2. Action after Inadvertent Release of Cytostatics).

Single-use overshoes are available made of liquid-tight, fluff free material. A decision must be made between simple, reasonable priced overshoes that simply protect the sole and part of the top of the foot, and overboots, that are correspondingly more expensive but offer considerably greater protection.

When selecting overshoes for use in the preparation area the aspect of product integrity must also be considered. Overshoes, or shoes to be worn only in the preparation area, are indispensable for preparations carried out in accordance with GMP conditions. Here too, boots offer a greater degree of protection than overshoe

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3.3.1. Technical Equipment for the Preparation of Cytostatics

Beate Predel, Tübingen

In order to guarantee a minimum standard of safety during the preparation of cytostatics, suitable technical equipment must be used that complies with the technical rules for hazardous substances *TRGS* 525 and the leaflets of the professional associations. This equipment must meet the requirements of the law on medical devices (*MPG*). Appropriateness to the special criteria of cytostatics preparation must also be taken into account. All equipment must be sterile or capable of being disinfected before use. The quality of the devices must be regularly inspected. The equipment must be included in the hazards evaluation.

Ready-to-administer cytostatic preparations are being increasingly prepared by pharmaceutical personnel, whether in the pharmacy workroom for ambulant chemotherapy or centrally in a hospital pharmacy. Since most of the preparations are intended for parenteral administration and are prepared aseptically for individual patients, suitable technical equipment must be used. In order to raise the level of personal protection and product integrity (see Chapter 3.5. Preparation), all employees must be familiar with how the sterile devices function, and this should be explained by means of practical training where necessary.

Technical Equipment

The preparation of cytostatics requires the following technical equipment:

- 3-layer work underlay
- compresses and swabs
- single-use syringes
- cannulas
- cyto set
- container for discarded cannulas
- waste container
- closure caps for single-use syringes
- filter cannula or filter straw
- transfer needles, transfusion cannulas
- adapters
- PhaSeal®, Securmix®
- pressure release systems, hydrophobic filters, spikes

3-Layer Work Underlay

A work underlay prevents the workbench from being contaminated if cytostatics are spilled. The work underlay consists of three layers. The upper layer is liquid-permeable and fluff free. The middle layer is absorbent (e.g. laminate) and can soak up liquids, and the lower layer is impermeable (e.g. polyethylene). Colour marking of these products facilitates their special use and disposal. A work underlay with a smooth top surface enables even small ampoules to stand securely. According to leaflet M 620 "Safe handling of cytostatics" from the *BGW* (professional association for the health service and social services) (04/2000) and in accordance with the technical rules for hazardous substances (*TRGS* 525) "Handling hazardous substances in facilities for human medical care", "care must be taken that the airflow situation of the workbench is not impaired as a result of the work underlay, i.e. the front air slots of the workbench must on no account be covered". The underlay is replaced if it becomes contaminated or at the end of the work period.

Sterile Compresses and Swabs

Compresses and swabs must be used in order to prevent contamination caused by the formation of droplets or aerosols. Ready-to-administer syringes are carefully and slowly vented using a sterile swab. Any droplets emerging during piercing and withdrawing a cannula from a septum vial, or while unscrewing a cannula from the syringe, can be caught using a swab. For microbiological considerations a compress soaked in alcohol is used when opening scored or friable ampoules. The compress also provides protection against cuts (M 174 "Opening ampoules without pain", *BGW).*

Single-Use Syringes

Disposable syringes comply with EN ISO 7886-1 "Sterile hypodermic syringes for single use" Part1: Syringes for manual use; Part 2: Syringes for use with power-driven syringe pumps (formerly DIN 13098-2).

The quality of all the materials must meet the requirements of the European pharmacopoeia or ISO 10993-1. The standards for syringes used in the preparation of cytostatics are:

- A clear, appropriate scale which can be easily read. The dosing accuracy must comply with EN ISO 7886. The stated margins of error are maximally 5%, depending on the measured volume and the nominal volume. Luer lock syringes are available in the following sizes: 1, 2, 3 [1], 5, 10, 20, 30, 50, 60 and 100 [2] ml. Dosing accuracy is regarded as sufficient if the size of syringe used comes closest to the volume to be measured. According to the recognised rules of pharmacy, the active substance content immediately after preparation should not deviate by more than 5% from the declared amount.
- Luer lock connection.
- Secure and detectable piston stop in order to prevent sudden disconnection.
- Easily moveable piston for safe working (possibly siliconised).
- Piston stop with double sealing ring if possible in order to prevent leakage of solution and to guarantee smooth withdrawal to the maximum volume.

In the case of two-part syringes [3] the cylinder is of polypropylene (PP) and the piston rod of polyethylene (PE). Three-part syringes [4] contain in addition a piston gasket of synthetic rubber (polyisopropene). Single-use syringes with natural latex-free rubber pistons [5] nave been commercially available since spring 1999. When preparing cytostatics care must be taken that solvents or solubilisers do not attack the rubber. Restrictions for amsacrine [6] apply only for a contact time of longer than 10 minutes between PVC and the solvent (dimethylacetamide). A glass syringe must be used for longer contact times. Dark (amber, opaque) syringes and infusion systems must be used for light sensitive substances such as dacarbazine (Fig. 1).

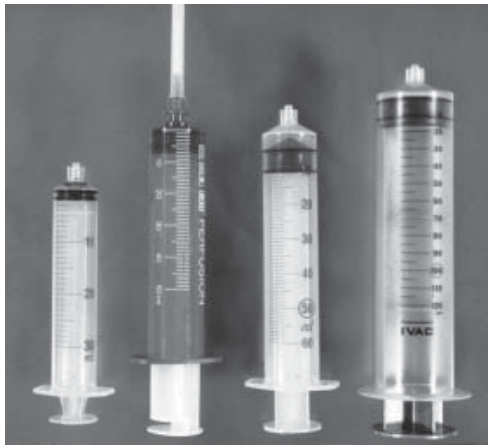

Fig. 1: Amber syringe (centre)

Cannulas (ISO 7846/DIN 13097 Part 1-3)

Cannulas of proven suitability are of stainless V2A steel (iron nickel chromium), with an extremely smooth surface, triple ground and with a finely dosed silicone coating (e.g. polydimethylsiloxane). The diameter and grind of the cannula are decisive for avoiding pieces of rubber being stamped out when inserting the cannu-

la through the septum. In order to avoid stab wounds the protective cap of the cannula should not be replaced (*BGW* M 620, no recapping). An alternative are BD Eclipse™ safety cannulas [6] (Fig. 2), which, however, are only available in

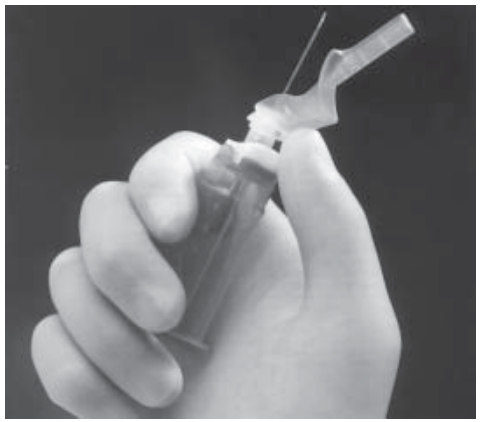

Fig. 2 BD Eclipse (TM) safety cannula

combination with 1 and 3 ml syringes. These are safety cannulas with an integrated one-handed activation protective system (see safety.service.de@europe.bd.com).

In order to avoid possible sources of contamination single-use syringes and cannulas should remain connected for disposal (s. 13 *UVV* (accident insurance regulations) "Health service" *VBG* (rules of the professional association) 103). If a connection must be separated in order to perform the work involved, unprotected cannulas must be unscrewed using a swab and disposed of in a puncture-proof container. Safe disposal of all contaminated materials is necessary in order to exclude any possibility of endangering third persons. The risk of

Fig. 3: syringe block

1 ALARIS Medical Systems, Schützenstr. 62, 35398 Gießen

2 Z.B. Injekt Luer-Lock; B. Braun Melsungen AG, Sparte Medical Postfach 1120, 34209 Melsungen

3 Z.B. Omnifix® Luer-Lock; B. Braun Melsungen AG, Sparte Medical Postfach 1120, 34209 Melsungen

4 B. Braun Melsungen AG, Sparte Medical Postfach 1120, 34209 Melsungen

5 Auskunft vom Fachreferat Med.-Wiss. Gödecke-AG, Mooswaldallee 1, 79090 Freiburg

stab wounds can be reduced by using a syringe block [7] (Fig. 3). This is a block with recesses into which the cannula protective cones can be inserted, thus enabling the syringe with cannula to be replaced one-handed from above into the protective cap.

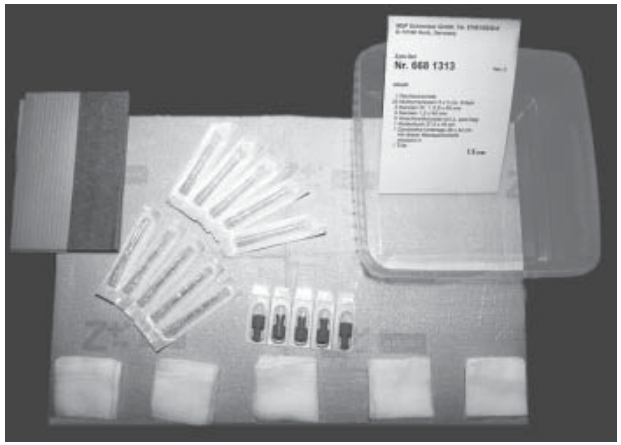

Fig. 4: Cyto Set

Cyto Set

The cyto set contains basic sterile equipment for the daily preparation. A rectangular dish holds all the items needed, e.g. swabs and compresses, closure caps, cannulas, work underlays, etc. The set can be put together individually (e.g. Zyto-Set Art. 6681313 [8]). The entire content is sealed in a bag and sterilised by means of UV radiation (Fig. 4).

Container for Discarded Cannulas

Since containers for discarded cannulas normally remain in the safety workbench for more than one day they must be non piercable, able to be tightly closed and easy to disinfect.

Waste Container

The airflow situation in the workbench must not be negatively influenced by the waste container and the size of the container must therefore be carefully chosen.

6 Becton Dickinson GmbH, Tullastraße 8-12, 69126 Heidelberg

7 Zyto-Set Art. Nr. 668 1313 oder Verband-Set Nr. 726; MSP Schmeiser GmbH Siemensstr. 14, 72160 Horb

Slightly contaminated wastes can be collected underneath the safety workbench, e.g. in sterile single-use kidney bowls [7]. Heavily contaminated wastes must be collected in labelled, sufficiently robust, tightly sealed containers and sent for disposal in accordance with the safety measures and in compliance with the statutory waste regulations of the regional authority.

Closure Caps for Single-Use Syringes

Combination stoppers [8] with a double function must be used for closing ready-to-use cytostatics syringes. These are of polyethylene, have a recessed internal and external Luer lock system. Closure caps and are produced and type tested according to DIN 58362-S-P.

Fig. 5: top: Filter straw, bottom: Filter needle

Filter Needle, Filter Straw with Integrated 5 µm Particle Filter

The use of a filter needle (Sterifix® filter needle - Fig. 5 bottom) or a filter straw [9] (Sterifix® filter straw - Fig. 5 top) is a sensible measure in the case of particle-loaded solutions (e.g. fluorouracil) and with friable ampoules. The 5 µm particle filter is of nylon, the tube of the filter straw is of PVC and the filter case of ABS (acrylonitrile butadiene styrene) plastic.

Closed System

A closed system enables the dry substance or lyophilisate to be dissolved with pressure equalisation and without the risk of aerosol release. A closed system consists

8 Z. B. Combi-Stopper®, B. Braun Melsungen AG, Sparte Medical, Postfach 1120, 34209 Melsungen

9 Z.B. Sterifix® Filterhalm (4,5 cm, 10 cm Schlauch); B. Braun Medical AG, Postfach 1120, 34209 Melsungen

of a septum bottle containing cytostatic, adapter and a container with solvent or infusion solution.

"A closed system is a system in which there is no necessary connection between the contaminated inner space and the surroundings during the mixing and preparative process. It consists of defined connectors, drug vessels, separating elements and a user part. Closed systems must be conceived for a defined purpose and for single use. Multiple use and disconnection must be technically impossible. Errors in use must not lead to a dangerous situation. A closed system is always only approved for a single drug ..." (M 620 *BGW*, Appendix II).
A closed system can be achieved using the following components:
mixing adapter, PhaSeal®, Securmix®, transfer needles, transfer cannulas.

Mixing Adapter

By using suitable adapters a closed system is obtained to the respective carrier solution systems. In this case the solvent is also the carrier solution. This is forced under pressure from the bag into the septum bottle containing the cytostatic and then shaken. The dissolved cytostatic is returned to the bag as a result of pressure equalisation. Flexible containers of carrier solution [10] are also suitable for this. Mixing adapters are of only limited use for withdrawing partial amounts because dosing may be inaccurate in such cases.

Fig. 6: right: Protector with expansion membrane,
centre: Connector,
top: Injector

10 Z.B. Glucose 5 Plasco®, B. Braun Melsungen AG, Postfach 1110, 34209 Melsungen

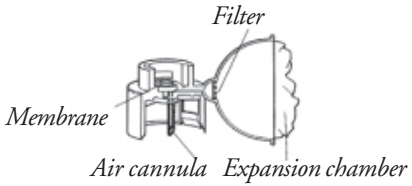

Abb. 6a: PhaSeal Protector Lock

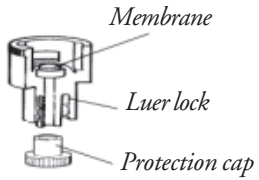

Abb. 6b: PhaSeal Connector Luer

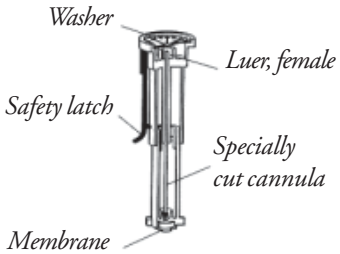

Abb. 6c: PhaSeal Injector Lock

Abb. 6d: Schutzwirkung vom PhaSeal-System: Aerosol wird zurückgehalten

PhaSeal®

PhaSeal® is an elaborately constructed closed system from Sweden. It consists of a protector, injector and connector and is intended for drug bottles with a closure diameter of 14 or 21 mm.

Pressure equalisation is achieved by means of an expansion membrane of double-coated polyamide film, which can accept a maximum volume of 50 ml. This is the protector (Fig. 6 right) of PhaSeal® [11], which effectively prevents aerosol release. The Luer injector (Fig. 6 top) contains a specially ground encapsulated cannula, which is locked to the syringe and can only be released after unlocking a safety clamp.

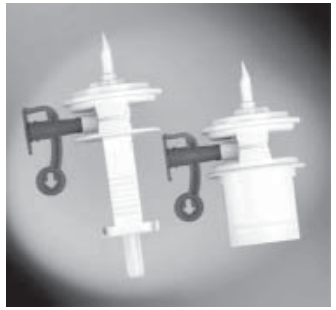

Fig. 7: left: Securmix bag, right: Securmix bottle

The connector (Fig. 6 centre) provides a closed connection between syringe/injector and the i.v. access of the patient.

Securmix®

Securmix® [12] is another closed system available in two versions: Securmix® Flasche (bottle) (Fig. 7 right) has a spike with a plastic tube for attaching to bottles with a rim cap maximally 33 mm in diameter; Securmix® Beutel (bag) (Fig. 7 left) consists of a spike with a cannula for attachment to an infusion bag. Securmix® simultaneously connects the drug to be prepared, the necessary solvent and a syringe. It enables the transfer of exact amounts of solvent to the drug, and vice versa, and venting of the syringe, without having to disconnect it. The withdrawal of partial amounts is also possible; it should be borne in mind, however, that the device retains a dead-space volume of 0.13 ml. Two 0.2 µm filters separately vent the channel to the drug and the channel to the solution. The main part of the system is of polycarbonate, the valve is of polypropylene, the filter housing of PVC and ABS and the filter fabric of acrylic polymer on nylon mat.

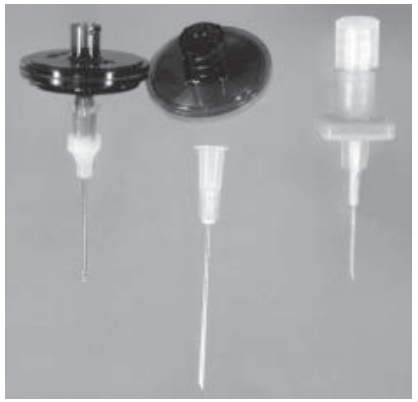

Fig. 8: left: Millex filter cannula, centre: Hydrophobic filter with separate cannula,
right: Short filter cannula

Transfer Set with Plastic Spike, Transfer Needles, Transfer Cannulas

Transfer systems serve for dissolving dry substances by enabling the contents of a solvent bottle to be transferred by gravity into a septum bottle containing the dry substance. The device consists of a two-way cannula or plastic spike with internal pressure equalisation so that no pressure difference arises after removal of the system.

11 Carmel Pharma ab, Box 5352, SE-40228 Göteborg, Schweden

12 Hersteller: Eurospital S.p.A., Via Flavia 122, I 34147 Trieste, Italia;

According to *TRGS* transfer systems are regarded as suitable devices for the preparation of cytostatics, however, only for preparing and emptying drug vessels completely. For withdrawing partial amounts the system must be removed from the drug vessel and a spike fitted with an appropriate piercing needle. The outside diameter of the plastic spike [13] of approx. 6 mm can be disadvantageous since it may present problems in re-closing the stopper securely (tightness of the septum).

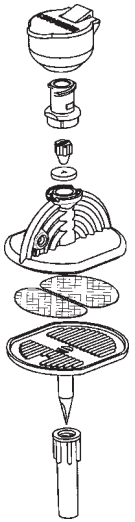

Fig. 9b:Braun Ventilspike Chemo

Pressure Release Systems: Hydrophobic Filters, Spikes

These compensate pressure differences which arise during the dissolution process. In the simplest case, a filter cannula [14] (Fig. 8) is used with a hydrophobic 0.2 µm filter, which is inserted through the septum in addition to the injection cannula.

A further possibility for releasing pressure is provided by diverse spike systems, which differ in the material, the pore size of the filter and the thickness and length of the spike. The inflowing air is subjected to sterile filtration. The aerosols potentially formed during the preparation of cytostatics are retained only by a 0.2 µm hydrophobic aerating and venting filter. Therefore, the only spikes suitable for the preparation of cytostatics are those with a filter membrane with a pore diameter of 0.2 µm.

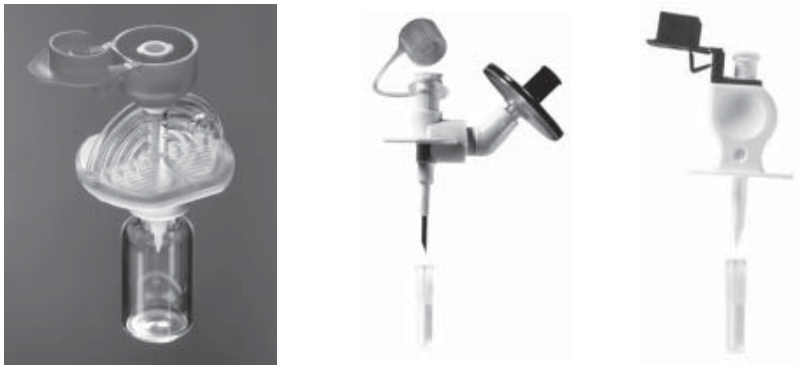

Fig. 9: Braun Chemospike, Fig. 9c:Medac Ultrasafe, Fig. 9d:Medac Chemo spike

13 Z.B. PPS Transfer-Set; PPS Pharmapack Stute, In der Brückenwiese 4, 53639 Königswinter

14 Millex®_25 Millipore GmbH, Hauptstraße 87, 65760 Eschborn

The nature of the system means that air bubbles can never be completely avoided during preparation. In the case of conventional spikes, directly injecting back from the syringe into the bottle standing on its head frequently leads to liquid running out of the syringe set because of liquid being forced into the air channel. The Mini-Spike-V-Chemo [4] (Fig. 9b), commercially available since 2002, has the advantage of an integrated valve through which the air bubbles can be easily removed. For the user, this means simple, fast and safe handling.

In respect of materials it must be noted that etoposide may not be used in combination with ABS plastic. Filters consist of acrylic copolymers supported on nylon mat, or of PTFE (polytetrafluoroethylene = Teflon®). These filters are integrated in the spike or mounted on the side. For solutions loaded with particles, a spike can be used with an additional hydrophilic 5 µm particle filter located in the liquid channel. Spikes are available either with V2A steel cannulas (Fig. 8b [15]) in different lengths and diameters, or with a piercing needle (plastic) (Fig. 9d [16], 9e [17], which enables faster filling with large volumes but is unsuitable for small bottles.

In the meantime, the Chemo-Mini-Spike Plus® [4] has become available with microtip but without particle filter. The microtip ensures optimal residual emptying of bottles between 3 and 1000 ml. For a spike to be suitable, the diameter of the piercing needle must not impair reclosure of the septum, whereby the dead-space volume of the spike must be kept as low as possible.

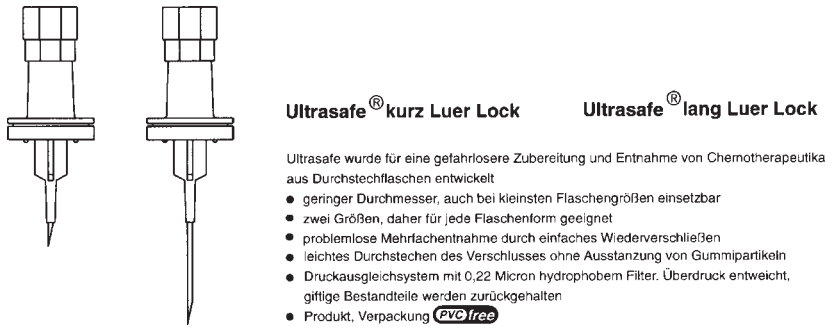

Fig. 8b:Ultrasafe short (left), long (right)

During use, care must be taken that the Luer lock negative connection (DIN 13090) of the spike is firmly screwed to the syringe to ensure safe working. Single piercing with a spike for multiple withdrawal significantly reduces the risk of stamped out pieces of rubber compared with several piercings with a cannula. The protective cap [e.g. 18] on the spike serves to close the aspiration channel and secures the inside sterility at the same time. For microbiological considerations a limit should be placed on the duration of use. According *TRGS* 525 pressure release systems must be used during the preparation of cytostatics.

Fig. 9e: Taky-Spike

Care and Storage

Single-use articles must carry the CE mark and thus meet the requirements of the law on medical devices. Sterilely packaged single-use articles must be stored in dry, dust free rooms and should remain in their original boxes until they are used. The items are kept at a relative humidity of 50 - 60% and a temperature between 10 °C and 25 °C, protected from direct sunlight and moisture. Recommended time limits for storing sterile materials for use under normal aseptic conditions (DIN 58953 Part 7) must be observed and regularly checked. A shorter shelf life results if the packages are opened. The composite packaging or paper must not be damaged during storage. Outside packaging must not be stored in the sterile area.

Interactions between Drugs and Equipment

The different materials must be checked individually for their suitability in order to exclude interactions between drugs and technical equipment. Unfortunately the information provided by manufacturers is not always clear. It would be desirable if in future clear labelling for every user were visible on the product.

15 Z.B. Ultrasafe® kurz (lang) Luer-Lock; Berner International GmbH, Mühlenkamp 6, 25337 Elmshorn

16 Z.B. medac Spike Chemo oder Ultrasafe® medac Chemo; Vertrieb: Medac Gesellschaft für klinische Spezialgeräte mbH, Fehlandtstraße 3, 20354 Hamburg

17 Z.B. Taky-Spike® Chemo Luer-Lock; Berner International GmbH, Mühlenkamp 6, 25337 Elmshorn

18 Z.B. Codan Filterspike; CODAN Medizinische Geräte GmbH & Co KG, Postfach 1220, 23735 Lensahn

References

1 ALARIS Medical Systems, Schützenstr. 62, 35398 Giessen

2 (e.g.) Injekt Luer-Lock; B. Braun Melsungen AG, Medical Division, P.O. Box 1120, 34209 Melsungen

3 (e.g.) Omnifix® Luer-Lock; B. Braun Melsungen AG, Medical Division, P.O. Box 1120, 34209 Melsungen

4 B. Braun Melsungen AG, Medical Division, P.O. Box 1120, 34209 Melsungen

5 Information from Medical Sciences Department, Gödecke AG, Mooswaldallee 1, 79090 Freiburg

6 Zyto-Set Art. No. 668 1313 or Verband (dressing) Set No. 726; MSP Schmeiser GmbH, Siemensstr. 14, 72160 Horb

7 (e.g.) Combi-Stopper®; B. Braun Melsungen AG, Medical Division, P.O. Box 1120, 34209 Melsungen

8 (e.g.) Sterifix® Filterhalm (filter straw) (4.5 cm, 10 cm tube); B. Braun Medical AG, P.O. Box 1120, 34209 Melsungen

9 (e.g.) Glucose 5 Plasco®; B. Braun Melsungen AG, P.O. Box 1120, 34209 Melsungen

10 Carmel Pharma ab. P.O. Box 5352, SE-40228, Göteborg, Sweden

11 Manufacturer: Eurospital S.p.A., Via Flavia 122, I 34147 Trieste, Italy; sales in Germany: Delta-Pharma GmbH, Benzstr. 5, 72793 Pfullingen

12 (e.g.) PPS Transfer Set; PPS Pharmapack Stute, In der Brückenwiese 4, 53639 Königswinter

13 Millex®-25, Millipore GmbH, Hauptstrasse 87, 65760 Eschborn

14 (e.g.) Ultrasafe® kurz (short) / lang (long) Luer-Lock; Berner International GmbH, Mühlenkamp 6, 25337 Elmshorn

15 (e.g.) medac Spike Chemo or Ultrasafe® medac Chemo; Sales: Medac Gesellschaft für klinische Spezialgeräte mbH, Fehlandtstrasse 3, 20354 Hamburg

16 (e.g.) Taky-Spike® Chemo Luer-Lock; Berner International GmbH, Mühlenkamp 6, 25337 Elmshorn

17 (e.g.) Codan Filterspike; CODAN Medizinische Geräte GmbH & Co KG, P.O. Box 1220, 23735 Lensahn

Further Reading:

Baumann B., *Schutzmassnahmen beim Umgang mit Zytostatika* (Protective measures during handling cytostatics), PTA heute, 1999; 11; No. 12 pl 1210-1216

Manufacturer's information from the particular firm

3.3.1.1. Infusion Pumps for the Administration of Cytostatics

Medical devices may be set up, operated and used only for their intended purpose in accordance with the „law on medical devices“ and associated statutory orders, and conforming to accepted technical standards and to working safety and accident prevention legislation.

Thanke Mehrtens, Hannover

1. Types of Infusion Pump

The portable infusion pumps described below are intended for the precise infusion of cytostatics which must be administered slowly and continuously, or in accordance with circadian rhythms, over a period of several hours to days.

Elastomeric pumps

Principle of function: The pump housing contains a balloon of elastic material, which is „pumped up“ by being filled with a solution of the cytostatic. The pressure thus generated forces the drug solution out of the balloon and into the infusion tube. The volume delivered is regulated by a flow controller in the infusion tube. Depending on the model, air and particle filters may be integrated in the tube. Because not every pump has an exact level indicator, the end of the infusion can often only be estimated from the level of fluid in the bag. Since every pump has a fixed, pre-set delivery rate (accurate to within +/- 10 - 15 % according to the manufacturer), the duration of the infusion is determined by the filling volume, and the dose of drug by the concentration. In addition, the flow rate is influenced by the temperature (skin or ambient temperature), the viscosity of the solution and the height difference between pump and access (observe manufacturer's instructions). The range of pumps offered by individual manufacturers is wide, so that the right pump can be chosen for each therapy. Elastomeric pumps may be used only once and must not be refilled or re-sterilised.

Product Examples:
- Easypump (B. Braun / Ribosepharm)
- Intermate / Infusor (Baxter)
- Surefuser (Medac)
- Accufuser (DeltaSelect)

Spring operated infusion pumps

Principle of function: The re-usable infusion pump consists of a housing with an integrated spring drive. The infusion bag (disposable) containing the cytostatic solution is laid in the housing. When the housing is closed, the spring exerts pressure on a plate which, in turn, presses on the infusion bag. The flow rate is regulated by a flow controller in the tube. In addition, air elimination and particle filters are integrated in the tube. A level indicator is provided. The flow rate is influenced by the temperature (skin or ambient temperature), the viscosity of the solution and the height difference between pump and access (observe manufacturer's instructions). The flow rate may deviate from the nominal value by up to +/- 10 %. A wide range of disposable articles with the same filling volume but different delivery rates enables widespread use. Every pump has a serial number and an expiry date. Up to the expiry date, the pump can be used without maintenance and without a safety inspection.

Product Examples:
- Onkoworker (Onkoworks)
- Ultraflow (Fresnius)

Peristaltic pumps

Principle of function: Infusion of the cytostatic solution is controlled by a microprocessor in the head of the battery-driven pump. The solution is placed in disposable material (cassette or bag) which is specific for the pump and which is then connected to it. Different programming possibilities allow continuous, intermittent or circadian infusion, or a bolus administration of one or more solutions. Depending on the manufacturer, different filters are integrated in the disposable material. The pumps are fitted with an alarm function, and frequently with an electronic memory for monitoring and evaluating the therapeutic data. Safety checks and maintenance tasks must be performed according to the manufacturer's instructions. Infusion accuracy is approx. +/- 5 %.

Product Examples:
- I-Pump (Baxter)
- Multi-Therapie-Infusionspumpe 6060 (Baxter)
- CADD Legacy series (Smiths Medical Deutschland GmbH)
- Graseby Series 9000 (Smiths Medical Deutschland GmbH)
- Melodie Mehrkanalinfusionsspumpe (Logomed)
- Multifuse (B. Braun)
- Pegasus series (Logomed)

- Walkmed 350 (Logomed)

2. Statutory Requirements

The regulations governing the setting up, operation, use and maintenance of medical devices (*Medizinprodukte-Betreiberverordnung, MPBetreibV*) ensure that the medical and technical quality of the medical devices is also maintained for as long as possible after they have been brought into circulation. The regulations consist of 6 sections. In respect of infusion pumps, the first section (area of application and general regulations) and the second section (special regulations for active medical devices) are of relevance. However, not all the pumps described above are subject to the *MPBetriebV* (ask manufacturer). In the following, an attempt will be made to clarify certain parts of the legal text.

General requirements (s. 2 *MPBetreibV*)

According to the provisions of the *MPBetreibV*, infusion pumps may be set up, operated, used and maintained solely for their intended purpose. This also applies for combinations of different medical devices (pump and single-use material). Thus before buying a particular pump it is important to ascertain whether its intended purpose makes it suitable for the administration of cytostatics and which disposable materials can be used in this case.

Operation and use (s. 2 and 5 *MPBetreibV*)

Medical devices listed in Appendix 1 to the *MPBetreibV* (e.g. certain types of diffusion pump) must not be put into operation until the manufacturer or supplier has tested the proper functioning of the device at the location where it will be operated and has given instructions on using the device to a person nominated by the operating authority (s. 5 *MPBetreibV*). All persons using the infusion pump must have the necessary education or skills and practical experience to ensure that they can operate the pump properly, and must also have received instruction in using it from the person nominated by the operating authority. This instruction must be documented.

Before every use of an infusion pump, the respective user must ensure that it is in good condition and functioning properly. Instructions for use, safety information and maintenance instructions must be followed (s. 2 and 5 *MPBetreibV*). The functional description of the pump and the operating instructions must be made available to the user in such a way that they are always accessible (s. 9 *MPBetreibV*). The medical devices book must also be accessible to the user during work time (s. 9 *MPBetreibV*).

Operating authorities are, for example, bodies operating hospitals, owners of medical practices or other in-patient and ambulant health facilities, hospitals or health centres. The operating authority is responsible for ensuring that the relevant provisions of the law on medical devices and the *MPBetreibV* are implemented properly. It creates the organisational requirements for the implementation of the provisions and, within the scope of its organisational authority, is responsible for ensuring that the medical devices are used according to their intended purpose and for the initiation, implementation and monitoring of all mandatory administrative and technical measures, e.g. maintaining inventories, creating the medical devices books and ordering the safety inspections to be carried out.

Before a medical product may be put into operation, the "person nominated by the operating authority" must be instructed in the proper handling, use and operation of the medical product. Only this person may then instruct the users in the proper use of the medical product.

Users are all persons who use the medical product in the course of their work.

Reporting incidents (s. 3 *MPBetreibV*)

The operating authority or user must immediately report to the *BfArM* (federal institute for medicines and medical devices) any malfunction, any change in the characteristics or performance and any error in the labelling or instructions for use of a medical product which has or could have led to the death or serious deterioration in the health of a patient, an employee or a third party. The *BfArM* passes the report on without delay to the authority responsible for the operating authority and also informs the manufacturer and the authority responsible for the manufacturer.

All users should be appropriately instructed as to whom they can contact in the event of incidents of this kind. The official "Forms for the mandatory reporting of incidents / near-incidents" should also be available there. Such forms are obtainable from the *BfArM* (Bundesinstitut für Arzneimittel und Medizinprodukte, Geschäftsstelle Medizinprodukte, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Tel.: 0228 207-5385, Fax: 0228 207-5300, www.bfarm.de) and the *DIMDI* (Deutsches Institut für medizinische Dokumentation und Information, Weisshausstrasse 36-38a, 50676 Köln, Tel.: 0221 4724-1 or Fax: 0221 4724-444, wsww.dimdi.de).

Maintenance and safety inspections (s. 4 & 6 *MPBetreibV*)

The statutory requirements of Section 4 and 6 must be observed (which person with which qualifications is permitted to perform which tasks).

The service work (maintenance, including inspection, repair and preparation) and the safety checks to be performed are listed in the instructions for use of the medical product and any enclosed information relating to safety. The intervals at which specific tasks must be performed are also listed here. If this information is missing, contact must be made with the manufacturer or a qualified person with appropriate knowledge. In addition to the time limits for performing safety inspections, the operating authority must also comply with the inspection time limits for the corresponding accident prevention rules (insofar as the requirements are not integrated in the safety inspections) and with the time limits for any calibration checks.

Safety inspections are not mandatory for all infusion pumps. Nonetheless, every pump should be subjected to a regular inspection in accordance with specified criteria in order to ensure timely detection of deficiencies which could endanger patients, employees or third parties. The kinds of inspection and the results must be documented.

Medical devices book (s. 7 *MPBetreibV*) and inventory (s. 8 *MPBetreibV*)

For infusion pumps listed in Appendix 1 to the *MPBetreibV*, a medical devices book must be kept and used to record information for identification of the medical product, instructions, safety inspections, malfunctions and reports to the authorities. In addition, the operating authority must maintain an inventory for all active non-implantable medical devices at the respective location, which is used to record information for identification of the medical product, organisational allocations and time limits for safety inspections. The responsible authority can release the operating authority from the duty to maintain an inventory, or from the duty to record specific medical devices in the inventory, if the operating authority can adequately justify this.

The law does not specify which department should maintain these records. An agreement in the hospital with the medical technology department is a reasonable solution.

Keeping of the instructions for use and the medical product books (s. 9 *MPBetreibV*)

The instructions for use and the information enclosed with the medical product must be kept such that necessary information about the medical product is accessible to the user at all times. The medical devices book must be kept such that the information is accessible to the user during work time. After the medical product has

been withdrawn from service, the medical product book must be kept for a further 5 years.

Medical product book and inventory must be shown to the responsible authority on demand.

3. Practical Notes

If it is intended to acquire diffusion pumps for the in-patient sector, prior agreement between the pharmacy and the medical technology department is always useful. Normally, the provisions of the *MPBetreibV* for all the medical technical equipment in the hospital will be implemented by the medical technology department. However, if the pumps (and not just the infusion bags) are filled, issued, emptied, possibly checked for faults and stored in the pharmacy, and if the oncologically involved pharmacist must also instruct the patient on how to use the pump - in the sense of patient-oriented clinical pharmacy -, agreements must be reached about how the *MPBetreibV* should be implemented and these agreements must be documented.

Purchase of the pumps

The following checklist should be gone through when purchasing pumps:

- Does the product meet the requirements of the *MPG*?
- Does the intended purpose of the product conform with its intended use?
- Is the medical product suitable for the intended use in respect of the safety of patients, employees and third parties?
- Is the medical product approved for any intended combination with a different medical product (accessories)?
- Must a medical devices book be created?
- Are safety or calibration inspections necessary? Which, and at what time limits?
- Who will carry out the inspections (in-house technical staff / outside firm)?
- What follow-up costs may be expected?

Instruction

The personnel engaged in cytostatics preparation must receive instruction at regular intervals (see also Chapter 1.3 “Working Rules and Instruction” and Chapter 1.6 “Qualification of the Personnel”). Insofar as this is not already specified by the *MPBetriebV*, exactly who instructs users and patients and provides them with the necessary written information will depend on how the in-house tasks are allocated.

Preparation procedure

A preparation procedure must be defined for filling the pumps. This must include all the items listed in Chapter 3.6 “Preparation”. The respective manufacturer’s information on filling (and programming if applicable) must be followed. Any dead-space volume must be taken into account when filling the reservoirs. The preparation procedure must also specify whether the overfilling has already been allowed for in the computer calculation of the filling volume, or whether this overfilling must be calculated in addition by the person carrying out the preparation. Working procedures must be strictly aseptic.

Label

If overfilling is carried out for reasons of the dead-space volume, only the actual administered amount of the cytostatic (i.e. the amount prescribed) must be written on the label.

Delivery of the pumps

Since the breakage security of drug reservoirs for portable infusion pumps is subject to high standards, there is no need for sealing in film. This also applies for spring driven pumps if the infusion bag is delivered in the pump. Some manufacturers recommend packaging the pump in liquid-tight snap-fit bags before these are pakked in the bags. Delivery takes place as described in the corresponding chapters 4.5, 4.6 or 4.7.

Waste disposal

The single-use material is disposed of as described in the section “Waste Disposal”. Unusually high residual volumes must be documented and the causes determined and remedied (malfunction or wrong use).

References:

1. Law on medical devices (*Medizinproduktegesetz - MPG*) of 2 Aug. 1994

2. First law on amendment of the law on medical devices (1. *MPG-ÄndG*) of 1 Aug. 1998

3. Second law on amendment of the law on medical devices (1. *MPG-ÄndG*) of 1 Aug. 1998

4. Regulations on the setting up, operation and use of medical devices (*Medizinprodukte-Betreiberverordnung - MPBetreibV*) of 29 Jun. 1998

5. Amendment to the *MPBetriebV* of 13 Dec. 2001

6. Product descriptions from the manufacturer

7. AMD Medizintechnik (publisher): *Anwender- und Betreiberpflichten für Medizinprodukte* (“Duties of users and operating authorities for medical devices”), MediVision GmbH, Berchtesgadener Str. 26, 10825 Berlin; IssN 1433-3414

List of Manufacturers

1. Baxter Deutschland GmbH, Bereich Therapiesysteme, Edisonstr. 3-4, 85716 München-Unterschleissheim,
Tel: 089 31701-0, Fax: 089 31701-177, www.baxter.de

2. B. Braun Melsungen AG, Carl-Braun-Strasse 1, 34212 Melsungen,
Tel.: 05661 71-0, Fax: 05661 71-4567, www.bbraun.de

3. Fresenius Kabi Deutschland GmbH, 61346 Bad Homburg
Tel.: 06172 686-8135, Fax: 06172 686-5546, www.fresenius.de

4. DeltaSelect GmbH, Hermann-Burkhardt-Strasse 3, 72793 Pfullingen
Tel.: 07121-9921-0, Fax: 07121-9921-31, www.accufuser.de

5. Logomed GmbH, Klarenplatz 11, 53578 Windhagen
Tel.: 02645 9531-0, Fax: 02645 9531-31, www.logomed.de

6. medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstrasse 6, 22880 Wedel
Tel.: 04103 8006-0, Fax: 04103 8006-100, www.medac.de

7. Onkoworks, Schallbruch 5, 42781 Haan / Rhld.
Tel.: 02129-94270, Fax: 02129-942727, www.onkoworks.de

8. ribosepharm GmbH, Berg-am-Laim-Str.127, 81673 München
Tel.: 089-454404, Fax: 089-4544-1130, www.ribosepharm.de

9. Smiths Medical Deutschland GmbH, Hauptstr. 45-47, 85614 Kirchseeon
Tel.: 08091 551-0, Fax: 08091 551-100, www.sims-deutschland.com

3.4. Aseptic Procedures

Aseptic procedures include all the mutually coordinated, necessary steps which - using the best available methods for reducing the microorganism count and the possibility of contamination - lead to a sterile product.

Making ready for the actual process of aseptic preparation and clearing up afterwards exert a decisive influence on the quality of the product.

3.4.1. Validation of Aseptic Procedures
3.4.1.1 Validation

The preparation of a cytostatic in a cytostatics workbench is aseptic drug preparation whose process must be validated. Compliance with the standards set by the European Pharmacopoeia for preparations for parenteral use is mandatory.

Validation is only possible by inspection of the entire work process and the circumstances under which the aseptic preparation takes place, i.e. the following items must be taken into account:

1. the rooms in respect of cleaning and hygiene
2. the cytostatics workbench
3. the work materials
4. the starting materials and
5. the aseptic preparative procedure.

Validation of the entire process includes all the well thought-out measures which guarantee that the production and inspection procedures ensure the preparation of a product meeting all the requirements and conforming to the specified quality profile in respect of safety, identity, content, quality and purity.

3.4.1.2 Methods for Inspecting Aseptic Procedures

Instead of examining the properties of the product prepared, appropriate microbiological methods must be used to test for the absence of microorganisms capable of reproduction. A test plan must be drawn up. The number of tests and their frequency will depend on the circumstances in the particular pharmacy.

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A) Validation means furnishing and documenting the proof that a method leads reliably to the expected result within defined limits [1]. Although proof can be furnished that the ready-to-administer cytostatic solution is sterile - i.e. that the solution contains no viable microorganisms -, this test of sterility is a microbiological method that can in no way be regarded as validation of a process. It must also be noted that certain standard procedures of aseptic working are part of the preparative method, and that the use of specific cleaning procedures belongs to the appropriate hygienic measures.

The European Pharmacopoeia under 5.1.1. „Methods for the production of sterile preparations“ states: „The sterility of a preparation cannot be ensured by means of a test; sterility must be guaranteed through the use of a suitable and validated production method.“ [2]

The procedure of aseptic preparation of ready-to-apply cytostatic solutions in the pharmacy has in the meantime achieved its own status between that of prescription and industrial production. This production method is no longer compared to aseptic industrial batch production in respect of the methods or parameters of validation. According to the guidelines of the *Bundesapothekerkammer* (”federal association of pharmacists”) [3], this is a continuous aseptic individual preparation under ”low-risk conditions”. The preparation takes place predominantly in the closed system. The guidelines of the *Bundesapothekerkammer* are oriented on the American USP Monograph 1206 ”Sterile Products for Home Use”. The guidelines of the American Society of Hospital Pharmacists (ASHP) [ ] also divides the risk class of an aseptic preparation according to possible risks of contamination during the process of preparation and during storage.

The United Kingdom, the Netherlands and Switzerland have also prepared GMP guidelines specifically for aseptic preparation.

Cytostatics solutions for parenteral use (intravenous, intrathecal, intrapleural) must comply with the monographs „Preparations for parenteral use“ and „Preparations for injection and infusion“ and must therefore be sterile, be free of particles and pyrogenic agents and meet the requirements of „Test for sterility“ (2.6.1. European Pharmacopoeia, 4th Edition 2002) and also „Test for freedom from pyrogens“ (2.6.8.). A final sterilisation of the cytostatics solutions is not possible because of the instability of many drugs and the urgency of the requisition.

Since the „Test for sterility“ and the „Test for freedom from pyrogens“ are destructive tests on the end product, which are possible only for batch production, the entire aseptic work process of an individual preparation must be validated.

In the AHSP ”Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products” and the guidelines of the *Bundesapothekerkammer* the process validation is referred as process simulation to every single employee and to every typed of preparation. Revalidation should take place at least annually [3]. In the case of ”low risk” preparations the USP requires a three-monthly revalidation; for ”high risk” preparations this is supplemented by a more demanding process validation every year.

Validation of the aseptic work must be integrated in a quality management system that ensures the required product characteristics in their entirety.

Validation of the process of aseptic preparation of cytostatic solutions must be referred to the situation in the particular pharmacy.

In the European Pharmacopoeia under 5.1.1., preparation under aseptic conditions is defined as follows: „The purpose of a preparation under aseptic conditions is to retain sterility in a preparation derived from the combination of sterilised components“.

Thus the primary aim of aseptic preparation is to take measures to prevent contamination at every phase of the preparative process. From this point of view, every individual preparative step is of equal importance [ ]. Inspections of the surroundings and the personnel are indispensable in ensuring proper aseptic procedures.

The following points should be characterised with reference to aseptic working methods:

1. the rooms with respect to cleaning and hygiene
2. the safety workbench (LAF - laminar air flow)
3. the work materials
4. the starting materials
5. the aseptic preparative procedure (work routine).

In Germany, isolators for the preparation of cytostatics solutions are the exception. Because of the different method of creating a clean working environment, the use of these devices generates different critical interfaces in the work routine in respect of the clean room class and the necessity for different handling steps. The points presented here must be applied analogously and problems typical for isolators (e.g. glove replacement) must be solved.

1. Rooms

The rooms and their characteristics have already been described in 2.1. ”Rooms and Equipment”. A dispenser of hand disinfectant must be provided in rooms which do not have an air lock. The hands must be disinfected on entering.

The preparation itself must be carried out in a clean room of Class A (safety workbench, see Section 2.2 ”Ventilation and Air Conditioning Systems”). The safety workbench must be installed in a room of cleanness class B (EU GMP Guide, [4]). In practice, however, LAF workbenches are still frequently located in other types of room.

The clean room class can be achieved only through structural measures which control the filtration of inflowing air and the appropriate outflow of this air. Control procedures are particle counts of the air and airborne microorganism counts using various methods (cf. p. 169).

We shall not discuss here the equipment used for determining airborne particle counts. It is important to note that completely different particle counts are measured during quiet periods compared with periods during which work is being performed. Limited access to the working area or complete gowning with clean room overalls reduces the particle count in the air.

The ratio of microorganism count to particle count fluctuates between 1:1000 and 1:5000 [cf. 6 p. 169]. Thus there must be no detectable microorganisms in the LAF zone (max. 3,500 particles $\geq$ 0.5 µm) and, therefore, only the particle count is

monitored in the LAF zone. This test is due every six months as part of the inspection of the LAF equipment.

Airborne microorganism counts are used both for the validation of facilities and for routine monitoring of the rooms.
In the cytostatics production area, airborne microorganism counts are suitable for routine monitoring of the rooms. The microorganisms detected can be subjected to „differential classification“ in order to reveal atypical patterns in the flora present [7].

Determination of the airborne microorganism count [cf. 6 , p. 170 ff] by means of sedimentation plates is a semi-quantitative method. To perform this, CSA plates with the cover removed are allowed to stand open for a period of 60 minutes to 4 hours and are then incubated appropriately. Agar types used are blood agar, Sabauroud glucose or CSA agar plates. Particles < 5 µm are not detected. This method is simple and provides good comparative values for routine inspections in rooms of class B, C and D. The USP XXIII requires that sedimentation plates be left open for 60 minutes in the area of Class A and for three hours in the other areas. Sedimentation plates in the area of the LAF are also useful under working conditions [7]. In the 1996 EU GMP Guide the required standards for clean room classes can be tested using sedimentation plates (kept open for 4 hours) [5].

Filtration methods and centrifugal procedures for counting airborne microorganisms require complex equipment and differ in their sensitivity. In the filtration methods, a specific volume of air is passed through a gelatine filter. As an alternative to the gelatine filter, a culture medium or buffer solution is placed in an „impinger“ and the air is passed through this solution. In the centrifugal procedures, air is sucked in and impelled against a culture medium. After appropriate incubation, the gelatine filter, solution or culture medium is subjected to microbiological evaluation. For determining the airborne microorganism count, a decision should be made for one method and this should then be used consistently.

The cleanliness of surfaces can be checked using contact tests or the smear method (cf. 6 p. 49 ff). Contact tests are semi-quantitative methods for which - for example - Rodac agar plates can be used. In the direct method, the agar is brought into contact with the surface to be tested. It is also possible to use an indirect method in which a sterile film or adhesive tape (Sellotape) is placed against the surface and after a contact time of a few seconds is then pressed onto the agar plate. Since the contact

method with agar plates is easier to standardise and also allows comparisons to be made with other pharmacies, this is the method of choice.

The rinse method uses cotton swabs or rubber wipers, mostly with the additional use of detergents. Cotton swabs enable corners and angles to be tested that are not accessible to a contact test.

Monitoring the surfaces with Rodac plates is suitable for routine use and for validation.

A weekly sampling of surfaces can be described as frequent. During routine operation after a new department has been established the interval can be longer. In any event, control samples must be taken immediately on detection of microorganisms in the sterile area. USP XXIII (Sterile Drug Products for Home Use) stipulates the determination of the initial situation in respect of microorganisms/plate at previously defined positions daily for one week (or better two weeks) at the beginning. This test should be repeated every six months. During the intervening period samples are taken weekly at a few selected positions. The initial microorganism count is used for defining how far the microorganism count can change before appropriate measure must be taken. Warning and action limits must be defined. The AHSP also counts the testing of surfaces as part of the monitoring of microbial contamination originating from the air.

Examples for microbiological and particle monitoring in a hospital pharmacy are presented by Lange/Krämer and Semenitz et al. [7, 8].

Aseptic procedures must include a cleaning plan [3] listing the personnel instructed to perform the cleaning, the type of cleaning agent used and the frequency of cleaning. A distinction must be made between the cleaning of floors, walls and surfaces of cabinets or equipment. Disposable cloths are suitable for the disinfective cleaning of surfaces; the two-mop method should be used for the floor. The cleaning personnel must verify the cleaning measures carried out, stating the date, in a suitable form of documentation.

Suitable cleaning and disinfecting agents, and the concentrations at which they should be used, are given in the list of disinfecting agents tested in accordance with the „directives for the testing of chemical disinfectants“ and found to be effective by the *DGHM* („German Society of Hygiene and Microbiology“). The American Society of Hospital Pharmacists requires in addition a periodical change of disinfecting

agent and the USP a three-monthly change in order to prevent the generation of resistant microorganisms [9]. Disinfecting agents diluted ready for use should not be kept in stock.

Refrigerators in the preparation rooms must not include automatic defrosting devices. The condensate which collects during defrosting and then evaporates from the heating element into the room air is a potential source of contamination (see Section 2.1 "Rooms and Equipment").

It is advisable to fit computer keyboards with protective covers through which the keyboard can still be used and which can be wiped and disinfected.

2. Safety Workbench

The features of a safety workbench are described in Section 2.2. „Ventilation and Air Conditioning Systems". The question as to whether an LAF system must be operated constantly in order to guarantee clean room conditions during the production phase is the subject of controversial discussion. On the one hand, it is claimed that the equipment must run continuously in order to maintain constant clean room conditions. On the other, it is not necessary to generate a continuous stream of air because the displacement air flow of the LAF system would restore the standard conditions. The ASHP Guidelines require 30 minutes run-up and then disinfection of the work surfaces before starting work [9]. The manufacturers now offer models that operate in power-saving standby mode overnight. The work surfaces must be disinfected before the start of work [DAB 10 Commentary V.2.1.1 Testing for Sterility].

UV-light must be regarded as an obsolete method of disinfection because of its inefficiency. Moreover, it presents problems of personal protection. In addition, plastic material forming the panels of the LAF equipment is liable to age prematurely if exposed to UV light.

3. Work Materials

Work materials in this case means all the sterile single-use articles necessary for the production of the cytostatic solution:

3.1 Articles directly connected with the production such as syringes, cannulas, spikes, containers (empty bags)
3.2 Articles indirectly connected such as swabs, absorbent underlays, gloves.

3.1: These work materials are transferred from the peel packaging into the LAF without coming into contact with non-sterile hands or other non-sterile objects. The packaging from the disposable articles is not brought into the LAF zone because this would increase the particle carry-in and therefore the probability of contamination.

There are diverse opinions on the exact technique to be used for „throwing in". One method is to tear open the packaging just in front of the air curtain and throw the contents into the LAF space without touching it. Others are in favour of holding the opened packaging out such that the person performing the preparation can take the contents from it. In any case, bringing in the objects generates a disturbance in the laminar air flow and this disturbance should be kept to a minimum. It is also not clear how long it takes for laminar air flow to be re-established.

3.2: Aids such as swabs or absorbent underlays are brought into the LAF as described above. Swabs must be used only once, primarily on grounds of working safety in the context of handling hazardous substances. The work underlay is the area used most during preparation and can therefore also becontaminated. If a spillage occurs, the underlay must immediately be replaced.

On grounds of the safety of the persons carrying out the preparation, gloves must be changed frequently (see Section 3.2.2. Disposable gloves for protection during the preparation of cytostatic solutions). For hygienic reasons it is advisable to change every 30 minutes [7, 8]. Contact tests can be used for microbiological monitoring: The finger tips are pressed onto an agar plate, which is then subjected to appropriate microbiological evaluation. The EU GMP Guide requires less than one colony-forming unit (CFU) per 5 fingers. The two publications cited did not reach this limit. In the guidelines for "Preparation of ready-to-administer cytostatics solutions in pharmacies" a change of gloves every 20 minutes is specified for reasons of safety at work [10].

Leaflet M 620 from the professional association specifies a change of gloves every 30 minutes, regardless of whether there is visible contamination or damage.
The hands must be cleaned using surgical hand disinfecting agent before donning the sterile gloves [3].

4. Starting Materials

Starting materials in this case means the components of the preparation, bottles of cytostatic agents, bottles of solvent and carrier solutions (glass bottles or other non-

sterile packaged containers), which must be brought into the LAF. Sterilely pakkaged carrier solutions are brought into the LAF as described in Section 3.4.1 „Work Materials“. At present the starting materials can be disinfected either by spraying or by wiping with or dipping into disinfecting solutions. It may be doubted whether spraying or wiping off with a disinfecting solution guarantees the necessary contact time in view of the rapid evaporation. The impact on the air breathed by the personnel and the load on the filter are considerable for these methods. Langer et al. used filled infusion bags for carrier solution, which were brought into the workbench using the peel-in technique. The cytostatics septum bottles and labels are not disinfected [7]. Microbiological monitoring is possible by pressing the bottle with the closure onto an agar plate after disinfection. The agar plate is then subject to appropriate microbial evaluation. Semenitz has demonstrated that wipe disinfection of stoppers is an adequate method only at low microorganism counts [8]. According to claims by the manufacturers, some plastic infusion bottles are sterile underneath the tear-off strip and therefore no longer need to be spray disinfected [11].

An effective means of disinfecting a vessel is to immerse it in a bath. However, using this method is associated with the risk of contamination caused by residues of cytostatic material adhering to the outside of the bottle and the method is not established as being in accordance with accepted principles.

Further experiments are necessary in order to determine which of the above methods is reasonable and appropriate. The current situation is that, unfortunately, immersion, spray and wipe methods are equally unsuitable. Furthermore, it may be asked whether the starting materials need to be disinfected at all before being brought in.

The use of residual solutions of cytostatics and of carrier solutions is an important economic factor for central preparation. However, the use of residues presents a considerable challenge for the validation. The disinfected cytostatics bottles are removed from the sterile space of the LAF and brought into surroundings at a lower clean room class. They are then frequently sealed in normal household freezer film before being stored in the refrigerator.
The question of a suitable closure for these bottles has yet to be settled; the following solutions are implemented in practice:
• Cannulas or spikes are closed with sterile adhesive film (surgical film).
• Cannulas are closed with combination stoppers (disposable article).
• Spikes are closed using the stoppers delivered with them.

• Cannulas are withdrawn before storage; the septum is pierced again on re-use.
• Spikes are withdrawn before storage and replaced on reuse of the bottle.

On grounds of safety in dealing with hazardous substances, it is not permitted to remove cannulas or spikes before storage because of the possible formation of aerosols. *TRGS* 525 [12] states that aerosol formation must be prevented. Some regard the risk of possible bacteriological infection if the cannula or spike is left in place as being greater than the risk of inadvertent release of cytostatic agents. In a study on the disinfection of hands and work surfaces, the authors reported that septum bottles with cannulas left in place - whether covered or not - were more likely to be contaminated than those bottles where material was removed using withdrawing cannulas or by inserting a new cannula every time. However, this work was not performed under clean room conditions [13]. The tightness of pierced stoppers of chlorobutyl or bromobutyl rubber is the subject of controversial discussion. As part of the inspection of the aseptic preparation routine, it is especially difficult to simulate the use of bottles containing residues. The fact that one stopper has been found to be tight does not allow conclusions to be drawn about the tightness of a different stopper material.

Handling plastic film is subject to uncertainty. Closure with a combination stopper, or stopping the spike, is probably the best solution available at present.

The question of suitable disinfection of the bottles on their later return to the LAF has yet to be answered since it is not known how much disinfecting agent can penetrate into the flask through the damaged stopper or closure.

The reuse of bottles containing residues is a critical aspect of aseptic procedures. Microbial contamination has a multiplier function.

The microbiological testing of sample solutions containing cytostatic agents presents problems in connection with dealing with hazardous substances in the microbiological laboratory. In any case, testing a „left over“ stock solution is an individual test that does not allow any conclusions to be drawn about the solution as a whole. This ”left over” stock solution should therefore not be tested.

In order to reduce the handling of cytostatics to a minimum and in the sense of *TRGS* 525 on the testing of substitute materials and alternative procedures, the inspection of cytostatic solutions should be abandoned and the work performed with substitute solutions. The substitute solutions must be subjected to the same

manipulations and work routines as the genuine bottles and should then be subjected to microbiological testing. A test plan must be prepared.

5. Work Routine of Aseptic Preparation

Aseptic working cannot be ensured until the different working and organisational steps have been properly linked together. This linking process is best performed as part of a quality management system. The work routine and the qualification of the personnel must also be considered (see Section 1.6. Training and Further Training of Staff).

From a hygienic point of view the work routine can be divided into making ready, the actual preparation and clearing up.

5.1 Making ready includes several steps such as gowning, defining the scope of the work and the provision of single-use articles, cytostatic solutions and carrier solutions.

Gowning is essentially defined by measures of work safety. The minimum requirement for aseptic preparation are sterile gloves with long cuffs which securely cover the sleeve bands of the gown. The wearing of surgical caps in the preparation room can help to reduce the number of particles carried in. Shoes must have non-slip soles and should be worn only in the pharmacy or, better still, only in the area reserved for aseptic working. Overshoes increase the number of particles carried into the preparation rooms. The ideal solution is to use dedicated, sterilisable work shoes, as worn in the operating theatre. In the context of reducing particle carry-in, consideration should be given to the wearing of low-particle or clean-room overalls.

The scope of the work must be defined in order, on the one hand, to make ready sufficient material and, on the other, to plan in advance the changes of (e.g.) gloves and work underlays necessary for hygienic reasons.

The required single-use articles, cytostatic solutions, carrier solutions, etc. are placed in readiness immediately next to the safety workbench. The containers of cytostatic and carrier solutions are disinfected as necessary using a suitable method (see above).
5.2 The preparation itself includes bringing the starting materials and work materials into the LAF, and the dissolving, withdrawing, re-injecting and decanting (because of the need for verification of correct stoichiometric preparation and of fulfilment of the requirements, q.v.)

Sterile work materials are thrown into the LAF in such a way that contact with non sterile hands or objects is impossible. The starting materials are placed in the LAF while they still carry drops of disinfecting solution.

All work routines of dissolving, withdrawing, re-injecting or decanting must be performed according to a fixed scheme. Every unnecessary connection should be avoided. The syringe set should always be connected directly with the other set, whether that be the cannula, the spike, or the empty bag. Contacts with other parts or objects must be avoided. Sterile single-use articles must not be used more than once.
The disinfected hands must remain under the LAF during the preparation sequence. Removing the hands can lead to involuntary movements at the nose or in the face, which are not even noticed by the person performing the work.

5.3. Clearing up includes cleaning the workplace and storing the residual materials that will be used on some later occasion.

The workplace must be cleaned after every work routine by the personnel carrying out the preparation. A suitable procedure must be defined for cleaning and the cleaning agent must be specified in the hygiene plan.

The stainless steel surfaces of the LAF can be cleaned using materials on the list of disinfecting agents tested in accordance with the „directives for the testing of chemical disinfecting agents“ and recommended by the *DGHM* („German Society of Hygiene and Microbiology“). A disinfecting material recommended by the manufacturer of the workbench should be preferred. Caution must be exercised with plastic panels and seals, which are attacked by some materials. If alcohol is used to clean the front panel, this should be subjected to sterile filtration as a precaution against possible spore forming organisms. Ethanol should be used at a concentration of 80% and isopropanol at a concentration of 70%; according to the NRF (”new prescription formulary”) it is possible to add 0.3 % H_2O_2.

The residue bottles intended for storage (for closure possibilities see above) should be sealed in plastic film and kept in the refrigerator (if the chemical and physical stability allows).

The shelf life for residues of cytostatics derives from their chemical and physical stability, the validation of the working steps and the selection of suitable starting materials.

6. Summary

Summary of the most important microbiological aspects to be monitored routinely:

- perfect equipment
- airborne microorganism count (sedimentation plates) at defined positions
- contact sampling of defined surfaces
- contact sampling of the gloves worn by the persons performing the preparation, just before changing gloves
- systematic testing of multiply used carrier solutions
- process validation of the staff (and training).

B) Inspection of the Product with regard to its Microbiological Status

Inspection of the final product for freedom from microorganisms is of much less importance that the entire process of validating the aseptic procedures [14]. Nonetheless, the 2002 European Pharmacopoeia does not dispense with this test.

The pharmacopoeia allows the membrane filter method and the direct inoculation method, whereby the membrane filter method is preferred.

For testing by means of the membrane filter method, the solution is placed over a sterile membrane filter (pore diameter <= 0.45 µm). This membrane filter is then laid in culture medium and incubated. Firms supply single-use systems that can be inoculated directly under the LAF.

Placing the material to be tested directly in the culture medium is referred to as direct inoculation. The ratio of product to medium should be 1:10 [6, p. 121]. Filling empty bags, which contain a nutrient solution, is regarded as a direct inoculation method. The European Pharmacopoeia defines the amount of sample in relationship to the capacity of the containers and referred to the method used (q.v.). The question as to how many samples should be tested is defined by the European Pharmacopoeia under 2.6.1. as a minimum number of samples related to the total number of items in the batch.

Comments and publications dealing with testing for sterility as part of the validation process deal mainly with the production of a defined product on the industrial scale, or preparation for the hospital sector in quantities of up to 100 dispatch-ready packs per day.

The differences in the aseptic production of ready-to-administer preparations for parenteral use between industry and (hospital) pharmacy are discussed at length in the article by Krämer [15]. The same article also recommends the establishment of a separate directive for the production of the aseptic ready-to-administer preparations for parenteral use. The *Bundesapothekerkammer* is currently revising its 2000 guide to aseptic preparation.

In the section „Sterile Products for Home Use“ the USP XXIII differentiates between industrial production and preparation in a pharmacy. In respect of the preparation of sterile products a distinction is made between „low risk“ - i.e. few manipulations, sterile starting materials - and „high risk“ work routines. In the context of the central cytostatics preparation usual here, low risk production may be assumed (with the exception of pumps running over a period of days). The validation plan also includes ambient monitoring (see also above) and media fill methods. The media fill methods must simulate the kinds and numbers of preparation routines and should also take account of peak periods for fatigue, stress and requisition frequencies. In accordance with the situation at the particular pharmacy, an initial situation is defined and the findings are specified at which there is a need to take action (cf. also [16]).

According to the AHSP guidelines the preparation of cytostatics is classified as a Level 2 risk (if the preparation is stored at room temperature for longer than 28 hours). A final product control is not required at risk levels 1 and 2. Only at the highest risk level, where, for example, non-sterile components are used, do ASHP and USP specify testing the final product for sterility in accordance with a sampling plan. Since aseptically prepared ready-to-administer preparations are prescriptions, s. 7(2) *Apothekenbetriebsordnung* (pharmacy regulations) allows a test to be omitted on condition that the quality of the drug is guaranteed by its method of preparation. A successful validation of the aseptic preparation therefore establishes the quality of a preparation.
In the context of successful aseptic preparation of cytostatic solutions in pharmacies, the discussion about batch sizes and the associated number of containers to be inspected has become superfluous. These concepts are not appropriate for the aseptic preparation of ready-to-administer cytostatic solutions. The designation suggested by the *Bundesapothekerkammer* as ”continual aseptic individual preparation” is also not really satisfactory because work pauses must be included and different products are prepared, from small intrathecal injections to large-volume infusion bags.

The samples for microbiological monitoring of the final product must be prepared according to a defined sampling procedure. The sampling plan with the dummy preparation must encompass all the relevant working steps. The samples taken serve simultaneously for validation of both the process and the personnel! The number of samples taken depends on many different factors, which must be carefully considered:

- How many preparations are produced in the respective pharmacy?
- How many different work routines must be simulated?
- Is a new central cytostatics department being established?
- How well trained are the personnel performing the preparation?
- What are the results of other environmental monitoring procedures?

The following sampling methods come into consideration:

- The work routine is simulated and dummy solutions are added to a nutrient medium.
- At the end of a production day (or production period) the residues of the infusion carrier solutions, which are exposed to a high risk of contamination as a result of being handled frequently during the work routine, are microbiologically tested [15].

Dummy solutions should be used in principle for microbial inspection of the final product instead of the cytostatic solutions (see above).

The *BAK* guidelines state that for initial validation no contaminated sample should be detected during three consecutive validation procedures. At least 10 nutrient medium products free of contamination must be prepared at the revalidation. The samples must be prepared at the end of a working day [3]. This revalidation should take place at least once every year [3, 9].

Setting up a new central cytostatics preparation unit must be accompanied by close monitoring, i.e. more samples must be prepared than during the subsequent routine operation. The degree of certainty achieved for sterility depends on all the process steps during the preparation. In the final analysis the certainty of sterility cannot be greater than that of the process step with the lowest probability of achieving sterility [17].

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3.5. Requisition of Ready-to-Administer Cytostatic Solutions

3.5.1. Requisition Form

Cytostatics are requisitioned by the doctor in writing on a prescription form.

The prescription is checked in the pharmacy in accordance with s. 7 *Apothekenbetriebsordnung* (pharmacy regulations) and the preparation is authorised by the pharmacist responsible.

The prescription must be unambiguous and must include at least the following information:

- **name and gender of the patient**
- **patient's date of birth and/or admission number**
- **body weight, height and/or body surface area**
- **ward / department / therapeutic unit or section thereof**
- **cytostatic prescribed (INN)**
- **regular dose and the resulting dosage for the patient**
- **adapted dosage according to clinical chemical and pharmacokinetic parameters as target value**
- **correction factor for an indicated dose reduction or dose increase**
- **pharmaceutical form**
- **type of carrier solutions**
- **volume of the ready-to-administer solution**
- **required administration time**
- **signature of doctor, date.**

Dr. Birte Schlenzka, Kiel

In order to comply with the pharmacy regulations the requisition signed by the doctor must have been presented before the cytostatic solution is handed over.

In addition to the "minimum information" for a requisition form, a large number of other items can also be recorded.

The scope of information recorded on the requisition form depends on the extent to which this form is used on the ward during the therapy and incorporated in the patient's file, and also on whether the information will be needed in the course of pharmaceutical care (see Chapter 5.)

Such additional information can include:

- data specific to diagnosis, disease and therapy
- laboratory parameters
- further therapy-relevant information
- type and name of the therapeutic regimen
- period of administration of the cytostatic solutions
- scheduled day of repetition
- cycle number
- concomitant medication (type, quantity and duration of the administration)
- additional medication
- pre- and posthydration (type, quantity and duration of the administration).

This information enables a check to be carried out of the chemotherapeutic regimens, which generally also include a standardised concomitant medication.

The laboratory parameters include:

- blood group
- leucocyte count
- platelet count
- haemoglobin value
- serum creatinine
- alkaline phosphatase
- bilirubin value
- GOT.

These parameters cover some of the side effects listed in the WHO toxicity index (1979).

Table 1: Correlation of blood parameters and the dosage of cytostatics (see Chapter 3.5.5. Dose Modification in the Case of Blood Picture Changes)

Leukocyte count per mm³	Platelet count per mm³	Haemoglobin g/l	Dose
over 3500	over 100000	over 110	100%
3500-3000	70000-100000	95-110	75%
3000-2000	50000-70000	80-95	50%
below 2000	below 50000	below 80	0%

Table 2: Dosage modification for hepatically eliminated cytostatics (see Chapter 3.5.4. Dose Modification in the Case of Limited Liver Function)

Bilirubin (mg/dl)	GOT (IU/l)	Dose
< 1.5	< 60	100%
1.5 - 3.0	60 - 180	75% - 50%
3.1 - 5.0	> 180	50% - 25%
> 5.0		25% - 0%

The parameters bilirubin, GOT and alkaline phosphatase are used in the case of limited liver function.

For dose modification in the case of renally eliminated cytostatics see Chapter 3.5.3. Dose Modification in the Case of Limited Kidney Function.

The data included in the above laboratory parameters indicate whether it could be necessary to reduce the dosage of chemotherapy, or even to discontinue the therapy. Awareness of the pharmacist for these problems enables the therapy to be analysed at an early stage and can therefore make a contribution towards avoiding unnecessary drug preparation.

This information offers a possibility of assessing changes in the patient's condition during the therapy and provides the pharmacist with an early opportunity to offer advice and suggestions for the drug therapy.

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3.5.2. Sending the Prescription

The prescription from the doctor must be at hand before the prepared solution is handed out. The prescription may be sent by electronic means if the statutory requirements are met.

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Dr. Karla Domagk, Cottbus

The conventional procedure up to now in this sector of drug preparation whereby the ready-to-administer cytostatic solutions are prepared and handed over after presentation of the original doctor's prescription is being increasingly adapted to recent technical developments. Whether it is possible in the hospital - in the interests of prompt patient care - to hand over the cytostatic solution on receipt of a telefacsimile is a matter to be agreed with the supervisory authority in the concrete individual case.

In the case of direct networking of a pharmacy preparing cytostatics with the prescribing doctor, it is also necessary to take into account aspects of competition and professional law in the sector of registered doctors with their own practices.

The automatic transmission of data in a sensitive area like drug prescription demands special measures for securing the transmission route. Since a drug prescription is not valid until it bears the signature of a doctor, the primary problem is the verification of automatically transmitted prescription and requisition data.

After the law on electronic signatures came into force on 1 August 1997 there was considerable euphoria and many sectors - not least medicine - expected tremendous progress as a result of documents based on writing being replaced by secure and reliable online communication; but the technical and organisational implementation was unable to keep pace with the aims of the concept.

The small extent to which the use of digital signatures has spread up to now is revealed by the founding by the state and by industry on 3 April 2003 of an association for electronic signatures, with the goal of standardising the many different signature applications and of making it possible to use different applications with a single card [1].

The latter objective puts its finger on the problem of the electronic signature: using which medium (which card) can the signatory identify him/herself to the many available systems which are possibly already capable of using electronic signatures but have only realised this for the system's own hardware and software?

In this context the breakthrough for the medical sector could be achieved by the Health Professional Card (HPC) - an identity card for all persons employed in the health service which is already equipped with the feature of electronic signing [2].

But as long as there is no universal standard, different, independent pilot projects will be carried out and solutions will be presented at trade fairs; but there will still be no binding organisational or technical standard.

A number of current projects are of considerable interest for the area of cytostatics prescription. Thus a project group at Frankfurt University of Applied Technology in collaboration with Children's Hospital III (haematology, oncology and haemostaseology) of Frankfurt University Hospital is developing the system DiSi-Med: *"Medikamentenverordnung mit Digitaler Signatur"* (Drug prescription with digital signature) that was presented at the CeBIT 2003 and was supported with funds from the Federal Ministry for Education and Research. According to the description on the pages of the Hessen ministry for science and art [3], however, important sections of the system have yet to be realised so that, here too, there are probably no results available from routine use.

A further interesting project with an international aspect is the use of the HPC for encrypting and sending documentation data to the hospital tumour register in Madgeburg, Saxony-Anhalt. Since the end of 1999 the doctors there have even been able to exchange their documentation over the Internet using the secure method of signature and encryption.

Since, however, the two applications are supported by different cards and use self-developed standards, the results from these projects are certainly interesting but incapable of being transferred simply to a wider environment.

Basic concepts for the implementation of an electronic prescription (*eRezept* = "ePrescription") have also been developed by the *Aktionssforum Telematik* within the health system (*ATG*) [5], culminating in the *"Gemeinsamen Entwicklungsvorhaben der Spitzenorganisationen im Gesundheitswesen zum Elektronischen Rezept"* (Joint de-

velopment plan of the leading organisations within the health service for the electronic prescription) [6].

This is intrinsically welcome, but in view of the lack of standards decision takers in the hospitals and associations are awaiting further developments in order to avoid choosing an isolated solution with moderate prospects for the future. We can only hope that through the influence of the association for electronic signatures success is achieved in accelerating the implementation of standards - not least in order to ensure the passing of up-to-date cytostatics regulations.

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3.5.3. Cytostatics Dosage in case of Impaired Renal Function

Cytostatics are drugs with a narrow therapeutic range. An impaired renal function may increase the toxicity of cytostatics and active metabolites through cumulation. Dosage reduction may therefore be necessary for substances which are eliminated renally to a significant extent. The basis for the decision must be the glomerular filtration rate as the parameter of renal function, and the most recent pharmacokinetic and pharmacological knowledge about the cytostatics used.

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Pharmacotherapy always includes knowing about and taking account of the pharmacokinetics and pharmacodynamics of a drug. Since cytostatic agents are drugs with a narrow therapeutic range, reduced elimination associated with higher plasma concentrations may lead to increased toxicity. If the proportion of renal elimination is 30% or more, it may be necessary to adjust the dose. Moreover, some cytostatics themselves cause renal damage, thus increasing the risk still further for patients with an already impaired renal function.

There are certainly still too few pharmacokinetic studies on patients with impaired renal function. Nonetheless, on the basis of general pharmacokinetic and pharmacological principles it may be assumed in the case of moderate to severely impaired renal function (30 - 60 ml/min creatinine clearance) that this will lead to a significant increase in the AUC (area under the plasma concentration - time curve) for a drug with linear pharmacokinetics and 35 - 40% renal elimination [1, 2]. The following recommendations can be derived from known pharmacokinetic, pharmacodynamic and toxicity data:

Alkylating Cytostatic Agents

N-nitrosourea derivatives

N-nitrosourea derivatives (e.g. carmustine, lomustine, semustine, fotemustine) are metabolised rapidly both enzymatically and non-enzymatically. The metabolites possess cytotoxic activity and are eliminated renally to between 60 and 70 %. Delayed and possibly cumulative bone marrow suppression is the most common

dose-limiting factor for nitrosourea derivatives. These cytostatic agents may lead to progressive and irreversible kidney damage. Excretion of the carbomustine metabolites in urine accounts for 30 % of the carmustine dose in 24 hours. 60 - 70 % is detected in the urine as metabolites within 96 hours. In addition to dose adjustment in the case of existing renal impairment, a therapeutic alternative should be considered if the renal impairment is severe.

Bendamustine

Bendamustine is metabolised in the liver to the cytotoxic hydroxy derivative. Both substances are eliminated renally to 50 %. The manufacturer (Ribosepharm) makes recommendations for a GFR < 50 ml/min.

Cyclophosphamide

Cyclophosphamide is excreted via the kidneys but because of the non ionised form of the inactive molecule, tubular re-absorption in the kidney plays an important role. A large proportion of the cyclophosphamide dose is metabolised in the liver. Renal elimination of the intact molecule amounts to 15 % of the creatinine clearance. The more polar, less fat-soluble metabolites are excreted via the kidney to a greater extent. A significantly prolonged retention of active, alkylating metabolites may occur in patients with severe renal insufficiency. Despite this, attempts to demonstrate a connection between severe renal insufficiency and increased myelosuppression have not been successful. The manufacturer (Baxter Oncology) recommends a 50% dose reduction in patients with a GFR < 10 ml/min. [6]

Ifosfamide

Isfosfamide appears to be qualitatively similar to cyclophosphamide. The pharmacokinetics for high bolus doses can be approximately described in terms of a two compartment model; that for fractionated dosage in terms of a one compartment model. During repeated therapy with 2.4 g/m^2, a plasma half-life of 7 hours was determined with a recovery rate of 73% in the urine. After the single dose the plasma half-life was 15.2 hours. In comparison with cyclophosphamide, of which 90% of the dose is metabolised, ifosfamide is metabolised to only 50%. Large interindividual differences were observed in pharmacokinetic studies on children. The renal clearance of ifosfamide is approximately double that of cyclophosphamide, i.e. 21.3 compared with 10.7 ml/min after bolus administration and 18.7 compared with 10.7 ml/min for fractionated administration. A prolonged half-life can be expected in the case of overweight patients (> 20% over the ideal weight). This may be connected with an increased distribution volume for such patients. However, the total body clearance for overweight patients was the same at 74 ml/min. Haemorrhagic cystitis is the most marked adverse effect of ifosfamide. Adequate hydration

and the administration of sulphhydryl compounds such as mesna (Uromitexan®) reduce this toxicity considerably. The Fanconi syndrome is observed relatively often, especially in children. Patients who have previously been given cisplatin or carboplatin are at greater risk of suffering this side effect. Dose dependent leucopenia is the most important undesirable effect of ifosfamide.
Toxic effects on the CNS may also occur during the therapy. It has been reported that patients with impaired renal function are at greater risk of suffering neurotoxic damage as a result of taking ifosfamide. [7-11]

Melphalan

Melphalan undergoes two-phase elimination with 6 - 8 minutes (a-phase) and 40 - 60 minutes (b-phase). Although the major fraction of the active substance is not eliminated renally, renal elimination still plays an important role. The proportion of melphalan excreted unchanged was 21 - 34%. Bone marrow suppression, which is the most important side effect of melphalan, is higher in patients with renal dysfunction because intravenous administration to such patients leads to an accumulation of the active substance. The dosage should therefore be adjusted for patients with impaired renal function. [12-17]

Dacarbazine

Dacarbazine undergoes microsomal metabolism to 5-aminoimidazole-4-carboxamide and a methyl cation. The substance is excreted renally, 41% unchanged as the inactive parent compound and the rest in the form of metabolites. Hepatic and renal dysfunction lead to a prolonged elimination half-life. A dosage reduction is recommended in the case of impaired renal function. (see Table) [18-20]

Platinum Complexes

Carboplatin

Carboplatin has a similar molecular mechanism of action to that of cisplatin. Platinum released from carboplatin has a plasma half-life of 90 minutes. The main pathway for the elimination of carboplatin is glomerular filtration and tubular excretion. Only very little of the substance, if any, is metabolised. Under haemodialysis a half-life of 4 hours was observed, compared with 36 hours for peritoneal dialysis. The clearance of free carboplatin, measured as free plasma platinum, correlates with the glomerular filtration. 60 to 80% of the administered dose of platinum is eliminated renally within 24 hours. There is a linear correlation between the total clearance of carboplatin and the AUC and the creatinine clearance. In addition, the drug induced thrombocytopenia shows a linear correlation with the AUC of carboplatin. The dosage of carboplatin is primarily limited by thrombocytopenia and

neutropenia. The following dose adjustment formulae were derived for calculating the carboplatin dosage depending on the GFR (ml/min): [21-25]

% of the standard dose = (0.82 x GFR) + 18 [patients not previously treated with nephrotoxic substances]

% of the standard dose = (0.65 x GFR) + 18 [patients previously treated with nephrotoxic substances]

For dosing in accordance with the AUC the formula is:
dose (absolute in mg) = target AUC x (25 + GFR)
Target AUC: 3 - 5 for polychemotherapy, 5 - 7 for monotherapy

Cisplatin
30% of the cisplatin is renally eliminated and excreted as free platinum within 24 hours after administration. It displays a 3-phase elimination process with a half-life of 20 minutes in the a-phase, 48 - 70 minutes (b-phase) and 24 hours (d-phase). The first two phases represent clearance of the free cisplatin and the third phase probably represents the protein bound fraction. 90% of the drug is eliminated renally; less than 10% is excreted via the biliary route. Because of the renal damage it causes, hydration and monitoring of renal function are essential with dose reduction if necessary. [26-28]

Oxaliplatin
Reduced clearance and restriction of the distribution volume has been observed in the case of impaired renal function. In a study involving patients with mild, moderate and severe renal dysfunction, increased toxicity was observed during a monotherapy with oxaliplatin at a creatinine clearance below 20 ml/min. Specialised information therefore contraindicates the use of this substance in patients with severe renal dysfunction (creatinine clearance < 30 ml/min) [48].

Antimetabolites

Cytarabine
A study showed that serum creatinine values over 1.2 mg/dl were an independent risk factor for the occurrence of neurotoxic symptoms during therapy with high doses of cytarabine. Similar findings were verified in retrospective investigations. Patients with a creatinine clearance below 60 ml/min were especially prone (60-76% of cases) to neurotoxic side effects when treated with high doses of cytarabine.

The recommendations in Table 1 apply only for high-dose treatment and not for conventional therapy. [29-33]

Fludarabine
The bone marrow suppressive effect of fludarabine is the dose-limiting side effect of this drug. There is a significant inverse correlation between the granulocyte concentration in the nadir and the AUC of the fludarabine plasma concentration. There is also a correlation between the creatinine clearance and the total clearance for fludarabine. For this reason a dose adjustment is also recommended for this substance in the case of impaired renal function. [34]

Methotrexate
The fall in the plasma concentration of methotrexate can be described in terms of two, or probably even three phases. These divergent experimental results can possibly be explained on grounds of the selected doses and/or the different age groups of the patients. Over 60% of the methotrexate dose is excreted renally. The most important adverse effects of methotrexate are bone marrow suppression and mucositis. The elimination of methotrexate may be different in patients previously treated with cisplatin. Methotrexate itself also causes renal damage, especially at doses in excess of 50 mg/m^2. High-dose therapy in particular may lead to concentrations of methotrexate or 7-hydroxymethotrexate in excess of their solubilities, especially at normal urine pH values. This hypothesis is supported by the fact that alkalinisation of the urine accompanied by adequate hydration suppresses the incidence and severity of this side effect. It is possible that direct tubular toxicity and restricted glomerular filtration also play a role. Since significant amounts of methotrexate are eliminated renally, dose adjustment should be made in the case of impaired renal function, or a different cytostatic agent should be selected if this is at all possible. [35-38]

Pentostatin
Significant amounts of this intravenously administered drug are subject to renal elimination and appear unchanged in the urine. Unfortunately the results of studies published to date are somewhat contradictory. Nonetheless, account should be taken of renal function when setting the dosage. The use of alternatives is especially indicated in the case of severe functional impairment. [39-41]

Raltitrexed
Raltitrexed (Tomudex®) inhibits thymidilate synthetase and is used to treat colorectal carcinoma. In a study on patients with normal and with slight to moderate renal

insufficiency (GFR 25-65 ml/min) the AUC and the elimination half-life were doubled. The authors recommend a dose reduction of 50% and prolongation of the interval between doses of 3 to 4 weeks if the GFR lies between 25 and 65 ml/min. If the GFR falls below 25 ml/min raltitrexed should be discontinued. [42]

Antibiotics with Cytostatic Activity

Bleomycin

Approximately half of the bleomycin administered is excreted renally. A correlation exists between the clearance of bleomycin from plasma and the creatinine clearance. It has been observed that in the case of impaired renal function the plasma half-life of bleomycin is prolonged by a factor of 2.5. If the creatinine clearance is less than 25-35 ml/min, it even increases exponentially. A dose reduction is indicated if the creatinine clearance lies below 40 ml/min. [43-44]

Mitomycin C

Mitomycin C is eliminated renally to less than 20%. Nevertheless, the nephrotoxicity of mitomycin C itself must be taken into account. Thus the possibility of using a different cytostatic agent should be considered for patients with moderate to severe renal dysfunction. The renal function of patients under treatment with mitomycin C should always be monitored on principle.

Topoisomerase Inhibitors

Etoposide

In the case of this epipodophyllotoxin bone marrow suppression is once again the most prominent adverse affect. If the substance is administered as a continuous infusion, there is a correlation between bone marrow suppression and the plasma concentration in the steady state. Moreover, a correlation exists between the creatinine clearance and the systemic clearance of etoposide. The half-life of etoposide is 7 hours, regardless of the method of administration. Approximately 30% of the dose is eliminated renally. Plasma protein binding in normal patients is very high at 95%. This means a reduced protein binding in patients with lowered serum albumin. The free fraction can fluctuate between 6 and 37%. Because of the above connections between bone marrow toxicity, plasma concentration and systemic and creatinine clearance, the dose should be adjusted appropriately. In addition to the recommendations from Dorr, Sauer gives a formula for calculating the dose [45]:

dose = (standard dose / 2) x [(patient clearance / normal clearance) + 1]

Topotecan

Topotecan is believed to have a renal elimination between 20 and 60%. A drop in renal clearance was observed in patients with renal dysfunctions. The dosage should therefore be adapted to the GFR [46].

A dose adjustment is not normally made for cytostatics which are eliminated renally to the extent of 30% or less as intrinsically toxic compounds or as metabolites. An exception is made for compounds that exhibit renal toxicity (see mitomycin C). A well-known example is allopurinol, whose metabolites thiourea and 6-mercaptopurine may crystallise out of urine at doses over 750 mg/m^2. If allopurinol is used in the case of secondary hyperuricaemia occurring under cytostatic therapy, the renally excreted amount of 6-mercaptopurine may double, accompanied by a proportionate decrease in the amount of thiourea excreted. The reduced breakdown of 6-mercaptopurine during concomitant medication with allopurinol would be a reason for reducing the dose.

For patients with impaired renal function for whom chemotherapy is indicated, it may be necessary to consider most carefully which cytostatic agent should be administered. If the use of a particular drug with high renal elimination appears to be unavoidable, an appropriate dose adjustment must be made.

In addition to their carcinosis, a few patients suffer impaired function of internal organs; the kidney is frequently affected. Despite this, the wish remains to treat the malignant tumour with cytostatic drugs. Knowledge of the pharmacokinetics and renal elimination of cytostatic agents enables dose adjustments to be made. Treatment of the tumour can be performed in such a way that the toxicity towards other important organic systems of the body (which is associated with almost every substance) can be calculated, thereby restricting the degree of damage to healthy or previously damaged organs. In addition to a knowledge of the pharmacokinetics, this also requires appropriate clinical observation and care of the patient. (see Chapter 3.5.1. Requisition Form and 5. Pharmaceutical Care). For the patient, this provides the chance not to have to do without appropriate chemotherapy even if also suffering from damage to other organs.

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Fachinformation (specialised information) Eloxatin®, April 2003

Recommended dose adjustments for renally insufficient patients

Active substance (INN)		Reduction to % based on the creatinine clearance of the patients		
	f	60 ml/min	45 ml/min	30 ml/min
Alkylating agents				
Bendamustine	50		75	50(<10 ml/min)
Carmustine	43	80	75	n
Lomustine	50	75	70	n
Cisplatin	30	75	50	n
Carboplatin	66	*	*	*
Oxaliplatin				n
Cyclophosphamide	15			50(<10 ml/min)
Ifosfamide	41	80	75	70
Melphalan	34	85	75	70
Antimetabolites				
Cytarabine**	80	60	50	n
Fludarabine	44	80	75	70
Methotrexate	77	65	50	n
Pentostatin	65	70	60	n
Raltitrexed		50	50	n
Topoisomerase inhibitors				
Etoposide	30	85	80	75
Topotecan	39	80	75	70
Other				
Bleomycin	62	70	60	n
Dacarbazine	40	80	75	70
Hydroxyurea	35	85	80	75

f = % of the dose excreted as active metabolite or toxic product
n = if possible change over to alternatives
* = dose can be calculated for dosing to desired AUC
** = during high-dose therapy

3.5.4. Dose Modification in Case of Impaired Hepatic Function

Impaired liver function can exert considerable influence on the hepatic clearance of cytostatics. Limited metabolic clearance leads to slower biotransformation, whether cytochrome P450 dependent or not, whereas a reduced biliary clearance hinders the natural excretion over the bile ducts.

It is known that some cytostatic agents accumulate if hepatic clearance is reduced. The evaluation of laboratory parameters and dose modifications therefore represent an important clinical pharmaceutical service.

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If patients show elevated liver values or changed bilirubin values, the issue must be addressed as to whether and to what extent the dosage of a planned chemotherapy may have to be modified. Particularly when using cytostatics, which have a narrow therapeutic range, failure to modify the dose appropriately can result in severe side effects for the patient. Although a series of recommendations do exist concerning dose modification for patients with impaired liver function (Table 1), it must be borne in mind when consulting such tables that they are based on a much smaller collection of data than are, for example, the recommendations in case of impaired renal function. Information of the kind presented in Table 1 must therefore be interpreted as no more than a guide. The following not only deals more closely with the principle of impaired hepatic function, but also presents an objective discussion of selected classes of active substance.

Consequences of impaired hepatic function

Functional disturbances of the liver can lead to a diversity of changes in active substance elimination: if a cholestasis results in biliary elimination being obstructed, a critical cumulation of active substances or their metabolites must be expected if these are predominantly or entirely eliminated via the biliary route. Important indications of flow impairment are elevated bilirubin values and evidence for increased serum concentrations of enzymes normally localised in the epithelium of the bile duct, such as alkaline phosphatase or gamma-glutamyl transferase (?-GT).

If there is a massive loss of liver cell mass (for example as a consequence of necrotic changes) associated with a serious decline in cytochrome 450 activity, active substances normally metabolised by enzymes that metabolise foreign substances may accumulate unchanged in the plasma.

If the hepatic dysfunction is associated with restricted albumin synthesis, there will be a significant increase in the freely biologically available, pharmacologically effective fraction of drugs such as etoposide which bind strongly to plasma protein.

Finally, it must also be borne in mind that the use of drugs that are potentially hepatotoxic despite undergoing neither extensive hepatic metabolism nor elimination via the biliary route (e.g. methotrexate) may be expected to cause a critical worsening of the existing liver disease.

Evaluating toxicity becomes somewhat complicated when patients suffering both from severely limited liver function and from ascites are treated with cytostatics (e.g. methotrexate, fludarabine) which can accumulate in the special compartment. In such cases it is helpful to remove water deposits associated with ascites before beginning with the actual therapy.

Changed pharmacokinetic parameters in patients with hepatic dysfunctions

The elimination of active substances through the liver (hepatic clearance) is regulated by three parameters: the flow of blood through the liver (Q), the plasma protein binding (P) and the intrinsic (metabolic) clearance (C):

$$\text{hepatic clearance} = \frac{Q \times P \times C}{Q + P \times C}$$

For active substances subject to a high rate of metabolic clearance the rate of flow through the liver becomes the limiting step for elimination (perfusion-limited clearance). For active substances for which the rate limiting step is the number of interactions taking place per unit time with the enzymes which metabolise foreign substances, clearance proceeds independently of perfusion. In the case of hypoproteinaemia, the above formula shows that the fraction of protein binding can be decisive for the elimination of substances with a high level of binding to plasma proteins.

Severe limitation of the functional reserves of the liver can often not be measured until approximately 30 percent of the normal value has been reached. In this connection the most important methods world-wide are the determination of hepatic clearance using the dyestuff indocyanine green (ICG), which enables the flow of blood through the liver to be quantitatively ascertained, and determination of the galactose elimination capacity, with which the cytoplasmatic liver cell mass can be measured.

Dose reduction on the basis of elevated liver values

Without a doubt, it would be desirable if the routinely measured parameters such as the transaminases, bilirubin or serum albumin could be used directly in defining dose reductions for patients with impaired hepatic function. However, correspondingly changed parameters must be analysed more closely.

Transaminases

The function of the transaminases AST (SGOT) or ALT (SGPT) consists of transferring an amino group from amino-acids to 2-ketoacids such as 2-oxoglutarate or oxalacetate, leading to the formation of the corresponding amino acids such as glutamic acid and aspartic acid. AST (SGOT) can be detected in diverse tissues whereas the activity of ALT (SGPT) is primarily restricted to the liver (Table 2). It is therefore not possible to immediately conclude the existence of hepatobiliary disease on the basis of an isolated elevated AST value since this may also have arisen as the result of an extrahepatic event, e.g. myocardial infarction or rhabdomyolysis. If both enzymes (AST and ALT) are elevated, however, a disease of the liver is more likely.

Alkaline phosphatase and ã-GT

Alkaline phosphatase (AP) catalyses the hydrolysis of different esters of phosphoric acid. The highest levels of activity of this enzyme are normally found in the liver (Table 2), the mucous membrane of the small intestine, the bones, and the placenta in pregnant women. In the liver, the enzyme is primarily expressed in the epithelial cells of the hepatic duct. As a result, obstruction of the bile ducts may lead to elevated AP values as high as 1000 U/L. If at the same time, however, serum bilirubin values are normal, the cause may well be a completely different disease, e.g. a sarcoidosis, a hepatic candidiases or a lymphoma. In the case of parenchymatous liver disease without involvement of the bile ducts, only a moderate elevation of AP is detected in comparison with the transaminases. Since the serum AP value increases naturally after the consumption of food containing fat, it is generally recommended that this be determined while the patient is in the fasting state.

Gamma-glutamyl transferase (ã-GT) is predominantly expressed in the organs kidney, liver (Table 2) and pancreas. Since the highest levels of activity of this enzyme are detectable in the epithelial cells of the intrahepatic bile duct, the level of this enzyme in serum is elevated in the case of a cholestasis.

Albumin

The concentration of albumin in serum is normally at least 35 g/L (Table 2). A fall in this value to below 35 g/L may indicate a disturbance to the synthesis in the liver. However, since on average the half-life of albumin in the serum is approximately three weeks, a hypoalbuminaemia is of no value as an early indication of hepatobiliary disease. If other parameters (e.g. SGOT) do not provide additional evidence of hepatitis, a nephrotic symptom may also be the cause of the hypoalbuminaemia.

Changes in blood coagulation parameters

A severe hepatic dysfunction generally also results in impairment of the vitamin K dependent biosynthetic performance of blood coagulation factors II, VII, IX and X. If the coagulation factors fall below specific minimum values the prothrombin time becomes longer, resulting in smaller and larger haemorrhages. If other parameters indicative of hepatitis (e.g. albumin values) are not elevated, however, the prolonged prothrombin time can also be the result of insufficient vitamin K synthesis over the intestinal flora, or a malabsorption syndrome.

Evaluation of individual parameters within a hepatobiliary disease

A slight impairment of the hepatic function means AST values still within the normal range (e.g. 28 to 34 U/L) and serum bilirubin between 2.1 and 4 mg/dl. A significant impairment of the hepatic function exists when the AST values are over 200 U/L and the serum bilirubin values are greater than 4 mg/dl (Table 2).

Different liver diseases result in different patterns of modified laboratory parameters, which allow tentative conclusions to be drawn as to the particular disease involved (Table 3). An increase in **total bilirubin** over 1 mg/dl, for example, may be the first indication of a slight obstruction of the bile ducts by a gallstone. Depending on the extent of the obstruction, the serum bilirubin values can reach 6 to 15 mg/dl. In the more detailed analysis a distinction is made between **direct bilirubin** (mainly bilirubin diglucuronide) and **indirect bilirubin** (non-conjugated, protein bound fraction). Normally, approximately 20 percent of the total bilirubin is present as direct bilirubin. The terms “direct” and “indirect” relate to the reactivity towards the reagents used for the quantitative determination. A direct fraction below 20% (“**non-conjugated hyperbilirubinaemia**”), may indicate a hereditary

defect in bilirubin glucuronation (e.g. Gilbert syndrome) or an oversaturation of the metabolic capacity (e.g. in association with a haemolysis). In both cases the total bilirubin value can reach (2 -) 6 mg/dl. In such cases, for example when using irinotecan, severe toxicity may result if no dose modification is made. Especially severe cases of hyperbilirubinaemia with values over 15 mg/dl have been reported for patients suffering from sepsis or from acute or chronic graft-versus-host disease (GVHD) after allogenic transplantation.

Recommendations for dose reduction in case of impaired hepatic function using a few selected cytostatics as examples

Anthracyclines

The anthracyclines doxorubicin, daunorubicin, epirubicin and idarubicin are mainly metabolised in the liver. Elimination of the parent substances and the metabolites proceeds predominantly via the biliary route. With the exception of idarubicinol, none of the metabolites formed exhibit any clinically relevant antineoplastic effect. An approximately 3-fold increase in the doxorubicin AUC was observed for patients with 6-fold increases in their bilirubin values. The best pharmacokinetic correlation occurred between the increase in the AST values in association with reduced ICG clearance values, and the decrease in doxorubicin clearance. Hepatic clearance was also slower for the structurally related epirubicin when the bilirubin values were increased by a factor of between 2 and 10.

Up to now the recommendation has been that patients with elevated bilirubin values (1.5 - 3.0 mg/dl) and elevated transaminases (60 - 180 U/L) receive only 50% of the originally planned dose of doxorubicin, epirubicin and mitoxantrone. If the values lie between 3.1 and 5 mg/dl and over 180 U/L, 25% of the planned dose should be given. In the case of daunorubicin the corresponding scope for dose modification is stated to be 75% and 50% since there is the possibility of compensation as a result of the kidneys being able to eliminate somewhat more daunorubicin (in contrast to epirubicin and doxorubicin). It remains difficult to formulate clear recommendations for idarubicin since the active metabolites also exert an important neoplastic effect. Nonetheless, it is recommended that AML patients over the age of 60 be given 8 mg/m2 i.v. (instead of 12 mg/m2) since this dose modification leads to almost the same idarubicinol AUC values as for younger patients.

The pharmacokinetic behaviour of the liposomal compounds (e.g. DaunoXome, Caelyx, Myocet) differs considerably in some respects from that of the conventional anthracyclines. Referring to the use in case of hepatic dysfunction, Hong et al.

administered 30 mg/m2 i.v. pegylated liposomal doxorubicin to a patient with advanced hepatocellular carcinoma. Before treatment the patient's total bilirubin was approximately 3.6 mg/dl; the direct bilirubin was clearly elevated. The AST values were around 20-fold the normal whereas the ALT was barely elevated at all. The disease-related elevated liver values had already been successfully lowered after the first administration. The therapeutic interval was extended to 4 weeks in order to keep bone marrow toxicity as low as possible. The authors describe the therapy as tolerable and very effective. More extensive studies on the use of liposomal anthracyclines in patients with severely limited liver function would therefore be desirable.

Vinca alkaloids

The vinca alkaloids vincristine, vindesin, vinblastine and vinorelbin are extensively metabolised in the liver. Both the metabolites and the unchanged starting materials are eliminated via the gall bladder. In view of this pharmacokinetic behaviour, a corresponding dose reduction in the case of elevated serum bilirubin values is recommended for all members of this group.

The actual dose recommendation are as follows: only 50% of the originally planned dose if the bilirubin values lie between 1.5 and 3.0 mg/dl and the transaminases between 60 - 180 U/L; only 25% of the dose should be given if the bilirubin values are between 3.1 and 5 mg/dl and the transaminases are over 180 U/L.

Taxanes

Similarly to the vinca alkaloids, the taxanes paclitaxel and docetaxel undergo extensive hepatic metabolisation and biliary elimination. Because of the paucity of study data, paclitaxel should on principle not be used for patients with severely impaired hepatic function; however, its use for patients with moderately elevated serum bilirubin and transaminase values is perfectly possible. Similar observations were also made for the structurally related docetaxel.

There are still no clear recommendations for dose reduction of paclitaxel in patients with elevated bilirubin or AST values. On the basis of results obtained up to now, however, it would appear that patients with slightly impaired hepatic function (e.g. transaminase values below 2.6 to 10 times the normal values and serum bilirubin below 1.25 times normal) can still be treated relatively safely with doses of 175 mg/m2 paclitaxel. Dosage guidelines for serum bilirubin values higher than this are currently being investigated in studies. In the case of docetaxel it has been observed that the docetaxel clearance was reduced by approximately 30% in patients with AST values over 1.5 times the upper limit of normal and AP values greater than 2.5

times the normal. Up to now it has been recommended that only 75% of the calculated dose be given up to 3.5-fold elevated transaminase values (e.g. < 125 U/L) and up to 6-fold elevated AP values (e.g. < 720 U/L). If these values are exceeded and the bilirubin value is elevated at the same time, it is advised that docetaxel not be used on grounds of lack of relevant results.

Irinotecan

The camptothecin derivative irinotecan (CPT-11) is primarily converted in the liver by carboxylesterase into the highly active metabolite SN-38. SN-38 can be metabolised in the liver to the cytotoxically inactive SN-38 glucuronide (SN-38G). All the compounds named (CPT-11, SN-38 and SN-38G) undergo pronounced biliary elimination. Therefore if the bilirubin and AP values are elevated the CPT clearance decreases exponentially unless an appropriate dose modification is implemented. On the basis of the pharmacokinetic studies of Raymond et al. it therefore appears to be advisable to give patients with bilirubin values between 1.5 and 3 mg/dl a dose of only 200 mg/m2 i.v. every three weeks instead of the usual 350 mg/m2.

How difficult appropriate decisions over CPT-11 dose modifications can be is impressively demonstrated in a case report by van Groeningen et al. In the case of a female patient with serum bilirubin values of 77 µmol/L (89% conjugated) and g-GT values of 474 U/L given only 100 mg/m2 instead of the planned 350 mg/m2, the measured concentrations of CPT-11, SN-38 and SN-38G were still too high within 24 hours after CPT-11 infusion. They concluded on the basis of their investigations that as little as 30 mg/m2 i.v. would probably have been sufficient. For the above reasons, the necessity for using CPT-11 must be very critically considered in the case of patients with impaired biliary elimination. The same applies for the administration of CPT-11 to patients with Gilbert syndrome.

Etoposide and teniposide

Although the topoisomerase II inhibitors etoposide and teniposide are structurally similar, their pharmacokinetic properties are different. Etoposide is not so extensively metabolised, the fraction bound to plasma protein is smaller and it is more rapidly eliminated at the same time as its metabolites via the kidneys and gall bladder.

Different studies have established that at serum bilirubin values between 2 and 12 mg/dl and 3- to 6-fold elevated AST values, conventionally dosed etoposide does not cause any significant change in the pharmacokinetics in the plasma. It is probable that compensation for limited biliary clearance is possible as a result of increased elimination via the kidneys. The studies also demonstrated a very good correlation between the decrease in serum albumin and the fraction of unbound etoposide in

the plasma and thus the associated neutropenia. The authors therefore reached the conclusion that dose reduction should primarily be made at albumin values below 35 g/L.

Antimetabolites

Diverse enzymes that are responsible for the metabolic inactivation of the antimetabolites 5-fluorouracil (5-FU), capecitabine or gemcitabine are localised both hepatically and extrahepatically. The resultant metabolites no longer exert any cytotoxic effect. Thus up to now no dose modification has been demanded for 5-FU itself even at a hyperbilirubinaemia of 5 mg/dl. For capecitabine a dose adaptation is made dependent on the levels of transaminases and AP. Both oral examples, capecitabine and UFT, are contraindicated for patients with severely impaired hepatic function.

For a relatively long time the same applied for gemcitabine. However, studies by Venook et al. have demonstrated that although patients with isolated elevated transaminases (and increased serum creatinine values at the same time) did not require any dose modifications, significant increases in bilirubin and transaminases may be expected in patients with elevated serum bilirubin values who are given gemcitabine without appropriate dose modification. The authors therefore recommend that patients with elevated bilirubin values be administered only 800 mg/m2 i.v. (instead of 1000 mg/m2) to start with, that the trend in the above values be monitored, and that the usual dose of 1000 mg/m2 i.v. per cycle not be administered until tolerance is obviously good.

Oxazaphosphorines

The oxazaphosphorines cyclophosphamide and ifosfamide are pro-drugs that lead via several steps to the products displaying the actual DNA crosslinking activity. If severely impaired hepatic function is associated with limited capacity of the corresponding cytochrome P450 isoenzyme, a systemically attenuated oxazaphosphorine effect is more likely in this case. An empirical dose reduction would therefore probably result in a reduction of the systemic effect. More extensive results are currently not available.

Summary

Impaired hepatic function can have decisive consequences for pharmaceutical therapy in a number of ways:

- If necrotic changes result in a quantitative decrease in the hepatically localised enzymes responsible for metabolising foreign substances - e.g. the cytochrome P450 isoenzyme, the UDP-glucuronosyl transferases or the glutathione S-transferases -, the active substance administered will be metabolised much more slowly, resulting in a stronger and longer-lasting effect of the drug given.

- A similar phenomenon is also observed if the circulation of the blood through the liver is reduced in the course of the hepatobiliary disease. The issue then becomes especially complicated if an accompanying portal hypertension unfavourably affects the absorption of the active substance from the gastrointestinal tract.

- In the event of a cholestasis, the build-up of bile may limit the elimination of those drugs that are eliminated strictly via the biliary route.

- In the case of an elevated bilirubin concentration in the serum, it must be expected that certain active substances (e.g. methotrexate, etoposide) that bind strongly to plasma protein are forced out of their protein binding and thus contribute to a significant increase in the freely biologically available - i.e. active - fraction.

- The same phenomenon is observed if hypoalbuminaemia occurs in association with a hepatobiliary disease. If in the course of therapeutic drug monitoring (TDM) only the total is measured (i.e. the sum of the protein-bound and non protein-bound fractions), it is perfectly possible that unexpected si gnificant drug side-effects are observed despite the fact that the dose is within the standard therapeutic range (e.g. etoposide). In such cases a more accurate analysis of the non-protein bound fraction can quickly enable conclusions to be drawn about the actual situation.

Although it is currently possible to quantify the individually constitutively existing liver cell mass and the capacity of biliary elimination by means of the ICG test and the galactose test, there are still a number of open questions in respect of precise determination of the individually available metabolic capacity. The most useful approach would therefore be to administer a test dose of a model substrate for a specific cytochrome P-450 enzyme in order to ascertain the metabolic capacity for a drug that is also converted by this enzyme. Ideas of this kind (e.g. the introduction of a breath test in connection with radioactively labelled erythromycin [ERMBT]) are discussed in the literature repeatedly, but up to now it is not really possible to

talk about a practical implementation of this concept, even though it would be possible via ERMBT to predict much more accurately the individual conversion rate for the cytostatics isfosamide, the vinca alkaloids, the podophyllotoxins, irinotecan or the taxanes.

Current practice, and basic prescribing information and package leaflets, usually base a decision for dose modification on changes in the transaminases, bilirubin or albumin values, knowing full well that this decision will hardly bring precision in respect of pharmacokinetics and pharmacodynamics. The hope remains that in the years to come efforts will be intensified towards producing concrete recommendations based on appropriate initial parameters.

Table 1: General recommendations for empirical dose reduction of cytostatics eliminated primarily via the hepatic route (see text for further discussions)

Bilirubin elevation	AST (GOT)	Dosage (% of the original dose)
< 1.4-fold	< 3-fold	100 %
1.5- to 3-fold	3-to 9-fold	75 - 50 %
3- to 5-fach	>9-fold	50 - 25 %
> 5-fold		individual decision
In case of elevated alkaline phosphatase		50 % dose reduction of vinca alkaloids and podophyllotoxins

Table 2: Normal ranges of different parameters in the case of unimpaired hepatic function

Parameter	Units in µg/L, g/L or U/L	SI units	Conversion factor
Serum bilirubin (total bilirubin)	0.1-1 mg/dL	2-18 µmol/L	17.1
Direct bilirubin	0-0.2 mg/dL	0-4 µmol/L	17.1
ALT (SGPT)	0-35 U/L	0-0.58 µkat/L	0.01667
AST (SGOT)	0-35 U/L	0-0.58 µkat/L	0.01667
ãGT	0-30 U/L	0-0.5 µkat/L	0.01667
Alkaline phosphatase	30-120 U/L	0.5-2 µmol/L	0.5872
Serum albumin	>3.5 g/dL	>35 g/L	10

Abbreviations: ALT (alanine aminotransferase), AST (aspartate aminotransferase), ã-GT (gamma-glutamyl transferase)

Table 3: Changes in different liver parameters depending on the type of liver disease

Disease	SGOT	ãGT	AP	Serum bilirubin	Quick value
Necrosis	+++++	+	+	= or +	lowered
Adiposis hepatica	+	+++	= or +	=	=
Anicteric cholestasis	= or +	+++	+++	=	=
Icteric cholestasis	+	+++	+++	++	=
Toxic hepatitis	+++	++	+	= or +	slightly lowered

Notes: Abbreviations for enzymes: (see Table 2); = : unchanged; + to ++++ = slightly to very strongly elevated

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3.5.5. Dose Modification in Case of Blood Picture Changes

The myelosuppressive effect of a cytostatic therapy may limit the dose for treating the patient. Continual observation of the individual patient will reveal the occurrence of myelosuppression. Since there are no established parameters for estimating the individual regeneration capability of bone marrow, it is not possible to make standard recommendations for modifying the dose. The use of haemopoietic growth factors has expanded the range of therapeutic possibilities.

Jürgen Barth, Essen

One of many organ parameters to be observed during the administration of antineoplastic substances is the blood picture and the so-called bone marrow reserve. In this connection, however, there is no established parameter that can be used to assess the individual patient, including in respect of the regeneration capability of bone marrow attacked by cytostatic agents (in contrast, for example, to the situation for renal or hepatic function, see 3.4.3. Dose Modification in Case of Impaired Kidney Function, 3.4.4. Dose Modification in Case of Impaired Liver Function). Among the reasons for this is that the underlying disease may have become established in this organ. Reliance must therefore be placed on more or less close (individual) observation of the course of events (2-3 times weekly after chemotherapy). This is the only way that the "real" existing myelosuppression can be detected.

A distinction must be made between a *curative* and a *palliative* therapeutic approach, bearing in mind the (biological) age of the patient. Subsequently, ***nadir-adapted*** dose modifications are made before the next cycle of therapy. In this context it should be noted that the administration of haemopoietic growth factors such as G- or GM-CSF during a curative therapeutic regimen often renders dosage modification of standard therapies unnecessary and therefore allows the dose intensity to be maintained. High dose chemotherapy and standard therapy in which dose intensity is increased by shortening the intervals are only possible with growth factor support.

Recommendations for dose modification on the basis of myelosuppression can therefore only be regarded as *aids to orientation* (see 3.4.1. Prescription Form). Particularly if myelosuppression occurs during therapy with a curative therapeutic goal, consideration should be given to continuing the chemotherapy in combination with the above supportive measures and with a longer interval between cycles.

3.6. Preparation

Preparation is carried out on the basis of the working rules (s. 20 *GefStoffV* (hazardous substances regulations)) and the production specification, which incorporates the results of the hazard evaluation.

The work techniques defined in the working rules and product specification are mandatory. Compliance with them must be regularly inspected.

Dr. Karla Domagk, Cottbus

The *Aphotekenbetriebsordnung (ApBetrO)* (pharmacy regulations) is legally binding for the preparation of drugs in German pharmacies. Pursuant to s. 7 *ApBetrO* the production of ready-to-administer cytostatic solutions for a specific patient is the preparation of a drug subject to prescription (x). S. 6 (1) *ApBetrO* stipulates that the drugs must be prepared and tested in the pharmacy in accordance with the recognised rules of pharmacy and that they must meet the quality standards demanded by the rules of pharmaceutical science. The requirements of s. 7 (2) allow the possibility of omitting an inspection only if the quality of the drug is guaranteed by the method of its preparation. Therefore, the preparative procedure for every cytostatic and every type of application are important components of the validation of the preparative process and of the quality management system in cytostatics preparation.

The federal pharmacists association guide to quality assurance - "Aseptic preparation and inspection of ready-to-administer agents for parenteral use with toxic potential" - should be consulted in this connection.

The preparation may not be started until receipt of a written requisition signed by the doctor; this document is the basis of a plausibility inspection of the prescription and of authorisation of the preparation by the pharmacist.

A computer program used during the preparation of ready-to-administer cytostatic solutions for specific patients guarantees not only consistent work, but also continuous, objective and clear documentation during the preparation. The use of a balance during the entire preparation process not only means that the actual quan-

tity can be recorded exactly, but also enables determination of the quantity of active substance for partial withdrawals. If a balance cannot be used during preparation, the least requirement is that a second person observes what is done.

According to the requirements of *TRGS* (technical rules for hazardous substances) 525, the following equipment must be used as a minimum: pressure release and transfer systems (see Chapter 3.3.1. Technical Equipment for the Preparation of Cytostatics). In addition, work must be carried out on an underlay impermeable to liquids, and infusion sets must be vented only with carrier solutions.

3.6.1. Production Specification

A production specification for cytostatic preparations includes the:

- **name of the cytostatic**
- **pharmaceutical form**
- **kind and name of the finished drug to be used**
- **types and names of the medical devices to be used**
- **name of the method for proper preparation**
- **name of the equipment to be used**
- **maximum permissible deviation from the value specified in the requisition**
- **kind of packaging and labelling**
- **information to appear on the label**
- **information on the shelf life of preparations and unopened stock solution**
- **information about special points to be observed when handing over the finished preparation.**

Matthias Klein, Kiel

The 1995 order of the Lower Saxony social ministry on the preparation of ready-to-administer cytostatic solutions already includes the requirement for a production specification.

Stipulating the finished drugs to be used in the production specification protects against errors in selecting bottles while making ready for the preparation. If the preparation is changed, the specification must then be modified.

Stipulation of the medical devices and equipment and the description of the method is intended to ensure a uniform quality of preparation. It must be borne in mind, however, that excessively detailed definitions may lead to acceptance problems among the employees.

The maximum permissible deviations from the required value stated in the requisition are legally defined in the specifications of the pharmacopoeias and in the *Füllmengenverordnung* (filling regulations). Although lower limits may be chosen,

these are mostly only of economic advantage and not so relevant for therapeutic safety.

Information on the stability and shelf life of the stock solutions, ready-to-administer cytostatic preparations and opened stock solutions must be laid down as part of the production specification. Data from the literature cannot always be used directly. The conditions under which corresponding investigations were carried out may differ considerably from those in the department (concentrations and composition of the solution, material of the container and the medical devices, effect of light, etc.)

Thus information from the literature on chemical and physical stability must be treated only as an indication and should wherever possible be verified by chemical tests performed on the actual product.

3.6.2. Documentation

The following data are recorded during the preparation and are documented using an appropriate method:
- **time at which the preparation started**
- **batch number of the finished drug and any residues (cytostatics, solvents, carrier solutions)**
- **volumes used of solvents and carrier solutions**
- **name and quantity of the cytostatic used**
- **unusual incidents during the preparations**
- **name of the person carrying out the preparation**

Dr. Karla Domagk, Cottbus

During the preparation of cytostatic solutions the quantities and batch numbers of starting materials used are documented and the date and time at which the preparation started is recorded, in accordance with the requirements of GMP.

Objective and clear documentation is necessary in order that the pharmacist responsible can instruct pharmaceutical personnel to carry out the preparation. In view of current trends in drug liability law, it cannot be excluded that a shift in the burden of proof in individual cases will result in the pharmacist having to prove that he has prepared a specific cytostatic properly. Continuous documentation during the preparation will help to reduce this risk of liability.

If a computer program is not used for this purpose, the preparation process must be documented within the LAF clean room by the person performing the preparation (while maintaining asepticity); alternatively, the individual steps must be documented by a second person outside the LAF during the preparation according to the principle of double checking.
Within the implementation of a quality management system for cytostatics preparation, it is recommended that the batch numbers of the sterile single-use products used are also documented.

3.6.3. Label

The label prepared on the basis of the preparation documentation contains at least the following information:
- **name and address of the pharmacy performing the preparation**
- **name of the patient**
- **date of birth or admission number of the patient**
- **ward, department or therapeutic facility**
- **name and quantity of the cytostatic contained**
- **type and volume of carrier solution**
- **method of administration**
- **required time of administration**
- **storage conditions**
- **time of preparation and shelf life or, preferably, date of expiry.**

Matthias Klein, Kiel

The prepared solution must primarily be labelled according to s. 14 *ApBetrO* (pharmacy regulations). S. 6(2) *ApBetrO* states that the requirement for labelling to take place immediately after preparation is an important measure for avoiding confusion. The cytostatic solution must be labelled in such a way that it can be assigned uniquely to the patient for whom it is intended. Since it is perfectly possible that patients with the same name are in the same ward, the data of birth and/or the admission number should be written next to the name as an identifying characteristic.

In view of the limited stability of ready-to-administer cytostatic solutions, it is essential to state the date of preparation together with the shelf life (period of time) and the storage conditions. Alternatively, the date up to which the preparation is stable (expiry date) and the storage conditions can be given. This applies both to stock solutions and to solutions prepared for a specific patient.
Stating the required time of administration supports compliance with the correct chronological sequence of administration according to the polytherapeutic regimen and the associated concomitant medication.

3.7. Delivery of Cytostatics

**Cytostatics deliveries must be clearly labelled by the sender.
The packaging must ensure safe transport and unpacking; the consignment must be appropriately labelled.**

Technical rules for hazardous substances *TRGS* 525 applies for in-house transport of ready-to-administer cytostatic preparations. These require that the finished preparations be transported in unbreakable, liquid-tight, closeable containers. The transport containers must also carry a warning label such as "Caution Cytostatics".

The return of cytostatics - whether internally or externally - must be agreed with the recipient.

The *Gefahrgutverordnung Strasse und Eisenbahn (GGVSE)* (dangerous goods regulations for road and rail) apply in addition for outside transport.

Gerhard Carstens, Hannover and **Hannelore Kreckel**, Giessen

The requirement that cytostatics deliveries be clearly labelled applies for every sender, i.e. not only drug manufacturers and wholesalers but also for pharmacies and, in the event of return, for hospital wards, out-patient clinics and medical practices. The label must consist of an unambiguous, succinct logo and an informative but short text. The logo should preferably be in a striking colour, best of all in a fluorescent colour. Unfortunately it has not yet been possible to persuade the cytostatics manufacturers to agree on a standard logo. The demand that a standard logo be used by manufacturers and suppliers, and possibly also in health service facilities, has lost none of its legitimacy and is worth pursuing further.

For safety reasons cytostatics should be delivered separately from other drugs. In order to achieve this it may be necessary in individual cases to place separate orders with the manufacturer or wholesaler.

The transport packaging must guarantee that breakage cannot occur, that the primary packaging is not contaminated by microorganisms or other particles and that

any traces of cytostatic substances adhering to the primary packaging cannot result in contamination of the transport packaging and consequent danger to the persons responsible for unpacking the consignment. For these reasons the transport pakkaging should comprise a) a liquid-tight enclosure of the primary packaging, b) protection against impact and c) an outer transport container. Additional climatic packaging may also be necessary for the purpose of product integrity. The liquid-tight wrapping of ready-to-administer packages from the cytostatics laboratory of the pharmacy can be implemented either using heat-sealed tube packaging or bags with a MicroSnap closure. Manufacturers should apply liquid-tight wrapping to septum bottles immediately after the production process or a subsequent cleaning step. A few model solutions are already being offered by different manufacturers.

The requirements of s. 31 (2) *Apothekenbetriebsordnung* (pharmacy regulations) concerning the issuing of drugs to wards and other departments of a hospital in suitable, closed containers are extended by *TRGS* 525. These stipulate that the cytostatic solutions prepared be delivered in unbreakable, liquid tight, closed containers, separated from other goods. The containers must carry the inscription "Caution Cytostatics". Closure may be realised by means of a key or a seal. The place where the key to the transport container is kept and and who has authorised access to it must be clearly and unambiguously regulated both in the pharmacy and in the unit performing the oncological therapy. For thermolabile products or those in danger of crystallising out, an insulated box to the same specifications must be used during transport if there is a risk of critical temperatures.

The prepared products are pre-packaged before being placed in the transport container. Filled pumps may in principle be delivered without a bag if the system is secure against leakage. [Additional packaging poses no problem, however, and is worth considering on formal grounds.] The cytostatics directive of the *AOLG* (association of the highest regional health authorities) requires that the prepared products are sealed in liquid-tight film. During sealing care must be taken that the welded seam does not develop a leak as a result of premature separation of the film. Light protection bags are used for light sensitive substances. Placing in clip-closure bags ensures protection against the leakage of liquids as long as the MicroSnap closure is fitted properly together. Enclosing packaging ensures that any leakage is contained without the transport container being contaminated. For safety reasons the boxes can be lined with absorbent material for binding any solution which does escape.

Deliveries are made directly. The prepared products are handed over punctually to the professional personnel in the department that placed the requisition.

Transport by non-pharmacy personnel is permitted only after these persons have been instructed on the action to take in the event of danger. The time of handing over must be agreed with the persons performing the transport.

An important aid during transport is a mobile telephone, since this enables the transporter to ask for instructions and assistance quickly. There is no need to wear special protective clothing for the transport. During transport in which it is not possible to hold the container, the box should be placed on or in the transport vehicle in such a way that it cannot fall. It may be reasonable to carry a suitably adapted decontamination set during transport over longer distances. As a minimum, however, two pairs of (non sterile) gloves must be kept in the vehicle and regularly inspected and replaced (see Chapter 1.1. Persons Handling Cytostatics,; 1.3. Working Rules and Instruction, Protective Clothing).

The regulations for the transport of dangerous goods by road and rail apply in Germany for the transport of CMR substances by road. Although cytostatics preparations count as dangerous goods, they must not be labelled with the UN number 1851, which includes "medicines, liquid, poisonous", but according to ADR "Ready-to-use pharmaceutical products, e.g. cosmetics and medicines, which are prepared for personal use and are packaged in trade or household packages (and) are not subject to the requirements of the ADR". (ADR - Accomodation des Affaires dangereuses en Route - *Zwischenstaatliches Übereinkommen über den Transport von Gefahrstoffen auf der Strasse/Eisenbahn* (International agreement on the transport of dangerous substances by road/rail) - in the German version *GGVSE*).

The cytostatics solutions for specific patients are taken to the requisitioning department by an employee of the pharmacy or the transport service and handed over to the professional personnel. If necessary, the preparation can after prior agreement be fetched from the pharmacy by an appropriately instructed employee of the requisitioning department.

The return of problem deliveries (suspected hairline cracks, contamination, etc.) must be made after prior agreement with the addressee, securely packed in accordance with the general transport criteria and clearly labelled. Deliveries which are clearly broken and seriously leaking are not returned but are disposed of locally after agreement with the supplier. When returning materials from the pharmacy to the

manufacturer or wholesaler the use of bags with twist packaging (e.g. Whirl-Pak®) are recommended. The bag, ideally provided by the manufacturer, should have an inscription area where the problem associated with the contents can be described. For safety reasons an appropriate procedure must be stipulated for returns by end users (wards, out-patient departments, medical practices) to the pharmacy performing the preparation. Details must be specified in service rules or delivery agreements.

3.8. Valuation

The costs of preparation are divided between the following areas:

1. Material costs
a) drugs
b) carrier solutions
c) single-use articles
2. Personnel costs
3. Additional charges

For valuation in public German pharmacies account must be taken of the contracts existing between the leading organisations of the statutory health insurance bodies and the pharmacists associations.

Klaus Meier, Hamburg and **Klaus Ruberg**, Bonn

3.8.1. Material Costs

a) Drugs and b) Carrier solutions

This means both the active substances used and the carrier solutions employed. In this connection particular attention should be directed at the calculation of residual quantities. As long as it is not necessary to assign costs directly to the individual patient, the calculation can be performed according to a general department-related method for apportioning costs.

c) Single-use articles

The costs of the disposable medical articles used in the preparation must be accounted for, as well as the costs for disinfecting and cleaning agents.

3.8.2. Personnel costs

The personnel costs to be charged for a ready-to-administer cytostatic solution are essentially determined by the working time.

The working time can be divided into

a) time needed directly for the preparation, which is determined both by

1. the properties of the substance and also
2. by the pharmaceutical form, and

b) time connected indirectly with the preparation, which arises through the work to be performed on the basis of defined standards of quality. [1]

The recording and classification of the time needed for this necessitates further calculations relating to the hospital as a whole, in order to arrive at generally applicable conclusions. [2]

3.8.3. Additional charges

These are primarily internal accounting items for balancing the budget and fiscal accounting items such as VAT. The internal charges, which are also accounted for in a full calculation of costs, should cover any management costs (overheads).

The times used must be correlated from two aspects:

1. The different number of preparations per year exerts an influence on the costs incurred through setting-up times, even if preparation is performed according to the same criteria.

2. Although a noticeable rationalisation effect occurs with increasing preparation figures, this is subject to restraint through parameters such as work conditions (e.g. number of workplaces) and limits to the flexibility with which the personnel can be deployed.

The following factors can be used for working times and setting-up times. [3]

Principles of staff requirement calculation:

Table 1:

1.	less than 1000 per year	factor 1.1
2.	1000 to 5000	factor 1.0
3.	5000 to 10,000	factor 0.8
4.	over 10,000	factor 0.6

In order to be able to correlate the working times for the individual preparations to the costs incurred, the following principles are available for internal calculations and staff requirement calculations:

In analysing reference figures, these must be fixed taking into account the currently applicable standard hours of work and absence quotas. Reference figures are updated (corrected) not only if standard hours of work are reduced, but also - according to the same principle - when adjusting for absence quotas, especially when accounting for absence quotas for the individual hospital.

Whereas changes in the working time are accounted for by updating reference figures, the "reference values" (minute factors) on which the (recognised) reference figures are based have "normative" character. [4]

It is therefore useful for this analytical method to break down reference figures into their components and to link the "normative" reference values with individual hospital working times.

The percentual starting point for calculating the staff requirement is basically defined by the 1969 reference figures of the *DKG* ("German hospitals association"), updated to the 40-hour week.

The fixed absence quota in the reference figures is derived as follows. The reference figures of the *DKG* for the year 1969 for the nursing service included an absence quota of 15% as "supplement to the effective working time for periods of absence" (supplement method, personnel supplement quota -*PZQ*).
This corresponds to a "deduction from the standard working time" (deduction method, personnel absence quota - *PAQ*) to the amount of 13.04%.[5]

Therefore, the reference basis for the personnel absence quota is either

- the "effective" working time (supplement method) or
- the "standard" or "gross" working time (deduction method).

Today, the "deduction method" in the narrower sense is generally employed. The term personnel absence quota (PAQ) will therefore be used.

In its recommendations of 1974 the *DKG* used the deduction method as the basis, but retained the fixed rate of 15%, which is generally accepted today.

Since the personnel absence quota on which the *DKG* reference figures for 1969 are based do not take any "weekday public holidays" into account, efficiency examinations are implemented in practice such that the standard working time is reduced (depending on the particular *Land*) by 10 or 11 weekday public holidays (gross annual working time) and the absence quota is applied to the reduced basis.[6]

In the case of 11 weekday public holidays, this increases the staff requirement by approximately 4.4%.[7]

The annual working time is calculated as follows:

Table 2:

365.25 calendar days p.a.
• 104.3 weekend days
• 10.0 weekday public holidays
intermediate total = 251.0 annual working days (gross)
x 7.7 hours/day (for a 38.3 hour week)
= 1923.7 hours p.a. (gross)
x 0.8225 for 17.75% absence time[8]
Result = 1590.0 annual working time (net)

Summary
In the past, calculations of working time and costs incurred through the preparation of ready-to-administer cytostatic solutions often did not define a total time value, but work performed on a regular or irregular basis was listed individually in the same way as for the individually accepted time values for preparation in its narrowest sense. The result was that - known to all those responsible - most of the work extending beyond the pure preparation itself was not accounted for in calculating the working times. An isolated viewpoint of this kind does not support the aim of creating a standard basis for calculating pharmaceutical services in central cytostatics preparation. Rather, the danger exists that by ignoring the quality aspects during future negotiations between funding bodies and hospitals or state governments - e.g. in connection with special payments and fixed payments for specific cases - prices will be agreed which do not even partially cover the costs.
On the basis of the available data it may be assumed that:

- the large majority of hospital pharmacies producing ready-to-administer cytostatic solutions centrally belong to the group to which the factor 1 applies (cf. Table 1). For these, the following values apply:

Table 3:

Activity	per Production
Setting-up times	26 minutes
Production	19 minutes
TOTAL	45 minutes

- The working time of a full-time employee includes the working time fractions of the participants as follows: 20% pharmacist, 70% pharmacy technician and 10% pharmacy auxiliary staff.

- The net working time of 1590 hours allows that - on the basis of the work documented in the quality standard - one full-time employee can perform 2120 cytostatics preparations per year.

Whatever can be recorded in minutes can also be calculated in terms of money. For the costing of so-called "post-inpatients" or "part-inpatients" we can derive the following:

- An average time of 45 minutes (at factor 1) yields mean preparation costs of 20 euros per administration.

- To this must be added drug and other material costs.

- A fixed price of 30 euros in addition to the drug costs has proved to be a practicable figure within the hospital.

For valuation in the ambulant sector and in public pharmacies account must be taken of the contracts existing between the leading organisations of the statutory health insurance bodies and the DAV (German pharmacists association), which deviate from the general conditions of the *AMPreisVO* (directive on drug prices) but is allowed for there in s. 5 (5).

A present the valuation of solutions for parenteral use is regulated in the still valid auxiliary charges 2002 with the extensions of 1 July 2003. Depending on the differences in preparation according to the properties of the substance and the indication the solutions are divided between the groups cytostatics, parenteral nutrition, antibiotic virostatics, solutions for parenteral pain therapy and "miscellaneous". The batch size and work price are calculated depending on the allocation to these groups.

In the case of generic prescriptions, i.e. prescription without proprietary drug name, drugs must be taken from the lower third of the price range, in accordance with the aut-idem rule. According to the DVA multiple packs need not be taken into account since each prescription is regarded in isolation.

Prices are based on the purchase price according to the *LAUER-TAXE*. For calculation purposes the respective most economical package size for the total quantity of substance prescribed is used, i.e. if necessary substance per ready-to-administer unit times number of units; this solves the formerly controversial problem of partly used packs. The additional charge according to the *AmPVO* is applied to this purchase price, but to a maximum of 30%. Carrier solutions are calculated at purchase price plus 30%, pumps, cassettes or other administration aids - which must be prescribed exactly - at purchase price plus 25%. The work price, which covers administration costs such as mask, gloves, spikes, underlays, gowns, disposal and documentation, is set at 19 euros for cytostatics and 15 euros for other solutions such as folic acid. VAT is applied to the total of these individual prices.

At the moment many detail questions are open in respect of the implementation in practice and continual revaluation procedures. Particularly the use of reimports, the general use of multiple packs, the basic use of the cheapest offer whether available or not, and substitution in general are the subject of many appeals against revaluation.

As a result of the planned *GMG* (law on modernisation of the health service) changes are possible in all directions, even as far as the abolition of the auxiliary charges; this means that new valuation rules may be expected to come into force after publication of the QUAPOS 2003.

It must be stated for the record that: The agreed work price in ambulant care is very close to the level calculated by us, even though inclusion of the equipment costs does not appear to be covered completely. It will certainly be possible to compensate for this shortfall by exploiting existing possibilities for economies in work costs.

Nonetheless, it is important to take appropriate steps to ensure that the quality of preparation does not suffer in the future and that the aspect of employee protection is awarded due importance:

1. An accompanying quality control through certification as performed by the *DGOP* for the last three years is an important instrument for the independent standardisation of the pharmacies carrying out the preparation.

2. The continuous documentation of the necessary material costs must contribute towards raising the agreed amounts to the necessary level.

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1) The so-called setting-up times are divided into: 1. Work arising on an irregular basis, 2. Work necessary for every preparation, 3. Setting-up times arising daily and 4. Documentation and organisation times.

2) In a study performed over a period of 4 years and started by the CYPRO users, average setting-up times of 26 minutes were obtained at factor 1 (presented at the 6th user meeting, Nov. 1995, Flensburg).

3) See (for example): Section 5.1 "Sterile and aseptic preparation" in the "Catalogue of pharmaceutical services in the hospital" (*KaphaLeiKh*) from the "committee for rates and contractual questions" of the *ADKA* (association of German hospital pharmacists); February 1996.

4. "Directives for examining efficiency and economical management of hospitals" (Baden-Württemberg 1984).

5. Effective working time = standard working time x 100/115 = standard working time x (100-13.04)/100 (PAQ = 13.04%).

6. The deduction of weekday public holidays for calculation of the effective annual working time is independent of whether the respective service operates on weekday public holidays.

7. Effective annual working time = standard annual working time x 250/261 x (100 - PAQ)/100. The staff requirement increases by 261/250 = 1.044 (4.4%).

8. This is the average absence time published by auditing firms for the medical technical sector in hospitals, to which the pharmacies are allocated pursuant to budget legislation.

9. In determining the basic prices for the substances a distinction is made between articles with and without a * (asterisk). For articles with no * the INN price is multiplied by the quantity prescribed; for articles with an * the INN price is multiplied by the amount of the smallest divided unit of a pack.

10. The work price covers management costs such as: mask, gloves, spikes, underlays, gowns, disposal, documentation.

3.9. Sources of Information

An oncology pharmaceutical service is based on resources for the acquisition and further communication of information relevant to all issues associated with tumour therapy; these resources must be appropriate to the importance of this interdisciplinary department. In addition to the maintenance of a library containing specialist print media, and PC equipment providing access to relevant software and digital information, connection to the Internet for the purpose of searching databases, employing search engines, following diverse links and using electronic mail and other services is indispensable.

Standard facilities must also include audio and video material for training.

Silke Braband, Michael Höckel, Hamburg

When acquiring information in the field of oncology it is advisable to formulate the question as precisely as possible before beginning the actual search. Once this has been done, those media are selected which are most likely to bring success within a reasonable length of time. Documenting and archiving the questions, the answers and the media used has proved to be worth the extra effort. If this procedure is properly structured it is possible to recall already existing knowledge in a minimum of time. A search for information can be effectively and chronologically planned only if it is performed systematically according to a locally defined procedure taking account of the available facilities. Although archiving in the form of databases enables information to be rapidly found again, this can also be done using card indices.

Textbooks on oncology and haematology (1) are the first sources of information on disease syndromes and diagnosis. An Internet search (2) in addition is helpful for current references and delivers an up-to-date answer. Specialist information and knowledge databases (3) with monographs (cost free, or possibly associated with a fee) are available for questions about active substances, though the validity of these data may depend on the revision status of the source concerned. The date of the most recent revision must be visible and should be recorded as part of the archiving procedure.

In the case of more recent or the latest information it will be necessary to consult the corresponding original work; literature databases are available for this purpose. Access to the databases (4) via the respective search masks and to the abstracts is free in most cases. However, acquisition of the associated original publication frequently carries a fee (5). The pharmacist then has the opportunity to contact a nearby university or similarly equipped library and order the necessary works. Further possibilities are a subscription with a commercial supplier (5) and/or contact with the medical sciences department of a pharmaceutical firm. In the case of clinically relevant questions from practice, informational material (e.g. manuals) from tumour centres (6) and the scientifically supported guidelines for diagnosis and therapy (7) provide a rapid overview and thus enable questions to be answered in a practical context.

A diversity of sources for searching is available to those seeking information and, not least as a result of the Internet, these frequently deliver an overwhelming flood of data. For this reason the selection of media should be made as a team in order to accumulate experience in the application. One person within the institution should be responsible for regularly updating the necessary print and non-print media.

In addition to the acquisition of data, an important aspect of answering questions is evaluation of the data acquired. Information from the Internet should be evaluated according to a checklist. Some owners of information pages check their information themselves using a tested catalogue of criteria and in this way monitor the quality and integrity of their Web pages. One example is the recognition of and compliance with the HON code (Health on the Net Foundation) as a quality feature recognisable by the authorised HON logo on the Web page (8). This logo is awarded to Internet pages whose operators recognise and follow the eight HON principles. These principles include, for example, identification of pages and articles prepared by non-medically qualified persons, preservation of confidentiality, clear references to sources of information, identification of sponsors, and financial independence from the results and products presented. The content of the pages must principally be maintained by qualified persons.

The Discern project (9) represents the first approaches to implementing aspects of quality control in the medical Internet and offers procedures for inspecting publications found in the course of a search. In respect of information for patients and lay persons, a Web site (10) is provided by the Ärztlichen Zentralstelle Qualitätssicherung (Medical quality assurance central office) (äzq).

However, even these "seals of quality" cannot completely guarantee the quality of the content of an article. The final evaluation and classification of the results in the overall context of the problem or enquiry remains the responsibility of the specialist oncology pharmacist. Very careful examination is especially important before any information is passed on to doctors and patients.

(1) Schmoll et al. (1999): Kompendium Internistische Onkologie (Compendium of internal oncology). Springer, Berlin and Standards in Diagnostik und Therapie (Standards in diagnosis and therapy) (2002) as CD-ROM; Berger D.P., Engelhardt R., Mertelsmann R. (2002): Das Rote Buch (The red book) 2002: Hämatologie und Internistische Onkologie (Haematology and Internal Oncology). Ecomed, Landsberg/ Lech; Bast R.C. (2000): Cancer Medicine. e. 5. Decker, Hamilton, Ontario; Hämatologie und Onkologie – Manual Tumorzentrum München (Haematology and oncology - Manual Tumour Centre Munich). Zuckschwerdt, Munich, also available as CD-ROM and online at http://www.krebsinfo.de/ - Tumour Centre .

(2) www.oncolinks.de (Search mask with access to pages from the oncology field); www.oncolink.upenn.edu (Medical- and Cancer Center, University of Pennsylvania); www.cancer.gov/cancer_information/ (latest research results gathered from Physician Data Query PDQ; www.nci.nih.gov/cancer_information/pdq/, from the National Cancer Institute Cancer Databases and Data from Cancerlit; www.cancer.gov/search/cancer_literature; Reviews on evidence based medicine: http://cochrane.de/, including oncology, see under Cochrane groups (46 review groups) e.g. Breast Cancer Group

(3) www.fachinfo.de - Fachinformationsservice Deutschland, Satz-Rechenzentrum Berlin und BPI-Service GmbH (specialist information service Germany, Satz computing centre Berlin and BPI-Service GmbH); www.documed.ch - das Arzneimittelkompendium der Schweiz (the Swiss drugs compendium); Micromedex[a] Thomson Healthcare, Drugdex Drug Evaluations as pharmacological full text database of drug information and Martindale as standard pharmacological reference work and also the Micromedex databases are available online for a fee at http://www.micromedex.com/ ; Medizinisches Informationssystem (Medical information system); www.pharmavista.ch- information on foreign, but also domestic preparations (supported by list of substances and ABDA database).

(4) www.medscape.com among others for medline searches or via www.nlm.nih.gov/ directly to the National Libary of Medicine of the USA and www.nci.nih.gov/ of the National Cancer Institute; www.dimdi.de - fee-bearing access to diverse databases.

(5) e.g. www.ovid.de; www.subito.de – document ordering; www.hbz-nrw.de/produkte_dienst/germlst/index.html- German libraries online.

(6) http://www.medizin.uni-tuebingen.de/itz/ - Interdisciplinary Tumour Centre, Tübingen (ITZ), including therapy recommendations; http://www.krebsinfo.de/ - Tumour Centre Munich, including tumour manuals.

(7) http://leitlinien.net/ - scientifically supported guidelines for diagnosis and therapy.

(8) www.hon.ch, lists the eight principals in several languages.

(9) www.discern.de, evaluation catalogue for publications and criteria for the preparation and evaluation of information for patients.

(10) www.patienten-information.de - information page of the *äqz*; www.inkanet.de - information network of affected persons for patients and relatives; www.krebs-kompass.de; www.meb.uni-bonn.de/cancernet/deutsch/index.html - German translation of the information for patients provided by the American National Cancer Institute about individual cancer diseases.

4. The Pharmacy as Coordination Point in Cytostatic Therapy

As the central unit in cytostatic therapy the pharmacy implements the quality management system for the oncological pharmaceutical service and thus accepts co-responsibility for patients and personnel in all areas of cytostatic therapy.

The pharmacy records and processes all data with medical and toxicological relevance for the cytostatic agents, including where possible the accompanying and supportive measures.

The information at hand is evaluated epidemiologically, examined from clinical, pharmaco-economic and ecological standpoints, documented, incorporated in consultation and used for training the personnel.

Annette Heiny, Braunschweig

When the preparation of individual cytostatic solutions for chemotherapy began in Germany almost twenty years ago, it was initially established centrally in hospital pharmacies. At that time, very few people considered that, in the years that followed, this particular area was where pharmacy would most strongly demonstrate its orientation on the future and its innovative capability.

By the time the preparation of cytostatics had spread to public pharmacies, and with the growth of out-patient oncological therapy, a field of activity had opened up in which the possession of a considerable amount of additional knowledge was essential. It became apparent that simply acquiring the necessary preparative skills and knowledge would not be sufficient.

Examination of the cytostatics prescription alone demands knowledge derived from examination of the sources of oncological medical information. At the same time, however, this examination widens the horizon for further questions.
Pharmacists developed more and more into the advisor of the doctor, the nursing personnel and the patient in all the specialised aspects of the cytostatic therapy. Because of the constant changes undergone by the therapies, they could and can meet this challenge only by means of continual further training and qualification.

As a result, it became increasingly clear that a comprehensive quality management system would be appropriate for this field.

The flowing together in the pharmacy of all the information on medicines and therapies leads directly to the idea of the pharmacy functioning as a platform for communication in the sense of providing a service.

Joint consideration of the therapeutic regimens with the medical specialists leads to an exchange of knowledge about cytostatics and about accompanying therapies and problems of administering the drugs, and to the correlation of local experience with the results of research in general. The outcome is quality improvements both for the therapy of the patient and for the working safety of the personnel.

The offer to collect together all the medical and pharmaceutical data relevant to the cytostatic therapy and safe preparation and to keep this information accessible to every member of the oncological team at any time enables and optimises the interdisciplinary collaboration of the specialist fields.

The patient and the documentation of the patient's data become the focal point of events. The possibility of epidemiological evaluation of the information at hand is perceived as helpful. This information not only contributes to transparency in the development of costs; above all, it enables the therapeutic results to be examined in a relative way and makes it possible to discuss the aim of the therapy.

A requirement for the establishment of a coordination point is the acquisition and processing of meaningful data. The application of modern information technology based on complete networking of the pharmacies with the prescribing doctors and the joint use of appropriate software enables all the relevant data to be processed and presented and makes it possible for the pharmacist to provide efficient and comprehensive consultation.

The pharmacist can and must be in a position to provide the services possible in order to give increasing substance to the professional image of the oncological pharmacist.

4.1. Waste Disposal

The principles of waste disposal - in order of priority - are:
1. Waste avoidance
2. Waste recycling
3. Waste disposal

Their purpose is:
1. Protection of persons
2. Protection of the environment

Hazardous wastes and objects contaminated with these are:
- **separated from other wastes**
- **at the place they originate and**
- **collected in appropriate labelled containers.**

Wastes containing cytostatics are in principle specially controlled wastes (hazardous wastes, special wastes). They must be collected in special bins that can be closed in an airtight way after filling. Wastes containing cytostatics are subject to the *GGVS* (regulations on the road transport of dangerous goods).

The applicable national and regional statutory requirements must be observed.

Anette Freidank, Fulda

The purpose of controlled disposal is to protect persons and the environment while complying with the statutory requirements.

Protection of persons means that contamination with cytostatics is avoided, i.e. that these are neither absorbed through the skin nor taken up via the respiratory passages as a result of inhaling dusts or aerosols.

This concerns all persons involved in handling cytostatics - not only the pharmaceutical personnel carrying out the preparation, but also the personnel responsible in the pharmacy for purchasing, medical staff administering the cytostatic on the

wards and in medical practices, cleaning personnel and members of the fetch and deliver service, who dispose of the cytostatic wastes, and patients and their relatives.

The environmental impact should be kept to a minimum, not only in respect of the direct release of cytostatics but also with regard to emissions resulting from transport or incineration. The individual hospital must decide whether to dispose of slightly contaminated wastes with the household wastes, or to transport these considerable distances for subsequent incineration.

Compliance with all the statutory requirements is not always easy since, in addition to federal legislation, laws and ordinances of the *Länder* and local authorities must also be observed. If larger amounts of waste are produced, the size of the facility generally requires the mandatory appointment of a person responsible for wastes, who is in charge of planning and implementation. In cases of doubt, the responsible authorities must be consulted.

1. Statutory Requirements

Pursuant to the *Kreislaufwirtschafts- und Abfallgesetz (*law on recycling), the principles of waste disposal are:

- avoidance of waste
- recycling of waste and
- disposal of waste.

A central cytostatics preparation unit contributes to the principle of waste avoidance in that fewer cytostatics (approx. 13%) have to be discarded and it is also generally possible to save on single-use articles. Although the requirements of drug safety limit the extent to which recycling is possible, cost considerations alone mean that the work is organised in such a way as to minimise the amount of cytostatics that must be discarded. Cytostatics that can no longer be used and materials contaminated with cytostatics must enter a controlled waste disposal system. Controlled disposal comprises the collection, packaging, preparing, storing, transporting, handling, recycling and disposal of the waste up to the **final** disposal. Responsibility is carried by the originator of the waste.

In addition to the law on recycling, the laws on waste, protection against infection, safety at work, chemicals and dangerous goods must be observed, together with regulations under *Länder* law and local authority directives.

The current regulations for the disposal of cytostatic wastes are cited below:

***TRGS* 525 - "Technical rules for hazardous substances - handling hazardous substances in facilities for human medical care" (May 1998)**

5.7. Disposal

When disposing of CMR drugs, of their residues and of contaminated materials, the requirements of the waste disposal regulations in the respective *Bundesland* must be observed.

As specially controlled wastes, residual substances and residual solutions must - in accordance with the law on wastes - be collected in labelled, sufficiently robust, tightly closing containers and given for disposal.

Reusable laundry items or alternative textile reusable materials must be changed immediately on being soiled, collected without further manipulation and sent to the laundry for cleaning.

Information on the labelling of waste collection and transport containers is given in *TRGS* 201 "Labelling of wastes being handled".

Further information on the proper handling of wastes within the health service is provided by the *LAGA* (wastes association of the *Länder*) leaflet *Vermeidung und Entsorgung von Abfällen aus öffentlichen und privaten Einrichtungen des Gesundheitsdienst* ("Avoidance and disposal of wastes from public and private facilities within the health service").

Since loading of the filters cannot be excluded, protective measures analogous to at least Number 5.4 para. 2 should be taken as a precaution while replacing filters. The protective overall need not be waterproof.

When acquiring new workbenches, it must be made certain that the filters do not need to be cut apart for disposal.

Federal directive on the preparation of ready-to administer cytostatic solutions in pharmacies

Working group of senior medical officials (September 1998)

7 Disposal

7.1. The separation of cytostatic wastes into wastes which should preferably be given for incineration as hazardous wastes, and other wastes which arise from the handling of cytostatics and can be disposed of if necessary with domestic waste, is governed by the statutory requirements of the particular *Land* (*TRGS* 525).

7.2. Collection of contaminated wastes (including residual substances) in sufficiently robust, tightly sealing single-use containers (s. 36(6) No. 6 *GefStoffV* (hazardous substances regulations).

7.3. Labelling of waste containers in accordance with *GefStoffV* (s. 36(6) No. 7 *GefStoffV*; *TRGS* 201).

7.4. Contamination-free filter replacement as a result of expert, properly performed, supervised and documented disposal of filter elements. When acquiring new materials, filters must be selected that do not need to be cut apart for disposal *(TRGS 525).*

7.5. Proper decontamination of used equipment before scrapping.

Leaflet M 620 - Safe handling of cytostatics

Professional Association for the Health and Welfare Services (October 1998)

5.5 Protective measures during disposal

5.5.1 Protective measures during the disposal of residual substances and residual solutions
- *TRGS* 525 5.7 para. 1 and 2 cited -

The disposal of waste is regulated by the communities and local authorities in their statutory orders. The local regulations must therefore be observed when disposing of material contaminated with cytostatics. Because of the difficulties associated with disposal, it may be advisable to engage a professional enterprise in the region.

Cytostatic residues and materials contaminated with cytostatics can arise both during preparation and during administration:

Preparation
1. Residues of concentrated cytostatic solutions (injections)
2. Residues of diluted solutions (infusions, instillations)
3. Empty containers (original containers, administration kits)
4. Aids to preparation (swabs, underlays, protective gloves, etc.), administration
5. Cytostatic residues of injections what were not used completely for the patient
6. Infusion residues

In order not to expose third parties to unnecessary risk from waste containing cytostatics, the waste materials should already be collected as hazardous waste at the point of origin (cytostatics workbench, administration preparation point, administration) and transported appropriately in-house.

5.5.2 Protective measures during the disposal of body fluids and excretions

The legislating authorities do not classify body fluids (and products of excretion) from patients undergoing cytostatic therapy as hazardous substances in the sense of the *GefStoffV*. For reasons cf. Chapter 4 "Hazard determination" p. 11. The *TRGS* only perceives a possible danger requiring protective measures in the case of vomit after oral administration and products of excretion after high-dose therapy (cf. standard text *TRGS* 525, Chapter 5.2 (2) in the above Chapter 4 p. 11). However, on grounds of working hygiene it is generally advisable to at least wear protective gloves when disposing of body fluids and excretions.

Guidelines on the disposal of wastes from facilities of the health service, January 2002

LAGA (January 2002)

These guidelines replace the 1991 *LAGA* leaflet on the avoidance and disposal of wastes from public and private facilities within the health service. The guidelines are conceived as recommendations and give practical advice on the disposal of wastes from all facilities within the health service with the aim of ensuring safe and proper disposal of waste. They conform to EU law.

The two groups that are relevant for disposal during the handling of cytostatics are the wastes classified under waste code 18 01 04 and 18 01 08. These are compared below.

Waste Code (*AS*)	
18 01 04	18 01 08*
AVV ("Waste Index Directive")	
wastes whose collection and disposal are subject to no special requirements from the viewpoint of preventing infection	cytostatic and cytotoxic drugs
Waste classification (control category)	
must be controlled during disposal	must be specially controlled during disposal
Waste definition	
wastes contaminated with blood, secretions or excretions, such as wound dressings, plaster dressings, single-use garments, faecal incontinence collecting bags, disposable articles, etc.	CMR drugs according to *TRGS* 525; wastes consisting of residues or wrong batches of these drugs, or clearly seen to be contaminated (**heavily** contaminated) with CMR drugs.
EAKV 1996 ("old" waste code according to the directive for introduction of the European Waste Catalogue)	
18 01 04	18 01 05 D1*
LAGA Group (earlier classification according to *LAGA* as A to E)	
B	D
Places of Origin	
entire patient care sector	area of patient care with use of cytostatics and virostatics (e.g. oncology), pharmacies, medical practices, laboratory sector

Constituents	
wastes slightly contaminated with cytostatics such as: • swabs, • gauntlets, gloves, • respiratory protection masks, • disposable overalls, • plastic / paper material, • wiping-up cloths, • empty cytostatics containers after proper use (ampoules, syringe bodies without cannulae, etc.) • air filters and other slightly contaminated material from safety work benches	• not completely emptied original containers (e.g. arising as a result of discontinued therapy or cytostatics not used as specified), - • expired CMR drugs in original packaging, • residues of dry substances and broken tablets, • syringe bodies and infusion bottles/bags with clearly recognisable liquid levels / residual content (> 20 ml), • infusion systems and other material contaminated with cytostatics (>20 ml), e.g. pressure release systems and transfer systems, • material known definitely to be contaminated by the release of large quantities of liquids or solids during the preparation or administration of cytostatics (e.g. underlays, personal protective equipment).
Collection, Storage	
Collection in tear-proof, moisture resistant and tight containers. Transport only in carefully closed containers. No transfers to a different container (even in the central store), sorting or pre-treatment (except when submitted in press containers).	In type-tested, puncture-proof and unbreakable single use containers. No transfers to a different container or sorting. No pre-treatment. Transport and storage firmly closed.

Disposal	
Incineration in licensed waste incineration plant (domestic waste incineration) or landfill disposal if still permitted. If there are no objections on grounds of infection prevention or hygiene, containers with larger quantities of body fluids may be emptied into the sewage system (observe local authority water regulations).	Disposal as waste subject to special control with proof of disposal in licensed waste incineration plant, e.g. hazardous wastes incineration.

2. Disposal in Practice

Cytostatics wastes are divided into slightly and heavily contaminated wastes. Allocation to one of these groups has become much simpler as a result of the new *LAGA* guidelines.

Segregation from other types of waste is necessary for both groups. Sorting or transferring from one container to another is prohibited. Heavily contaminated wastes must be collected and transported in type-tested containers (*GGVS*) fulfilling specific standards (able to be disinfected, waterproof, impenetrable to cannulae, puncture proof, with lifting device, type-tested). Less contaminated wastes can be collected in tear-proof, moisture resistant and tight containers and disposed of with the household waste.

Labelling of the Containers

Containers for cytostatics wastes 18 01 08* must be labelled as follows:

Waste code 18 01 08*
UN designation as specified by the regulations for transport of dangerous goods by road, i.e.
UN 3249 (medicines, solid, poisonous, not otherwise named) or
UN 3291 (clinical wastes, unspecified, not otherwise named)
Originator of the waste

Although there are no labelling rules for containers with less contaminated wastes, an appropriate label is still recommended for in-house transport.

Air Filters

According to the *LAGA* guidelines air filters from safety workbenches can be allocated to the less contaminated wastes. These are certainly contaminated, but the level of contamination should be low if the work is performed carefully. It is therefore no longer necessary to transport the filters in type-tested transport containers to a hazardous wastes incineration plant for disposal. As a result, it is possible to dispense with the complicated sawing apart of these filters which was necessitated by the transport containers having a maximum capacity of 60 l. Transport can take place in thick, tear-proof and adequately large sacks.

From the aspect of safety at work, the "German Hospitals Association" also recommends having contamination-free filter replacement performed with appropriate precautions (e.g. encapsulation) by trained personnel.

The design of new workbenches complying with DINB 12980 makes contamination-free filter replacement more easily possible.

Safety Workbenches

Defunct safety workbenches which were used for the preparation of cytostatics are generally slightly contaminated in the same way as air filters. A decision must be made in each individual case as to whether for practical considerations they can be allocated to the less contaminated wastes and scrapped after being cleaned by informed and trained personnel. As yet there are no standardised concepts.

Excretions

Cytostatics can be excreted in high concentrations over a long period and excretions are therefore generally contaminated. Some cytostatics are unstable and rapidly inactivated; others can be detected for a long time.

It is recommended that excretions be flushed into the sewage system with generous quantities of water. Care should be taken to avoid the possibility of contamination. This means that the cleaning personnel on the ward, and the patients and any relatives, should be appropriately informed and should wear gloves when handling excretions.

Disposal Plan

Although a disposal plan is not mandatory until the quantities of controlled wastes have reached a certain level, the disposal of all cytostatics should be regulated and documented.

The following points must be observed:

- which wastes are produced
- where the wastes originate (at a few centres - distributed over many wards)
- spatial requirements (transport routes, fetch and deliver service)
- centralised or distributed disposal (transport of wastes in the case of a central disposal system)
- classification of the wastes produced (the more people are involved, the simpler should be the classification)
- communal rules
- information and training of the persons involved (how often, who presents the information).

All participants should be involved from the start (e.g. person responsible for wastes, pharmacists, medical personnel, hygiene department, etc.)

References:

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4. Cass Y, Musgrave CCF. Guidelines for the safe handling of excretions contaminated by cytotoxic agents. Am J Hosp Pharm 1992; 49; 1957-1958

5. Kaijser GP, Underberg WJM, Beijnin JH. The risks of cytotoxic drugs. II Recommendations for working with cytotoxic drugs. Pharm Weekbl (Sci) 1990; 12: 228-235

6. Kraft U. "Problems of waste disposal in the hospitals". Das Krankenhaus 1998: 683-686

7. *LAGA Richtlinie* (*LAGA* Guidelines) (http://www.laga-online.de)

8. Mehrtens T. "Handling excreta after cytostatics therapy". Krankenhauspharmazie. 2000; 21: 148

9. Pilz T. "Application of the European Waste Catalogue". Das Krankenhaus 1998: 678-682

10. Schaaf D. „Disposal of drugs and cytostatics in the hospital". Krankenhauspharmazie 1990; 11: 183-184

11. Schaaf D. „Handling cytostatics". Krankenhauspharmazie 1994; 15: 588-591

12. Scherrer M, Daschbner F, Strehl E, van Gemmern R. „Cytostatics: handling and disposal". Krankenhauspharmazie 1997; 18: 176-178

4.2. Decontamination after Inadvertent Release

Every pharmacy must have a hazard defence plan listing measures to be taken after an inadvertent release. This plan is prepared on the basis of a risk analysis and must contain instructions for preventing damage to persons and the environment.

One component of the hazard defence plan is specifying the existence of a decontamination set, also know as a spill kit. This spill kit must be available in all the areas where cytostatics are handled. The responsibility for installing and maintaining spill kits is ideally carried by the pharmacy as a central unit.

The spill kit includes:

- **instructions for performing the primary decontamination**
- **marking material**
- **single-use overall or gown**
- **overshoes**
- **respiratory protection mask (P3)**
- **protective gloves**
- **additional pair of protective gloves providing adequate mechanical protection against glass splinters**
- **protective eyewear with side protection, which can be worn over personal eyewear**
- **disposable cloths and wadding**
- **water and ethanol for dampening**
- **aids for collecting up broken glass**
- **adequate number of robust waste containers**
- **form for documentation of an accident**

The removal and disposal of spilled cytostatics may be performed only by properly instructed personnel.

The procedure to be followed after inadvertent release is part of the working rules and the annual instruction.

Simone Melzer, Hamburg
Ludwig Metz, Munich

Decontamination of persons has priority and must always take place first.

All staff handling cytostatics must be taught the theoretical knowledge and practical skills necessary for acting correctly in the case of contamination (see Chapter 1.3. Working rules and Instruction). For teaching the practical skills required it is essential to carry out the removal of a "test contamination", including donning the protective garments (see Chapter 2.3.3. Respiratory Protection, Protective Eyewear, Overshoes").

Written instructions listing briefly and clearly the actions to be taken in the event of an incident must be displayed in all the areas where cytostatics are handled. The actions described must be the subject of regular training.

The immediate actions to be taken and the proper disposal procedure to be followed after spillage of cytostatics are listed in *TRGS* (technical rules for hazardous substances) 525 and in s. 36 (6) (8) *GefStoffV* (hazardous substances regulations).

The following rules are given in *TRGS* 525 under Point 5.5 "Actions on inadvertent release of CMR (carcinogenic, mutagenic, reprotoxic) drugs":

(1) Contamination through spilled CMR drugs (dry substances, broken tablets, preparations) must be properly removed immediately. Disposable cloths or wadding are suitable for taking up the substances. If dry substances are spilled, the material used to collect them up must be dampened.

(2) If skin is contaminated with CMR drugs it must be flushed immediately with copious amounts of cold, running water.

(3) Splashes in the eyes must immediately be rinsed for at least 10 minutes with copious amounts of water or isotonic saline solution. An ophthalmologist must then be consulted without delay.

(4) Contaminated broken glass must be collected up using appropriate aids and an additional pair of gloves must be worn providing protection against mechanical hazards.

(5) The contaminated surfaces must then be cleaned.

S. 36 *GefStoffV* is less specific, but under (6) (87) summarises in general terms that suitable precautions must be taken for emergencies in which employees can be exposed to unusually high concentrations of carcinogenic hazardous substances.

Decontamination Set - Spill Kit

Spill kits can be put together individually by the user or purchased pre-assembled.

The protective clothing to be worn while removing contamination from surfaces consists of a liquid repelling overall or single-use gown, overshoes, respiratory protection mask (fine dust filter mask P3 (see Chapter 3.2.3.1. Respiratory Protection)), protective gloves (if there is broken glass a second pair should be worn over these, which are thick enough to provide protection against fragments of glass, e.g. household gloves), and protective eyewear (with side protection and capable of being worn over any personal eyewear (see Chapter 3.1.3.2. Protective Eyewear)).

Contaminated surfaces must be secured immediately to avoid further persons being endangered as a result of contamination being carried elsewhere. The area can be marked using chalk, for example. Putting up a warning notice is particularly necessary in areas which are relatively freely accessible (e.g. wards, medical practices, goods delivery areas in the pharmacy, etc.)

In addition, action must be taken to prevent draughts and air currents (ventilation, door) in areas where the contamination includes powdered material.

Spilled liquid is taken up using disposable cloths with a high capacity for binding liquids. In order to guarantee protection against further carry-over, cloths with one liquid-tight side are to be preferred.

For binding the liquid, granulated material can be used which forms a gel structure on being wetted by the liquid. The liquid is thereby bound and should be easier to gather up. In practice, collecting up the mass of gel is difficult because it tends to fall apart.

In order to avoid powdered cytostatics being swirled up during decontamination, the material used to collect them must first be dampened with water.

Any kind of water (e.g. tap water) can be used for dampening. If the spill kit does not include water, rapid access to water should be ensured for the area concerned.

If the spill kit does contain water, this should be sterile for hygienic reasons.

A scraper and dustpan are suitable aids for collecting broken glass safely; a brush should never be used in view of the danger of swirling up. All the articles used must be single-use.

All contaminated articles and broken pieces must be collected in a suitable waste container. When choosing the waste container it must be borne in mind that it may be necessary to dispose of broken glass. If using a waste bag, this must be of adequately strong material. These waste containers are disposed of as cytostatic waste (Chapter 4.1. Waste Disposal).

The contaminated surfaces must be thoroughly cleaned. During studies on the decontamination of primary packaging material the following two-stage procedure produced the best results: first cleaning with aqueous 0.05 M NaOH solution, followed by 98% isopropyl alcohol [1].

In order to avoid uncertainty during cleaning, it may be useful to place small containers of the cleaning solutions with the decontamination set. In any case, the instructions must include information about the cleaning agents, stating the name of the product and the concentration at which it is used.

Although chemical inactivation of cytostatics is possible in principle for many substances and has been described ([2, 3]), this demands detailed knowledge of the method (what with, how much, how long). Since the risk presented by the decomposition products formed cannot be estimated exactly and performing the inactivation in practice makes the decontamination procedure very complicated, the use of chemicals cannot be recommended.

Spill kits are used for clearing up smaller quantities of inadvertently released cytostatic substances or solutions. If larger quantities of CMR substances are set free, action must be taken according to the applicable alarm or catastrophe plan.

A reprint of the instructions for a spill kit developed in collaboration with the *ESOP* and the *DGOP* is presented in the appendix as an example for the possible layout of instructions for use.

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Instructions - Using the Spill Kit

Basic Principles

The contents of this spill kit enable small quantities of dangerous drugs, e.g. cytostatics, to be cleared up safely.

The spill kit may only be used by persons who have previously undergone a qualified, documented training course about handling dangerous substances and using the spill kit.

The respiratory protection mask only offers optimal protection if someone with appropriate knowledge has given instructions on how to wear it and the mask has been fitted properly. Instructions must also be given for wearing the other protective garments.

In every case of spillage the supervisor will decide whether the contents of the spill kit are suitable for clearing it up.

Procedure

If small quantities of cytostatics are spilled, the area in which the cytostatics or other dangerous drugs have been spilled must be secured immediately to prevent non-participants from entering this area. The enclosed warning sign can be used for this purpose. Contaminated persons must be cared for immediately. The spill must be reported to the supervisor without delay. The supervisor then takes command of the local situation. Contaminated surfaces are cleaned using the spill kit, which must be present in every area where hazardous substances are handled. The employee(s) selected to clean the contaminated area take(s) the protective garments from the spill kit and dons them in turn. A full protection suit, two pairs of nitrile gloves (two gloves for each hand), one pair of thick overshoes (3 gloves for each hand), protec-

tive eyewear, a respiratory protection mask, overshoes and a cap are provided for every cleaning operation. (Instruction must be given on wearing the protective garments.)

After the protective garments have been donned and everything fits properly, the cleaning material is taken out of the spill kit: one dustpan, one piece of cardboard, cleaning cloths, bags, cable ties, chalk and warning sign for securing the area.

The employee(s) performing the cleaning (instruction and training must have been given beforehand and cleaning may only be performed by persons with appropriate knowledge) now enter(s) the area and mark(s) out the contaminated part with chalk if this is necessary.

It must be ensured that no item of protective clothing is contaminated by cytostatics. This also applies for gloves. The dustpan and cardboard must therefore always be used for picking up anything at all.

The areas contaminated with liquid are cleaned using the enclosed absorbent cleaning cloths. Wiping must always be carried out from the outside inwards in order not to spread the contamination over a wider area. Glass splinters should be collected up first using the dustpan and cardboard and placed in the enclosed bag. The cloths are then placed in the bag as well and this is closed securely with the cable ties to prevent any further contamination.

If powder has been spilled, the dampened paper towel is laid upon it to prevent dust being swirled up.

The area is then cleaned in stages. A rough cleaning is followed by subsequent cleaning (disposable paper towels) with tensides or household cleaners. Absolute cleanliness must be achieved since even the smallest quantities of cytostatics can cause problems.

After the contamination has been completely removed, the entire area is then subjected to normal cleaning.

Waste Disposal

All wastes are placed in the plastic bags which are then tightly sealed using the cable ties. The plastic bags are immediately placed in designated cytostatics waste containers.

The garments are also placed in these containers in the following order: first the outer pair of gloves, then the cap (if the overall itself does not have a cap), then the overshoes; the overall is then taken off and finally the gloves are placed in the container. The container must be capable of airtight closure and it may not be opened again. This container is then given for waste disposal and labelled according to the normal regulations.

Release of the Area, Cleaning, Documentation and Replacement

The area is released by the supervisor.

The employees who have cleaned the contaminated area must clean themselves thoroughly. The spill must then be documented in writing and measures specified for preventing future spills. Every hospital may use its own form for documentation.

A replacement spill kit must be acquired after every incident.

4.3. Extravasation (Paravasation)

The unintended escape during intravenous cytostatic therapy of cytostatic agents with necrotising potency into surrounding tissue represents a serious complication demanding immediate treatment.

Guidelines for prevention, an action catalogue for treatment and a form for documenting treatment given for an extravasation must be at hand in all oncology wards and units providing therapy.

A kit for immediate treatment of an extravasation containing all the materials and medicines necessary for the recommended action must be available on the ward in an openly accessible place.

Kathrin Simon, Auckland and **Tilman Schöning**, Heidelberg

A possible complication occurring during intravenous cytostatic therapy - a complication which is frequently paid little heed to at the start of treatment - is the danger of extravasation. Extravasation means instillation or escape of a drug solution into perivascular spaces and subcutaneous tissue during administration.

Even the smallest quantities of a necrotising drug outside the vein may lead to serious consequences if suitable treatment is not initiated immediately. Severe ulceration, necrosis and pain to the skin may occur, which can result in tissue atrophy with damage to nerves and joints and loss of function of the extremities involved. Skin transplantation or even amputation may become necessary if immediate action is not taken or the measures initiated do not produce the desired effect.

Statements about the incidence of extravasation are difficult to make. The data available in the literature are inhomogeneous and vary between 1% and 6%, whereby the frequency increases in line with the risk factors for individual patients such as advanced age, long-term cytostatics therapy or previous radiological treatment.

The nature and scope of the local damage depend upon the properties of the cytostatic substance (which can be classified as "non tissue-damaging", "tissue-irritating" or tissue-necrotising"), the inactive ingredients and the quantity of substance released.

Classification of Cytostatics according to their Necrotising Potency

Non tissue-damaging cytostatics

These include all the hormones and proteins used in oncology, almost all the antimetabolites and a few alkylating cytostatics.

L-asparaginase	ifosfamide
bleomycin	interferones
carboplatin	irinotecan[1]
cladribin	methotrexate
cyclophosphamide	nimustine[1]
cytarabine	pegaspargase
estramustine[1]	pentostatin
etoposide phosphate1	raltitrexed
fludarabine	thiotepa
5-fluorouracil	topotecan
goserelin	

Irritants, tissue-irritating cytostatics

These cytostatics are usually associated with an inflammation after paravenous injection but do not cause necrosis. Necrosis may occur if very concentrated, larger quantities of the substances listed run paravenously.

bendamustine[1]	fotemustine
busulfan	gemcitabine
carmustine	melphalan
cisplatin (< 0.4 mg/ml)	oxaliplatin[1]
dacarbazine	streptozocin[1]
daunorubicin liposomal[1]	teniposide
docetaxel	treosulfan
doxorubicin liposomal[1]	trimetrexate[1]
etoposide	

Vesicants, tissue-necrotising cytostatics

These cytostatics exert a necrotising effect	
amsacrin	mitomycin C
cisplatin (> 0.4 mg/ml)	mitoxantrone
dactinomycin	paclitaxel
daunorubicin	vinblastine
doxorubicin	vincristine
epirubicin	vindesine
idarubicin	vinorelbin

1) The available data is insufficient to allow classification of the substance to be evaluated completely.

The therapy suggestions presented below are of an empirical nature and are no more than recommendations. They are based on data from animal studies and collected and evaluated individual clinical reports. The material is a summary of data published on the treatment of extravasation and may not be regarded as an established therapeutic standard. The therapy recommendations are liable to be updated at any time as a result of new results.

Prevention of Extravasation

1. Injections only by experienced, qualified personnel

2. By means of a patient information sheet the patient should be encouraged to report all symptoms, such as pain, stabbing, burning or reddening.

3. The extremities should be immobilised during the administration.

4. Wherever possible, central accesses or thick veins should be used. Accesses on the back of the hand, near joints, and in areas of local circulatory disturbances should be avoided. Because of the danger of irreversible functional disturbances after an extravasation, the wrist and elbow are not suitable. There should be no multiple injections.

5. The use of gentle, thin venflons is recommended (no steel cannulas!)

6. The proper placement of the cannula should be tested beforehand by administering 5 % glucose or 0.9% saline solution, or by the aspiration of blood. There should be no detectable resistance.

7. For peripheral administration the vesicant should be administered as soon as possible after insertion of the cannula so that the vein is still in a healthy, non irritated state.

8. The drug with the highest necrotising potency should be administered first wherever possible.

9. Avoid haste during the administration.

10. In order to reduce the concentration of drug in the vein, NaCl 0.9% or G 5% can be flushed after the administration of the drug.

Possible Symptoms of an Extravasation

- Pain, burning (not a feeling of coldness) in the region of the injection site
- Swelling
- Reddening (erythema)
- Reduction in the speed of infusion, resistance during the injection
- Little or no blood can be aspirated

Instructions for Treating Cytostatics Extravasations

When treating extravasations a distinction must be made between general and specific measures. General measures are actions that are always taken in the case of peripherovenous access, whereas specific measures are actions taken in dealing with particular tissue-irritating and tissue-necrotising cytostatics:

1. Stop injection/infusion immediately; leave i.v. access in place.
2. Notify a person experienced in handling cytostatics.
3. Put on sterile gloves.
4. Disconnect infusion line or syringe from the i.v. access.
5. Mark the area of the extravasation with a waterproof marker.
6. Connect a 5 ml syringe to the i.v. access and aspirate as much of the cytostatic as possible. Do not exert any pressure on the extravasation area while doing this. Dispose of the syringe and contents as infectious waste. Close the access with a red combination stopper.

7. Use a tuberculosis syringe and G26 cannula to aspirate the contents of any blisters which have formed near the site of the extravasation. Use a fresh cannula for each site of injection.
8. Elevate and immobilise the affected extremity.
9. Substance specific measures: Consult the accompanying table to determine whether a specific antidote exists for the cytostatic agent concerned. Administer the antidote using the i.v. access if still in place. If this is no longer in place or if infiltration is indicated, administer the antidote intra- and subcutaneously in a star-shaped pattern from peripheral to central in the area of the extravasation. Use G26 cannulas to do this. If different antidotes are indicated, these are administered successively through the same cannula. Then remove the i.v. access.
10. In the case of mild inflammatory erythema hydrocortisone cream 1% can be applied twice daily.
11. Cover the area of the extravasation with sterile compresses and fix these in place with Leukosilk.
12. With the exception of extravasations with vinca alkaloids, apply ice packs for 15 minutes 4 times daily for at least three days.
13. In the case of extravasations with vinca alkaloids, etoposide and teniposide, on the other hand, dry, gentle heat is applied once for a period of 60 minutes.

Substance Specific Measures

Cytostatic	Antidote
doxorubicin daunorubicin epirubicin idarubicin dactinomycin mitomycin C mitoxantrone amsacrin cisplatin	1. Apply dimethyl sulphoxide (DMSO) 99% to the entire extravasation area every 3 - 4 hours for at least 14 days using a sterile cotton wool applicator without exerting pressure and allow to dry in the air.[1] The extravasation area treated should be twice as large as the actual extent of the extravasation. 2. Optionally local cooling for pain relief.
vincristine vinblastine vindesin vinorelbin	1. Infiltrate hyaluronidase, up to 1500 IU, into the area of the extravasation. 2. Gentle, dry heat therapy, initially for 60 minutes, then for 20 minutes four times daily.
paclitaxel	Infiltrate hyaluronidase, up to 1500 IU, into the area of the extravasation.

1) Do not "soak" the affected area of skin with DMSO but only paint it with the applicator. Too much DMSO increases the permeability of the skin so that the cytostatic is absorbed more strongly.

14. Document the extravasation and the actions taken (see documentation sheet).
15. Keep the extravasation area under careful observation and in the case of tissue-necrotising cytostatics contact a plastic surgeon in good time for operative removal of the necrotic tissue.

The exact volumes of antidotes to be administered must be determined individually based on the extent of the extravasation.

On the oncological wards there is generally very little knowledge about this kind of adverse effect, about the cytostatic agents causing it, about preventive measures or - above all - about how an extravasation must be treated. In this context the pharmacy can offer support and attempt to remove the uncertainty concerning the therapy.

What possibilities for supportive intervention are open to the clinical pharmacist?

Introduction of an Extravasation Kit on every Oncological Ward

The introduction of such an emergency kit enables the physicians giving treatment and the nursing staff to intervene quickly and contributes towards preventing serious consequences.

Contents of the Extravasation Emergency Kit

• DMSO "purest" Merck 16743[2]	50 ml
• hyaluronidase 150 IU (Hylase Dessau®)	10 ampoules
• hydrocortisone cream 1%	30 g
• physiological saline solution 0.9% 5 ml	1 ampoule
• tuberculosis syringe 1 ml	3
• single-use syringe 2 ml	1
• single-use syringe 5 ml	2
• gloves, sterile, medium size	1 pair
• cold/hot pack	1 pc.
• single-use cannulas 26G	10 pcs.
• cotton balls, sterile	8 pcs.
• compresses, sterile	6 pcs.
• Leukosilk tape	1 roll
• applicator with cotton wool	5 pcs.
• combination closure, red	2 pcs.
• recommendations for general and specific actions	
• documentation form	

2) DMSO "purest" 99.9%, only available from MERCK for laboratory use
DMSO 70%, Kemsol® Horner, Canada
DMSO 50%, Rimso Solution®, UK

Further Training Seminar for Introduction of the Emergency Kit

Further training courses for physicians and nursing staff on the individual wards provide an opportunity to go into greater detail about the recommendations given and to discuss further information, e.g. concerning prevention and documentation. Answers can also be given to the numerous questions from practice which arise during these discussions.

Publication of the Recommended Rules for Dealing with Extravasation within the Hospital

The information can be disseminated in diverse ways, e.g. through publication in the hospital newsletter, through an information page in the internal hospital network, by deposition in the in-house list, or through introduction of a poster about the most important actions to be taken in the case of an extravasation. By means of the poster, for example, the emergency information has a permanent presence on the ward and can help to prevent possible delays in applying therapy caused by long searches for the information or even for the emergency kit itself.

Documentation and Reporting Incidents

Efforts are being made at both national and international level to document extravasations and their consequences, and the therapy used and results obtained. This may eventually lead to a catalogue of statistically verified therapeutic actions. The kit should therefore contain a documentation form in which an account of the extravasation incident is recorded, giving information on the patient, the symptoms, the kind of treatment and the results of the therapy.

One copy of the documentation sheet should be sent from the ward to the pharmacy. The documentation can be anonymous. It is not compulsory and its purpose is to continue to develop the existing recommendations and to base these on a wide collection of data.

Attempts are currently being made to create a network for evaluating the forms and developing the standard further. The completed documentation forms can be sent to the following address for anonymous recording and evaluation.:

Ms. Mag. pharm. Patrizia Fürst-Weger, c/o Sozialmedizinisches Zentrum Floridsdorf, Krankenhaus und Geriatriezentrum, Apotheke, Hinaysgasse 1, A-1210 Vienna Tel.: 0043 1 27522-5501, Fax: 0043 1 27522-5509, e-mail: office @paravasate.net

The Pharmacy as Coordination Point in Cytostatic Therapy

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4.4. Chrono-Oncology

Chrono-oncology is a method of treatment in which the times of administering cytostatic drugs are chosen in relation to the natural biological rhythms of the patient with the therapeutic goal of improving the bioavailability and efficacy of the cytostatic while reducing its adverse effects at the same time. Insofar as clinical data are available, experience gathered in the field of chrono-oncology is used for the benefit of the patient in the sense of optimising the relationships between dose, effectiveness and adverse effects.

Claus Roland, Flensburg

Chrono-oncology is a circadian scheduling of cytostatics (administration at particular times of the day) with the aim of increasing the medicinal effect and/or reducing the cytostatic-related side effects by taking advantage of the biological rhythms of the human body. The efficacy of a cytostatic agent and the extent of its adverse effects also depend on the time at which it is administered. This phenomenon arises from differences in sensitivity rhythms between normal tissue and tumour tissue.

Many bodily functions are subject to rhythmical changes. In this respect, distinctions are made between a circadian (24-hour rhythm, e.g. hormones such as corticosteroids or growth factors), an ultradian (less than 21 hours), a circaseptian (longer than 1 week), a circamensual (longer than a month, e.g. the menstrual cycle) or a circaannual (longer than a year) rhythm. These rhythms are controlled by "biological clocks", so-called oscillators, which can in turn be influenced by environmental factors (timers). Parameters such as the pH of the urine and the concentrations of electrolytes, glucose, hormones (cortisol) and enzymes vary with the time of day. The existence of circadian rhythms has also been demonstrated for body temperature, pulse rate, blood pressure, blood supply to different organs and renal and hepatic function. The cytosynthetic activity of specific tissue systems, for example the mucosal cells of the intestine and cells of the haemopoietic system, has also been found to depend on the time of day. Adverse effects occurring in just these tissues frequently hinder the optimisation of cytostatic therapy.
The aim of chronotherapy with cytostatics - or chrono-oncology - is to exploit the phenomenon of differences between tumour tissue and normal tissue in their time-of-day dependent cell division activity, to integrate into a therapeutic concept the

dependence on the time of day of cell division activity of specific cell systems, of cytostatic efficacy and of the kinetic properties of cytostatics with the option of increasing the effect of the drug and/or reducing the level of adverse effects. The result of this improved methodology (administration at specific times) is an improvement in the therapeutic index. This means that it is possible to achieve a stronger effect with a higher dose of cytostatic while keeping the adverse effects at the same level. This in turn leads to a greater probability of an improved tumour response rate.

The important mechanisms of chrono-oncology leading to more efficient therapy are:

1. Chronopharmacodynamics

The effect of cytostatics depends on the time of their administration. Administering drugs at the correct phase improves the therapeutic index of cytostatics. Some of the causes of changes in pharmacological processes are:

- circadian variations in the number, density and affinity of the receptors
- changes in membrane permeability
- different properties of cellular defence mechanisms, e.g. the glutathione level
- intra- and extracellular changes of pH with the time of day
- intra- and extracellular fluctuations in the concentrations of the cytostatics administered depending on the blood supply to the tumour tissue
- interactions of cytostatics with the body's own hormones (corticosteroids, interferons, interleukins, TNF) depending on their circadian concentrations. Interactions of this kind may lead both to potentiation and to attenuation of the effect.

2. Chronopharmacokinetics

Kinetic processes such as adsorption, plasma concentration, distribution volume, metabolism and excretion are subject to fluctuations dependent on the time of day. The influence exerted by the time of day on kinetic processes arises because:

- The enzymatic activity of many metabolising enzyme systems (Phase I reactions), including the cytochrome P-450 enzyme system, depends on the time of day and this in turn affects the toxicity of cytostatics both positively and negatively. The same applies for activating enzymes and for Phase II metabolising processes such as glucuronylation and sulphation reactions. The enzyme dehydropyrimidine dehydrogenase (DHPD), responsible for the degradation

of 5-FU, possesses a different enzyme activity depending on the time of day. It is possible to influence the therapeutic index of 5-FU by means of a sinusoidal adaptation of the dose to the enzyme activity of DHPD (lower doses at times when the enzyme activity is lower, and vice versa).

- The different activities of hepatic and renal function at different times, which in turn affect absorption, metabolism, excretion and volumes of distribution.
- The circadian changes in plasma protein concentrations causes fluctuations in bioavailability, e.g. for cisplatin.

3. Chronocytokinetics

Determination of how the synthetic activity of the cells of healthy and tumour tissue depends on the time of day.

Only very few tumours differ from healthy tissue in respect of the synthetic activity of their cells. However, ovarian carcinoma [2] and malignant lymphoma have developed their own biorhythms. The acrophase of the DNA synthesis activity for non-Hodgkin lymphoma [3] occurs at night, whereas it occurred during the day for healthy subjects. There are currently very few clinical results available, however. Clinical benefits for the patient are limited since practical and ethical reasons prevent acquisition of the necessary series of biopsies. It has also been found that slowly growing tumour entities have a similar circadian rhythm to healthy tissue, whereas rapidly growing tumours have largely lost their circadian regulatory principle. The loss of this circadian regulatory principle is frequently an indication of the progression of the disease. Moreover, temperature fluctuations on the surface of the skin in the case of carcinomas of the breast take place with a maximum approximately 6 hours earlier than the healthy breast [4].

4. Chronotoxicity and Chronoefficacy

Reducing the toxicity and/or increasing the effectiveness of cytostatics are the results of consistent exploitation of chronopharmacological, chronocytokinetic and chronopharmacokinetic mechanisms. The optimal time of administration can be determined by means of animal experiments. This involves keeping the animals under standard conditions of light and darkness (HALO = hours after light onset). Data is recorded using lethality studies with the administration of defined doses of cytostatics at different times of day (generally in a 4-hour rhythm). The time at which the proportion of surviving animals was at a maximum reflects the optimal time of administration. The basic data obtained can be extrapolated to humans using a time correction factor. Up to now, the effect of chronotoxicity or chronoefficacy has been demonstrated for more than 30 cytostatic agents.

Thus it was found in a non-randomised study of children with ALL that for equal dosage of the same substances (6-mercaptopurine and methotrexate) the 5-years survival rate was 80% for evening administration of the two substances and only 40% for morning administration [5].

Table:

Substance	Tumour model	Optimal time (HALO)	Parameter for efficacy	Effect through time of administration
cyclophosphamide	mammary carcinoma	8	tumour regression	considerable
cyclophosphamide	T9, T10 sarcoma	2	rate of healing	13-14%
cyclophosphamide	L1210 leukaemia	12	rate of healing	27%
ARA C + cyclophosphamide	L1210 leukaemia	10	rate of healing	20-50%
ARA C	L1210 leukaemia	8	rate of healing	18%
melphalan + doxorubicin*	13762 mammary-carcinoma	10	rate of complete remission	38%
cisplatin + doxorubicin*	plasmacytoma	18	survival	30%

All studies were performed on the mouse or the rat.

* For these cytostatic combinations the substance named second was given at the optimal time and the first-named at different times selected at random.

The largest number of studies have been carried out by the Lévi group (Paris) who have concentrated on 5-FU/Ca folinate and oxaliplatin, especially with metastasising carcinoma of the colon. In this work oxaliplatin 25 mg/m2 is administered on Day 1 - 4/5 from 10.00 a.m. to 10.00 p.m. with the peak at 4.00 p.m., together with 5-FU 600 - 1100 mg/m2 and Ca folinate 300 mg/m2 on Day 1 - 4/5 from 10.00 p.m. to 10.00 a.m. with a peak at 4.00 a.m. [8, 9, 10].

The most important results of a randomised multi-centre study, which compared a conventional therapy with a chronomodulated therapy given to 186 patients with metastasising carcinoma of the colon, are presented below [7]:

Cytostatics with the following action profile are especially suited for circadian administration:

Effect	Conventional	Chronomodulated	P
Hospitalisation because of toxicity	31*	10	0.001
Mucositis	76	14	0.0001
Functional impairment (peripheral neuropathy)			
Tumour response >50%	29	51	0.003

*patients in percent

from Lévi F,Zidani R Misset JL for the international Organisation for cancer chronotherapy. Randomized multicenter trial of chronotherapy with oxaliplatin, fluorouracil, folinic acid in metastic colorectal cancer. Lancet 1997;350:681-686

Substances
- with a broad activity against many types of tumour
- which exhibit strong dependence between tumour response and dose intensity
- which have a narrow therapeutic range and
- which have excellent tumour activity at high or very high doses but also high levels of adverse effects.

Improving the therapeutic index by means of the chronomodulation of cytostatics and the associated improvement in quality of life should be regarded as a therapeutic option or a therapeutic alternative, especially if intolerable side effects occur during the chemotherapy. In this context, Focan carried out a pharmaco-economic study for the substances Ca folinate / 5-FU (high dose) which revealed that despite the higher costs in the chrono-modulated arm incurred as a result of a greater outlay for the administration, the overall costs were less with chrono-modulation because of lower costs for treating the side effects of the therapy [6].

Conclusions:

The improved therapeutic index generates the following benefits of chrono-oncology:
- reduced adverse effects from cytostatics and/or increased quality of life
- specific cytostatic combinations can lead to an improved tumour response rate
- economically reasonable in view of lower costs of side effects needing treatment
- the creation of new therapy options since the opportunity arises to combine substances with each other which would otherwise not be readily combinable on account of their side effect spectrum.

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4.5. Handling Cytostatics on the Ward

Handling drugs containing cytostatics in the inpatient sector is largely the responsibility of nursing staff and doctors. This applies to receiving and storing the drugs, making them ready for administration, the administration itself, dealing with excreta (which may also concern the patient's relatives) and the management of inadvertent spills.

The pharmacist for oncological pharmacy supports the wards and the functional units of the hospital by preparing handling instructions for the procedures involved in order to facilitate safe working methods and the proper use of protective equipment.

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In the inpatient sector cytostatics are handled by nursing staff and doctors. Members of the nursing staff are involved during receipt of the ready-to-administer cytostatics, during delivery and subsequent storage of the preparations, during making ready for administration, during the treatment and care of the patient and disposal of materials no longer needed, and in the event of inadvertent spillage.

Handling of cytostatics on the ward by doctors primarily involves the administration of drugs for parenteral use. Relatives helping to care for the patient may also be involved if they come into contact with the patient's excreta. Cleaning personnel can also be given the task of clearing up inadvertent spills. Debatable is the relevance of danger to physiotherapists, who may come into contact with quantities of substance eliminated through the patient's skin.

For the particular tasks performed by all these groups, handling instructions are needed describing safe working techniques and proper use of the protective equipment. These instructions should be prepared with the focus on hygienic procedures and personal protection.

In addition, working rules must be drawn up for handling cytostatics on the ward and oral instruction appropriate to the particular workplace must be given annually (see 1.3. Working Rules and Instruction). The working rules can be supplemented with standard operating procedures. On the basis of his specialised knowledge

(which is expressly referred to in *TRGS* (technical rules for hazardous substances) *525),* the pharmacist can provide assistance in preparing the working rules and in giving instruction. Needless to say, the responsibility rests with the line supervisor.

Delivery of the Cytostatics (see also 3.7. Delivery of Cytostatics) and Keeping and Storing on the Ward

The ready-to-administer cytostatics are delivered sealed in plastic film in specially labelled containers that are unbreakable, liquid-tight and closeable. These boxes arrive at the ward and are accepted by personnel with appropriate knowledge. The tasks to be performed by these personnel include checking the delivery for completeness and bringing the products to the correct place where they will be kept or stored in accordance with the name on the label. The place chosen for keeping or storing cytostsatics must be separated from other drugs and products. For storage in the refrigerator a separate compartment must be provided, preferably in the bottom drawer, so that other products cannot be contaminated as a result of liquids leaking out.

Since it is known that the outside of the cytostatics containers may be contaminated and, despite careful working, cross-contamination of ready-to-administer preparations can never be completely ruled out, gloves should be worn when removing from the outside packaging.

Making Ready for Administration

Cytostatics are used in various pharmaceutical forms.

During everyday routine on the ward, most of them are administered parenterally as infusions or injections. These forms, and also rinsing liquids, solutions for instillation and drugs for treating the eye are delivered from the pharmacy ready-to-use since these are sterile formulations prepared in the pharmacy under aseptic conditions.

Orally administered medicines, on the other hand, are made ready on the ward in most hospitals. Capsules, tablets and liquid oral formulations such as drops or syrups must be made ready for administration. Dermatics, such as ointments, creams or solutions, are in most cases supplied by the pharmaceutical manufacturer ready to apply.
If it is still necessary to make certain cytostatics ready on the ward, this should be carried out in a quiet place to avoid disturbance to the person doing the work. The material of the work surface should be easy to clean. The person performing this task must wear appropriate protective garments.

Orally Administered Drugs - Solid Forms

TRGS 525 stipulates the use of forceps or a spoon for dividing solid formulations for oral administration.

Coated formulations such as film-coated tablets, capsules or dragees should preferably be used since the coating minimises the risk of contamination. Capsules should not be opened and tablets should not be divided or crushed in order to avoid the content becoming dust. If dividing is necessary on grounds of dosage, the required dosage in an appropriate form should be ordered from the pharmacy.

If dividing is unavoidable and must take place on the ward, this should be done with a separate tablet cutter kept exclusively for this purpose. This can also be placed inside a clip-closure bag and the dividing performed inside the closed bag.

In rare and exceptional cases it is necessary to prepare CMR drugs for administration by means of a tube. A number of different techniques are available. The simplest, though unsuitable for coated tablets, is to place the tablet in a syringe which is then used to take up liquid which forms a suspension with the tablet.

Crushing solid formulations into a uniform powder must only take place inside a closed unit. Tablet cutters from different manufacturers (Fig. 1, 2, 3) are suitable for this and can also be placed inside a large enough clip-closure bag. The powder is taken up with liquid into a syringe from the lower sections of the devices. A certain amount of practice is needed to be able to do this inside the sealed clip-closure bag. If the above possibilities cannot be realised and it is still necessary to divide tablets, a dust protection mask must be worn. The same applies for opening capsules in order to administer their content. It is helpful if a ready-to-administer formulation can be prepared in the pharmacy.

Orally Administered Drugs - Liquid Forms

The use of liquid formulations of cytostatics for oral administration is not very common for adult patients. If children are being treated, however, the oral administration of solid formulations can be challenging, especially if a large number of tablets are involved or these are very large. In some cases administration proves to be simply impossible. If liquid forms, such as syrups, are needed and are not available from a pharmaceutical manufacturer, they must be prepared in the pharmacy. They are filled into containers that allow easy, precise withdrawal without the container being contaminated. Withdrawal aids should be considered for multiple dose containers, though single-dose containers are to be preferred.

Drugs for Parenteral Use

In most cases cytostatics for parenteral use are now prepared by specialist personnel in the pharmacies. In addition to assembling the necessary materials, making ready for the administration of these drugs includes filling infusion systems with carrier solution free of active substance - if this step has not already taken place in the pharmacy.

If the nursing staff are responsible for filling the infusion systems, this work should be performed at a quiet workplace on a liquid-tight underlay. All the materials needed are gathered before starting work. After the infusion system has been filled it must be connected to the syringe or infusion container. For safety reasons, bottles must be pierced while they are standing and bags while they are lying on the work surface; a swab must be held around the Luer lock connection.

(See also 3.3.1. Technical Equipment: Braun, Maco, for information on contamination-free connection and disconnection.)

Virostatics are listed under CMR drugs in the *TRGS* 525 and are subject to the same rules. As a result there are a few hospitals where certain CMR drugs are prepared in the inpatient area and this work must be done under appropriate safety precautions. If this situation exists and cannot be changed, the pharmacist can offer assistance in ensuring that handling these substances takes place on the basis of the *TRGS*. The preparation must be performed in accordance with the minimum standard with underlay and a pressure release device for avoiding aerosol formation and preventing excess pressure. Closed systems (see 3.3.1. Technical Equipment) are to be preferred. As yet there has been no conclusive discussion as to what can be considered a closed system in the sense of *TRGR* 525 and the leaflets from the professional associations. Nonetheless, the safety standards must be set higher for work performed without appropriate additional protective equipment such as a safety workbench complying with DIN.

Administration of Cytostatics

Drugs for Parenteral Use

In the majority of cases the doctor administers the ready-to-administer cytostatic solutions for parenteral use. As protective garments while doing this he requires trousers, closed shoes and a gown, and wears gloves. The Luer lock connector is connected to the patient's access.

If the system does not enable contamination-free disconnection from the patient, disconnection takes place on an underlay with the connection point enclosed in a swab. Slightly contaminated material, e.g. swabs, are collected in a container, e.g. a waste bag. This is then closed and treated as household waste (see 4.1. Waste Disposal).

In the event that an extravasation occurs, the persons concerned must know where the extravasation kit is located and how to use what it contains (see 4.3. Extravasation).

Orally Administered Drugs - Solid Forms

All solid formulations for taking orally can be given to the patient in a beaker. Patients should be instructed to wash their hands after taking the medicine, i.e. after touching the drug.

Orally Administered Drugs - Liquid Forms

If liquid forms are delivered to the ward, measuring out is the only task that may have to be performed by the nursing staff. Preparation should take place on an absorbent underlay whose underside is impermeable to liquids and the volume should be measured using a syringe which is brought closed to the patient. The syringes used should preferably be unsuitable for administering drugs for parenteral use in order to avoid any possibility of confusion. A liquid can also be placed in a beaker with a lid and given to the patient. Patients are instructed to take the medicine, to then fill the beaker with a suitable drink of their own choosing and finally to drink this in order to ensure that they have taken the entire dose of the drug. If the pharmacy delivers single-dose containers, the residue can be rinsed from these using a liquid acceptable to the patient in order to ensure that the dose has been completely taken. If the patient is a child, the containers should be refilled by the nursing staff.

Topical Drugs - Dermatics, Ophthalmics

Drug formulations intended for topical application carry a high risk of contamination for the area surrounding the region being treated. Wearing protective gloves is mandatory during application or insertion of semi-solid and liquid forms. Industrially manufactured products are supplied with gloves and the instructions state which material these are made of. If the products are prepared in the pharmacy it is important to ensure that suitable gloves are used.

When applying eye drops the quantities of substance flushed out of the eyes by lacrimal fluid must be absorbed in a swab and the surroundings covered up as carefully as possible. Covering the surrounding area with oily underlays or with film - as is usual, for example, in the treatment of ulcers - cannot generally be recommended because increased migration into this medium can occur for reasons of solubility. The use of topically applied drugs must always include providing patients with adequate information as to how they should proceed when applying the drug themselves.

Dealing with Excreta

Dealing with patients' excreta is part of the everyday routine of the nursing staff on the wards and rarely needs to concern the patient's relatives. If this is necessary, however, the relatives should be informed about the proper way to proceed. (See 4.9. Dealing with Excreta for information on this topic).

Management of Inadvertent Spills

Actions to be taken after inadvertent spillage focus primarily on the decontamination of persons and surroundings, avoiding carry-over of cytostatics, and cleaning the contaminated surface. All employees on the ward must know where the spill kit is located. It is advisable to keep the extravasation kit and the spill kit in the same place.

The principle applies that persons must always be decontaminated before dealing with the surroundings. The most important actions are immediate replacement of the contaminated protective garments, thorough cleaning of the skin and flushing the eyes if necessary.

Room decontamination after spills comprises measures for primary clearing up of the spilled substances and is completed by the subsequent cleaning. In such cases cleaning tasks may be performed only by instructed personnel. During this work personal protective equipment must be worn appropriate to the risk situation, but at the very least a protective gown and protective gloves. Decontamination and cleaning are carried out according to a corresponding plan, the implementation of which is part of the training given during instruction. (see 4.2. Decontamination after Inadvertent Spills)

Disposal

Routine work on the wards is also governed by the principle that waste avoidance takes priority over waste disposal. This can be realised to a limited extent by returning unused preparations. Depending on the type and quantity, and on the

shelf lives, it may be possible to use these for another patient. Return transport from the ward to the pharmacy should be governed by the same guidelines as the delivery and must take place according to definite rules. Even if a product not used for the patient cannot be used in the preparation unit of the pharmacy, it should still be returned since disposal containers for larger quantities of substance are generally available only in the pharmacy and not on the ward.

For reasons of cost a disposal device for sealing in (see 4.1. Waste Disposal) used materials on the ward is only justifiable in departments producing large amounts of waste. Since the waste bins contain only slightly contaminated waste they can be included in the domestic waste. Disposal bins for separate collection of slightly contaminated materials are recommended since they instil greater awareness of the corresponding waste. According to *TRGS* 525 it is not necessary to wear gloves for this work, however, non-sterile protective gloves should always be used if contamination cannot be definitely ruled out.

4.6. Handling Cytostatics in the Doctor's Office

Drugs prepared in a pharmacy may only be accepted by appropriately instructed qualified personnel of the doctor's office.
The delivery must be examined for completeness, damage, plausibility and date of expiration.
Preparations intended for parenteral administration should be delivered as a unit together with an infusion system filled with carrier solution.
The pharmacist supplying the drug must give advice on the types of accesses that are suitable for its administration.
The so-called "replugging" of infusion systems should be avoided.
The preparations are administered by the doctor giving treatment together, with the nursing staff.
The use of cytostatics must be accompanied by continual monitoring of vital parameters.
Personal protection equipment worn by the personnel must comply with current regulations and should at least consist of a gown, gloves and an absorbent underlay.
After administration has been completed all contaminated materials are sealed and disposed of in accordance with their statutory waste classification.

Matthias Wriedt, Hamburg

Delivery to the Doctor's Office

The consignment must be handed over in the doctor's office to qualified personnel who have received appropriate instruction (through the pharmacy). These persons must ensure that the delivered cytostatic preparations are inspected without delay (see Chapter 1.1, 1.3).

Inspection of the Delivered Preparations

The preparation is examined visually for intactness (leakage: see Chapter 4.2., turbidity, precipitation, temperature). The individual preparations should be allocated to the patients in order to compare the prepared drugs with the scheduled patients' appointments. Any missing preparations can then be requisitioned at once. This

should keep to a minimum the occasional hectic activity associated with last-minute preparations.

Therapy Sheet

For this a sufficiently large area must be available in the doctor's office for storing the preparations in an organised way. It is helpful to keep any concomitant medication prescribed (above all anti-emetics, diuretics, etc.) in the same place (see Chapters 5.2. - 5.5.)

A care plan (referred to here as a therapy sheet/medication plan), which can be generated by most cytostatics programs, is a suitable method of documentation.

Plausibility Check

Before being administered the preparation must be examined for plausibility (regimen prescribed, correct patient if names are the same!) This is especially important for the stated stability of the infusion, whereby the maximum duration of the infusion must be taken into account.

4.6.5. Infusion System

The requisitioning party should be persuaded wherever possible to request delivery of cytostatic infusions for parenteral use together with infusion systems filled with carrier solution. Attaching an infusion is almost always accompanied by the release of infusion medium; delivery of a complete unit can also therefore reduce the load on the personnel administering the drug.

4.6.6. Personal Protection of the Administering Personnel

The personal protective equipment worn by the personnel should consist of a gown (which can also be a gown, separately washed, of the type worn in the doctor's office, but must not be private clothing) and protective gloves (4, 10). These must also be worn when handling cytostatic ointments, tablets and contaminated materials. The *TRGS* (technical rules for hazardous substances) 525 requires in 5.2 a hazard evaluation and appropriate protective measures for handling CMR drugs; this also includes the administration of injections or infusions. The *BGW* (professional association for the health service and social services) has published an advisory booklet for doctor's offices: *"Ermittlung und Beurteilung von Gefährdungen GP 5.1 - Arztpraxen"* (Ascertaining and evaluating hazards GP 5.1 - Doctor's Offices).

Concerning the wearing of gloves it is necessary to take into account that in many doctor's offices the personnel are inadequately aware and the comment is even made

that one does not want to "frighten" the patient. In this situation the pharmacist involved should strive, with the agreement of the therapist, to educate the personnel and the patients.

Cytostatics tablets or dragees must not be divided, dissolved or crushed in the doctor's office. If part doses are required, this should be discussed with the pharmacists and divided formulations prepared as needed.

A liquid-tight, absorbent underlay must be used when disconnecting the infusion.

Do not separate infusion bag from infusion system but dispose of together - i.e. no "replugging" of infusion systems. (The residual quantity of cytostatic remaining in the infusion system must be taken into account when calculating the dose, or administered in a closed system by means of an appropriate flushing process.) Inseparable systems would be of advantage here.

In addition to the danger presented by manipulated incompatibilities, the main source of contamination of the doctor's office derives from the formation of invisible aerosols.

4.6.7. Hygiene during Administration

One aspect is protection of the personnel and this is easy to communicate; in addition, gloves (even if non sterile) serve to protect the immunosuppressed patient from nosocomial infection by the personnel (patient protection).

The other is educating and informing the patient that he is receiving a powerfully active (but beneficial) drug that is intended only for his disease but that can be damaging for others, who must therefore protect themselves. The patient must be dissuaded from the perception of being "poisoned"; the idea of hygiene should also be integrated.

This is the moment in which the pharmaceutical personnel can support the planned therapy, e.g. by explaining the purpose of the concomitant medication in order to counter the opinion: "I'm taking so much already, do I really need this stuff as well?"

Handling the drugs in the home environmental can also be discussed (see Chapter 4.7).

Administration Access

The administration access also needs to be explained. Handling instructions must be prepared for this in an interdisciplinary discussion. Keywords are:

- No accesses on the back of the hand (for example)
- Only use veins on the extensor side of the lower arm
- In the case of mastectomy only use the arm on the opposite side (lymph outflow disturbance)
- Administer cytostatics with strong local toxicity only via central access as infusion (CVC; port with Huber needle)
- Cytostatics with local toxicity may be administered via a peripheral access only as bolus and only by an experienced doctor (no delegation to medical assistants)
- No steel cannulas to remain in the vein (butterfly), danger of perfusion
- Examine position, relocate in case of doubt.

These measures simultaneously serve to prevent extravasation (see Chapter 4.3). The general rules of hygiene correspond to those for taking blood, see above.

Monitoring Vital Parameters

Patients are kept under continual observation while being treated with the drugs. The following parameters are monitored:

- responsiveness (caution - some patients sleep!)
- blood pressure (RR) and pulse rate (P)
- excretion (diuresis), if necessary 24-hour urine, balance, patient's diary
- respiration/dyspnoea
- position of the access.

Disposal

During disposal of the system a cytostatics waste container should be placed in the treatment room in order to avoid spillage during transport. (see Chapter 4.1.)

Cleaning

Infusion stands, electric pumps, couches, chairs or beds must be regularly cleaned; gloves must be worn during this. Although bed linen does not require special

treatment, the question of excreta (urine, etc.) must be considered (see Chapter 5.8.)

The close cooperation deriving from initiatives taken "courageously" by the pharmacists - many things come about only as a result of discussion or the offer of a pharmaceutical service - is an important facet of the oncology pharmacist's function and in these politically difficult times serves to project the image of the profession in the sense of "for our patients".

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4.7. Handling Cytostatics at Home

An increasing number of therapeutic regimens involving cytostatics require continuous administration of the drug over a period of 24 hours to several days. Such treatments are also increasingly being given on an outpatient basis.

Patients, relatives and the outpatient nursing staff must be trained in how to handle cytostatics in a home environment.

The training should cover in particular the following points:

- **Special aspects of handling cytostatics**
- **Handling devices for administration**
- **Action in the case of incidents and spills**
- **Procedure in the case of extravasations**
- **Handling patients' excreta**
- **Waste disposal.**

An individual care plan should be prepared jointly with the pharmacist (see Chapter 5.1).

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Cytostatic therapeutic regimens considered suitable for implementation in a home environment can involve the continuous infusion of an active substance over a period of 24 hours to several days. The aim is to achieve an effective concentration in the plasma resulting in an improved response rate; simultaneous radiotherapy and chemotherapy also becomes a possibility.

In order to spare the patient a stay in hospital, diverse pump systems providing continuous infusion at home have already been used for administration for a number of years now. These pumps are connected to the appropriate catheter system in the doctor's office or outpatient department and disconnected there at the end of the infusion period. For the time in between the patient is at home and can lead his normal life to the extent that his condition allows.

In order to guarantee safe outpatient care, pharmaceutical services are necessary that go beyond simply filling the administration systems. In addition to advising the patient, the personnel in the doctor's office and the responsible nursing services are also given instruction. For purposes of ensuring drug safety it is recommended that written information be provided about special aspects of using of the respective system. It is advisable to prepare separate material for patients in order to inform them about how to handle the system and what action to take in the event of an incident.

Issues specific to the handling of cytostatics are essentially covered by 1.3. Hazard Evaluation, Working Rules and Instruction and 3.7. Delivery of Cytostatics (to the unit performing oncological therapy). See also 3.3.1.1. for further details about infusion pumps. Concerning action to be taken in the case of an incident, the pharmacy should provide the doctor's office and the patient with concrete, comprehensible instructions in accordance with 4.2. Decontamination after Inadvertent Release. Providing a telephone number for emergencies is part of the service performed by the pharmacy. The doctor, and the pharmacy if necessary, will explain to the patient how to recognise an extravasation in the rare situation that there is no central access. 4.3. Extravasation (Paravasation) deals with the occurrence of extravasations. For handling patients' excreta efforts are being made towards the provision of standardised information by the doctor's office and the pharmacy, analogous to 4.9. Handling Excreta. Waste disposal is regulated in accordance with 4.1. Waste Disposal in a binding way through the pharmacy in agreement with the unit performing the oncological therapy and, if necessary, with the nursing service and/or GP's office.

To summarise, the training and organisation of care within the home environment should include the topics listed below; written instructions for patients, relatives and nursing staff must also be provided:

1. Principles of the cytostatic therapy prescribed and the regimen implemented
2. Basic information about the type of the patient's parenteral access, e.g.
   - PORT system
   - Hickman or Broviac catheter
   - central venous catheter
3. Drug therapy type and duration of administration
4. Brief instruction on the types of mobile electronic pump systems and elastomeric pumps used

5. Hygienic standards for handling drugs for parenteral use

6. Hygienic standards for handling the catheter system
7. Special effects / adverse effects / interactions of the cytostatic therapy
8. Action in case of defects and/or leakage of the cytostatic solution, use of the spill kit
9. Action in case of problems during the cytostatic therapy, emergency telephone numbers
10. Handing over the emergency telephone numbers.

The training performed is appropriately documented.

Administration Systems for Continuous Infusion (see also 3.3.1.1. Infusion Pumps for Administration of Cytostatics)

A basic distinction is made between electronic and mechanical pump systems, which will be described here only in outline.

a) Elastomeric Pumps

These pump systems contain a tube of an elastomeric membrane which is filled with the drug solution similarly to a balloon and is housed inside a rigid or flexible case. The intrinsic elasticity of the membrane results in pressure being generated which forces the contents through the infusion tube into the catheter system of the patient. The flow rate is controlled by means of a flow limiter, e.g. glass capillaries. Particle filters with air separators are generally integrated into the infusion tube.

Advantages: very light pump systems; simple filling; visual monitoring of the infusion by diminishing volume of the balloon

Disadvantages: single-use system, therefore high costs; no alarm system in the event of an incident; depending on the pump system, inaccuracies since the glass capillaries regulate the flow rate dependent on the temperature; fluctuations in flow rate; in the case of a flexible case, danger of damage and leakage of the drug solution.

Product examples: Baxter LV, Medac surefuser, Braun easypump

b) Mechanical Pumps

Infusion bags, normally of ethinyl vinyl acetate, are filled aseptically and laid in a plastic box. Spring systems then develop the necessary pressure for emptying the bag. Flow limiters are integrated in the infusion tube.

Advantages: low costs since the infusion bag is a single-use article

Disadvantages: no alarm function; imprecision in the running time; fluctuations in the flow rate; heavy; inadequate visual monitoring of the residual volume; in some systems damage to the infusion bag can result in the drug solution leaking out

Product examples: Onkoworker, Fresenius Ultraflow

c) Electronic Pumps

Electronic pumps control the flow rate by means of peristaltic or rotary drives. All therapy relevant data, such as flow rate and duration, can be programmed and frequently also infusion profiles. In addition to circadian rhythms it is even possible to infuse several drugs through multi-channel systems (Pegasus Melody, 4 channels). Most pumps can also be used for other infusion regimens such as PCA, TPE, antibiotics, etc. The pump heads are linked to the filled single-use bags by means of appropriate connecting systems. The use of high performance batteries means that the patients enjoy just as much flexibility as with the other systems. Infusion pressures are also sufficiently high for intra-arterial infusion.

Advantages: high flexibility in the therapy; high precision; alarm function(pressure alarm, air alarm, etc.), therefore high therapeutic reliability; cost savings in long-term use

Disadvantages: often very heavy; high acquisition costs; depending on the model, false alarms possible; security against leakage from the infusion bag mostly inadequate

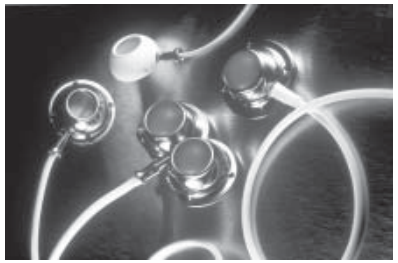
Product examples: Sabratek Homerun 6060 Baxter, Braun Multifuses, Pegasus Melody, Pegasus CADD 1, Graseby

The pump system is chosen according to the following criteria:
- sufficiently accurate flow rate
- therapeutic regimen (circadian rhythms necessary?)
- flexibility of the patient
- adequate security against leakage
- likelihood of false alarms in the case of electronic pumps
- costs

Catheter Systems

The implantation of a venous (or possibly arterial) port system is standard. Central venous catheters and Hickmann Broviac catheters need constant attention and

generate a high rate of complications. These systems should not be used for outpatient therapy. Indwelling venous catheters must not be used without medical supervision because of the danger of extravasation.



Port-(access-) catheder systems (Logomed company)

Pharmaceutical services are also provided here in respect of the necessary medical devices:

a) Port needles

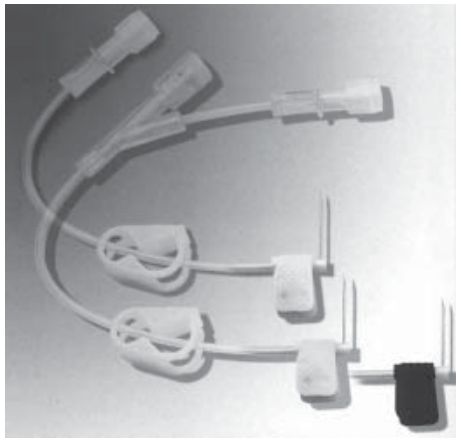
Huber type single-use needles must always be used for port systems. Different types of needle enable optimal piercing of the port. Needles between 15 mm and 25 mm long are generally used, depending on the thickness of the subcutaneous fat layer. Different internal diameters also allow gravity infusion in the doctor's office. Smaller diameters increase wearing comfort and reduce the risk of infection. These needles have a greater flow resistance, however, and must be used with a pump system. Different closing plates increase the wearing comfort; in some cases adhesive rings are already integrated to enable the needle to be fixed in place after piercing. Closure clamps are attached to the tube system in most systems.

Attention must be paid to the following points:
- selection of the correct needle length
- selection of the appropriate internal diameter according to the type of infusion
- selection of a possibly flat closing plate if the needle will remain in place for several days
- existence of a clamp
- possibility of visually inspecting the puncture site for longer indwelling duration, not possible in the case of and integrated adhesive ring.

Product examples: Gripper (Smiths Medical), Cytocan (B. Braun), Intrastick (Fresenius).

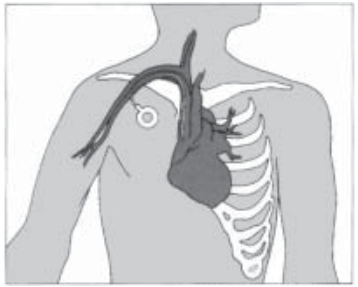
b) Dressing Systems

Sterile slit compresses, elastic plaster dressings and sterile polymer films are used for dressing the port needles. Selection depends on the type of needle and, above all, on the time it will remain in place.

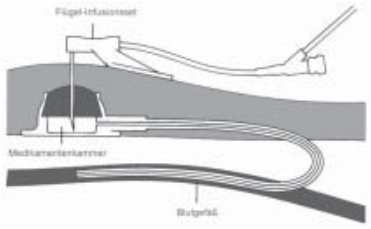


In vitro puncture of a port system – Huber infusions sets (picture material Logomed Training)

Huber-needle with tangential bevelled edge (Logomed company)



Port-A-Cath system – the tip of the catheder is in the large vein and goes to just inside the heart, the other end is under the skin below clavicle (Logomed company)



Schematically description where the venous access system is placed under skin (Logomed company)

Attention must be paid to the following points:
- non padded closing plates should always be padded underneath with sterile slit compresses
- in the case of longer indwelling duration, outer dressing with sterile polymer film, maximum 7 days (e.g. Tegaderm, Suprasorb)
- for puncture sites that are not directly visible, change of dressings at least every 3 day; in case of pain at the puncture site, change immediately, medical examination
- acceptable skin tolerance, change of dressing in the case of allergic reactions
- skin-friendly disinfecting agent, e.g. Softasept (B. Braun)
- port needle tubes always secured against being pulled (e.g. Fixomull stretch, 2 strips, 1 cm wide)

c) Closing Systems, Extension Systems, Inline Filters

If infusion systems are frequently changed at the tube of the port needle it is advisable to use safety closures, which are screwed onto the port needle tube in place of the usual closure cones. When connecting a new infusion system it is then only necessary to disinfect the Luer lock adapter of the valve; unscrewing, with the risk of microorganisms entering the catheter tube, is reduced (e.g. BD Posiflo 2-way i.v. adapter).

When using extension lines, additional non-return valves (e.g. R-Lock Impromediform) should be incorporated to prevent reverse flow in the event of an unnoticed disconnection. Since the so-called Heidelberg extensions are not pressure resistant and the patient may compress the lines when lying down at night, pressure resistant lines must be used. For mobile patients, pressure resistant spiral lines are the material of choice since they combine the maximum possible flexibility with simultaneous strain relief of central venous catheter systems. (spiral line, e.g. Impromediform)

For infusions over several days, microbiological safety is improved by the use of positively loaded 0.22 µm self-venting inline filters near to the patient, since these have a useful life of up to 96 hours (e.g. 0.22 µm + bacteria filter, Impromediform). Before using these, however, information on the compatibility of the drug with the particular filter must be requested from the manufacturer.

Attention must be paid to the following points:
- use of safety valves in the case of daily connection
- non-return valves if necessary
- pressure resistant extension lines

- use of pressure resistant spiral lines for mobile patients
- in the case of infusions lasting several days without system change, additional 0.22 µm inline filter after assurance of compatibility.

On-Call Service

If an incident occurs the patient must be able to obtain help immediately. If a pump develops a fault there is always the danger of the port system being displaced. In practice this may necessitate removal and renewed implantation. The Medizingeräte-*Betreiberverordnung* (sale of medical devices regulations) stipulates the establishment of an on-call service by sellers of pumps. Especially if an electronic pump fails, the seller must repair or replace the pump on site.

Since a defect in the bag system may result in contamination of the home environment, the pharmacist should be familiar with the sources of malfunction that are possible when using the various administration systems. In order to meet this requirement and avoid complications, the pharmacist should acquire an overview of the market and arrange demonstrations and possibly tests of the individual systems in order to be able to deploy the most suitable system for a particular usage. It goes without saying that a pharmacy aligned on patient-oriented service will take account of safety as well as cost-efficiency aspects. A useful and important task of the pharmacy would appear to be selection of the appropriate administration systems and early instruction of the patients as a means of avoiding dangerous situations. If problems arise despite this, the patient must be able to obtain help as soon as possible.

Responsibilities of the Pharmacy
- establishment of an on-call service over pharmacy and/or doctor's office or outpatient department
- teaching patients how to use the administration systems
- possibly providing a spill kit if the doctor insists on an administration system liable to leak.

4.8. Management of Clinical Studies

By participating in clinical trials and therapy optimisation studies of oncological drugs the pharmacist makes an important contribution to quality assurance in this field.

The pharmacist's particular responsibility concerns the trial drugs and covers their proper shipment, storage, preparation and/or making ready, distribution and destruction, taking due account of all applicable statutory requirements (GCP, GMP).

Robert van Gemmern, Wuppertal

Clinical studies in oncology are being increasingly regarded as an interdisciplinary task in which not only doctors but also pharmacists - employed both in the hospitals and in the pharmaceutical industry - can make their particular contribution to quality assurance. Protection of the patient and the gathering of valid data on the trial drug by means of a standardised procedure take highest priority during the performance of clinical studies.

Clinical drug trials are subject to extensive regulation by national and international laws, guidelines and recommendations. A selection of rules and regulations is included in the appendix. F. Feiden has summarised and published these "Arzneimittelprüfrichtlinien" (Drug testing guidelines) in the work of the same name [1].

This chapter discusses the role of clinical pharmacists (especially those employed in the hospital) in the performance of clinical drug tests. Their partners and their responsibilities are listed in Table 1:

Table 1: Partners in the performance of clinical studies (selection)	Tasks within clinical trials
Sponsor	Initiator of a study: can be the drug manufacturer, or also a doctor who initiates a study out of scientific interest.
Monitor	Commissioned by the sponsor to monitor the correct performance of the clinical study, especially the documentation; employed by the sponsor or contracted institute.
Investigating doctor (investigator)	Principal investigator: manager of the clinical study, Subinvestigator: subordinate investigating doctor
Clinical pharmacist	As employee of a pharmacy (e.g. in the hospital), responsible for the coordination of clinical studies in the pharmacy and in the collaboration with sponsors, monitors and investigating doctors.

More and more special study centres are being established at major hospitals, e.g. university hospitals. These are facilities entrusted with the performance of clinical studies, e.g. as part of large oncohaematological departments or as interdisciplinary institutions. They are often led by clinical pharmacologists and employ study nurses, documentalists, etc. Study nurses frequently come from the nursing service and are specially trained for deployment in clinical studies and the care of study patients. They support the investigating doctor in the administration of the medication being studied, in the diagnostic methods used, and also in the documentation. They are mostly employees of the study centres.

The tasks and functions of sponsors, monitors and investigating doctors are described at length in the ICH Guidelines. A few of these are listed in Table 1 (16 - 20).

The clinical pharmacist performs a number of services within his collaborative activity. These generally comprise the tasks listed in Table 2:

Table 2: Services provided by the clinical pharmacist during the performance of clinical trials
Acceptance of the trial drugs
Storage of the trial drugs
Randomisation if required
Blinding if required
Making ready if required
Handing over to the investigating doctor
Management of containers used if required
Destruction of unused containers
Documentation of all the above steps

The type and scope of the above tasks depend upon the characteristics of a clinical trial as listed in Table 3.

Table 3: Special characteristics of clinical studies	
Type of study	Clinical trial Phase I - IV For cytostatics: clinical trial Phase II - IV Therapy optimisation studies: primarily in the field of oncology: comparison of a novel chemotherapeutic regimen with a standard therapy - to be regarded as an attempt at healing
Trial drugs	cytostatics, antibodies, vaccines, genetic therapeutic drugs, e.g. using viral vectors, antibiotics, antiemetics, virostatics, etc.
Study design	open, blind, double-blind, cross-over

The services to be performed by the pharmacist and his rights and duties towards sponsor, monitor, investigator and hospital management must be defined exactly in the agreements made between the participating entities (hospital, medical practice concentrating on oncology, etc.) Since studies are financed by third parties, the standard procedure for sponsoring in the respective hospital must be followed, for example acquiring the approval of management. It is also important to clarify whether participation in clinical studies is covered by the contract of employment. This is necessary, for example, for insurance reasons.

The responsibilities of the pharmacy manager and subordinate employees must also be defined exactly in respect of the services demanded. Depending on the number and scope of the clinical trials it may be useful to appoint a person responsible for studies or a study coordinator in the pharmacy. Employees of a pharmacy who take part in a clinical trial in some way or other must be nominated and listed during the run-up. In most cases a signature and submission of a curriculum vitae are necessary.

Once these basic requirements have been met, further issues must be clarified in the run-up to a concrete study. These are listed in Table 4.

Table 4: Scheduling
Chronological scheduling
Procedures between pharmacy and sponsor, contracted institute, monitor
Procedures in the pharmacy
Procedures between pharmacy and investigating doctor, study centre, ward
Preparation and making ready of all necessary materials • informational material, e.g. investigator brochure, study protocol, instructions for the pharmaceutical area • trial drugs • equipment (medical devices: specifically syringes, infusion bags, infusion lines, infusion devices) • labels • documentation materials, e.g. pre-printed stock list (drug accountability form)
Spatial requirements • storerooms, cabinets • make ready rooms: sterile or aseptic or non sterile preparation
Staff training • imparting all the information necessary for performing the services demanded

After the ethics commission has voted and all preparations have been made, the preparatory phase of the clinical trial is finished. The main phase of the clinical trial begins with the ”initiation visit”.

The following points must be observed to ensure proper scheduling within the pharmacy [Table 5; (11)]:

Table 5: Arrival of the study medicines

- Nomination of persons authorised to take delivery
- Processing only by authorised persons nominated and listed beforehand
- Inspection for completeness and intactness, compliance with the transport conditions
- Documentation of goods received - confirmation of acceptance
- Copy of confirmation of acceptance to be returned to sponsor
- Documentation of addition and current stocks in the drug accountability list (stock list)

The test drugs must also be stored in accordance with specified criteria:

Table 6: Storage; authorisation to add and withdraw the test drugs

- Separate from licensed drugs
- Closed cabinet, refrigerator, freezer
- Regulation of authorisation to add and withdraw, as few persons as possible
- Monitoring of the storage conditions (relative humidity, temperature)
- Immediate documentation in the drug accountability list after every withdrawal

During clinical trials of oncological drugs making ready in the pharmacy is often mandatory. This must take place under the same quality and safety standards as apply for the routine preparation of cytostatics.

Table 7: Making ready (if required)

- Nomination of the authorised persons
- The general conditions for the preparation of drugs apply: GMP, PIC, GCP, pharmacopeias
- Preparation according to the binding instructions specified by the sponsor in the study folder
- Deviation from the specifications of the sponsor is not permitted even if contradicted by other knowledge from the medical and pharmaceutical sciences (e.g. in respect of stability data, individual steps in the preparative procedure)
- For i.v. preparations: an exactly defined number of vials to be used for each patient
- Opened vials not to be used again for other patients (complicates management of the drug accountability list)
- Identification of the ready study medicines using the label provided by the sponsor
- Every item to be identified with a label "For clinical trial only"
- Documentation of the making ready in the study folder - e.g. with a second label supplied by the sponsor, also include name of person performing the preparation, date and time of day
- Keeping the used vials (e.g. bag and apply study label), empty containers (e.g. for tablets) or blister packaging

An exact procedure must be followed when handing over the study medicines to the investigating doctor:

Table 8: Handing over the trial drug

- Exact procedure as defined in the study folder
- Coordination with the respective investigating doctor, the nursing staff on the ward or the study nurse, in particular in the case of drugs which must be administered quickly for reasons of stability
- Coordination with the transport service
- Conforming with the transport requirements, e.g. cooled storage, protection from light, transport duration
- Documentation of handing over: person, date, time of day

Concerning the return of study material to the pharmacy, see the points listed in Table 9:

Table 9: Returns to the pharmacy

- In the case of study drugs made ready on the ward: return of empty containers to the pharmacy; acceptance, identification and documentation, storage
- In the case of unused test drugs: acceptance, identification, documentation, storage; on no account to be re-used for other study patients
- Possibly after agreement with the monitor: return to the manufacturer for destruction, documentation of the return
- Possibly after agreement with the monitor: counting, destruction, documentation of the destruction

In addition to these tasks, additional services are frequently delegated by the sponsor to the clinical pharmacists.

Table 10: Support with blinding, e.g. for single-blind or double-blind studies

Approach depends on the formulation of the test drug, e.g. masking colour differences by wrapping, encapsulating, etc.

Table 11: Support with randomising

- In the case of comparison of different regimens for the same indication
- Comparison active drug/placebo
- Comparison test drug against standard drug

Example of simplest procedure:

- A randomisation list is prepared by an institute for medical data processing using a mathematical procedure
- Corresponding randomisation envelopes are provided to the responsible clinical pharmacists
- The investigating doctor communicates a corresponding randomisation number to the pharmacists

or

- The pharmacist requests the randomisation number from the responsible office
- The patient is allocated a randomisation envelope in accordance with this randomisation number
- In this randomisation envelope it is stated which therapeutic regimen the study patient will follow.

The activities of all the partners participating in the study is regularly checked by the monitor. Each of his visits should be carefully prepared by the responsible pharmacists. As a rule, the following visits are scheduled (Table 12):

Table 12: Audits - Sequence and Content

Before study begins: start-up visit

- Inspection of the store rooms
- Cabinets for receiving the test drugs
- Make ready rooms
- Inspection of procedures (e.g. the preparation of cytostatics)
- Information about the study
- Agreement of the requested procedure

Intermediate visits, by appointment (approx. every 6 weeks)

- Check for proper use of the study medicines
- Check for proper storage
- Check for proper making ready
- Handing over
- Returned containers and test drugs
- Documentation

Final audit

- Checks as above
- Definition of procedures for the return or destruction of unused study drugs
- Decision on keeping or returning study medicines
- Archiving the study documentation
- Keeping this for at least 15 years while conforming with the data protection requirements

The above conditions always apply if the roles of the individual partners are clearly assigned and there is no doubt that the statutory drug requirements are fulfilled.

A somewhat more critical approach must be taken to studies in which the risks for the participating pharmacists are less well known because these tasks have not yet - or only in a few cases - been performed by clinical pharmacists (see Table 13).

Table 13: Special issues of clinical drug trials	Approaches to a solution
Study on the personal responsibility of the investigating doctor - investigating doctor is acting as sponsor In the	In the case of novel substances and formulations the pharmacist accepts special co-responsibility for bringing the drug into circulation
case of multicentre studies	Delivery can be made by a single hospital pharmacy only if the hospitals concerned are inside the catchment area of this pharmacy. If not, a preparation permit must be applied for from the responsible authorities. This also applies for simple repackaging or relabelling.
In the case of studies with genetic therapeutic drugs in which the medicine is handled, made ready, etc.	The place of preparation must, for example, be licensed by the responsible authorities as a genetic engineering workplace. The special handling regulations apply.

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4.9. Handling Excreta

Excreta from patients being treated with cytostatics can contain significant quantities of cytotoxic substances.

Excreta must be handled in a way that protects all groups of person involved and that complies with the applicable waste regulations and statutory requirements for disposal (see 4.1. Disposal).

Thanke Mehrtens, Hannover

Investigations into the pharmacokinetics of antineoplastic substances have shown that their potential danger for doctors and nursing staff does not end after the cytostatics have been administered. The excreta of patients treated with cytostatics can contain significant quantities of substances with cytotoxic activity. These may be the cytostatic itself or its active metabolites. In studies, exposed persons suffered slightly (but significantly) more often than control subjects from gastrointestinal symptoms such as diarrhoea, or neurological symptoms (headache). The origin was identified as skin contact with cytotoxic substances [1]. When cytostatic therapy is transferred from the inpatient to the outpatient sector, the relatives of cancer patients are also affected by this problem.

Legal Principles

According to *TRGS* (technical rules for hazardous substances) 525, Chapter 5.2.4, bodily fluids of patients undergoing CMR therapy are not classified as hazardous substances. This statement derives from the *Gefahrstoffverordnung* (hazardous substances regulations), which classify carcinogenic and mutagenic substances and preparations as hazardous substances only if the mass of the substance contained reaches or exceeds 0.1 percent. On the basis of the dilution of the cytostatic in the patient's blood (approx. 5 - 7 l) and in the other body compartments, the *BGW* (federal association) assumes that the mass content in the bodily fluids of the patient lies below 0.1% [9].

Excepted from this rule are excreta after "high-dose therapy" (see below) and vomited stomach contents after oral administration of cytostatics, since in these cases the mass content of carcinogenic cytostatics may exceed 0.1%.

Unfortunately neither TRGS 525 nor Leaflet M620 define the quantity of substance per administered dose from which the therapy is regarded as "high dose". As a result of modern therapeutic regimens and improved supportive therapy, regular doses regarded some years ago as "high" are now regarded as normal. For example, literature from the 90s still refers to a maximum 5-FU dose of 1.5 g/day; nowadays, a regular dose of 2600 mg/m2 is considered normal. If necessary, therefore, calculations should be performed for individual regimens in order to determine whether the 0.1% limit has still not been reached.

Excretion Pathways and Duration of Excretion of Cytostatic Substances

A number of publications [2, 3, 4, 5, 6, 7] discuss the duration of excretion of relevant quantities, the excretion pathway and the recommended duration of the protective measures. The results are summarised in Table 1.

Excretion after Instillation into Body Cavities

Results are available of investigations on the content of cytostatics in bodily fluids, e.g. for an intraperitoneal administration of mitoxantrone to five persons with malignant ascites [10]. After administration of 20 - 50 mg/m2 the mean concentration in the peritoneal fluid was 8700 ng/ml after 4 h and 490 ng/ml after 168 h. There was only a very low level of systemic absorption of mitoxantrone out of the peritoneal liquid into the blood. In the above study the peritoneal fluid was drained after 4 h. Between 7 and 30% of the administered dose was recovered in the drained fluid.

An investigation of intrapleural mitoxantrone therapy in the case of malignant pleural effusion [11] showed concentrations of up to 10 ?g mitoxantrone per ml pleural fluid during the first 20 h after instillation of a dose of 30 mg; the values were very widely scattered between individual patients. Approx. 15% of the interpleurally administered dose migrated into the systemic circulation. Here too there was a very wide variation between individuals so that in a few cases the concentration of mitoxantrone in plasma was as high as after i.v. administration.

In the case of bladder instillation a small fraction of mitomycin is reabsorbed. It may therefore be assumed that the administered dose is eliminated almost quantitatively in the urine (intense blue colour). Because a dose of 20 - 40 mg mitomycin in 20 - 40 ml of liquid is recommended for bladder instillation, a concentration of 0.1% is already present; however, although the urine does contain a relatively large quantity of a cytostatic, the concentration of this will generally lie just below the limit of

0.1% and therefore does not count as a hazardous substance according the current legal situation.

Handling Excreta from Persons receiving Cytostatic Therapy as Inpatients

1) Information

In the course of the annual instruction, nursing staff and doctors should be informed about excretion pathways and duration of excretion of the substances playing a role in their field of work. 24-hour urine should not be collected from patients during the first two days of a cytostatic therapy. Relatives should also be informed as far as possible; this is especially important for child patients (changing napkins!). Information for relatives should be expressed in a comprehensible way and recommendations should be easy to follow.

2) Protective Garments

Protective gloves (cytostatics protective gloves or two pairs of normal examination gloves one over the other) must always be worn when disposing of excreta containing cytostatics. For larger soiling, protective clothing should be worn in accordance with the recommendations of the *BGW* (Personal protective clothing in the case of inadvertent release of CMR drugs, see also Chapter 3.2. "Personal Protective Clothing").

3) Disposal of Bodily Fluids

Excreta that can be expected to contain quantities of cytotoxic substances of less than 0.1% can be disposed of in the sewage system. Vomited stomach contents after oral administration of cytostatics, and the excreta of patients who have received high-dose therapy, must be disposed of as dangerous waste.

If a period of at least two hours has elapsed between taking the cytostatic and vomiting, the mass content of the cytostatic very probably lies below 0.1% and the simpler disposal over the sewage system is therefore possible.

4) Disposal of Contaminated Materials

Contaminated laundry should be kept damp, packed separately in the same way as infectious laundry, labelled and sent to be laundered. If the possibility of danger for the transport or laundry personnel cannot be ruled out, the laundry should be disposed of according to the statutory requirements applying to waste.

5) Cleaning Contaminated Surfaces

The surfaces should be wiped several times using a suitable agent for the decontamination of the particular substance, or with a commercial surface disinfecting agent. See also Chapter 4.2. "Decontamination after Inadvertent Release".

Handling Excreta from Persons receiving Cytostatic Therapy as Outpatients

1) Information

Information in an adequate form should be given to the patient or to the relatives orally during an advisory meeting and if possible in writing as well. All handling instructions must be explained. It must also be stressed that contamination of the surroundings must be avoided at all costs (it is practically impossible to decontaminate a carpet). Practical information, for example that if there is a guest toilet this should be used for the first 48 hours, or the tip that men should sit down while urinating, makes it easier for the patient and the relatives to put the information provided into practice.

2) Protective Garments

Recommended minimum protective garments include the use of normal household objects and clothing. Household gloves can be used for disposing of contaminated excreta but must be removed, turning inside out, immediately after use and disposed of. The hands must then be washed thoroughly. Protective clothing need not be worn in a home environment as long as it is pointed out that any clothing that may be contaminated must be changed immediately and cleaned.

Keeping a kind of "spill set" in readiness can be regarded as a service in the sense of pharmaceutical care of cancer patients. The set should be aligned on the particular substance and contain an adequate number of protective gloves, one or more liquid-repellant aprons, possibly protective eyewear and overshoes and surface decontamination agent for the specific substance. It is recommended that this set be assembled and kept ready for therapies with substances that are excreted within a short time and primarily renally (e.g. carboplatin). For substances that are excreted in small amounts per day over a longer period, information should at least be given about the minimum protective clothing.

When cytostatics are administered orally, surfaces may be expected to be contaminated if vomiting occurs within two hours of the drug being taken. A suitable agent for decontaminating surfaces should therefore be recommended during the advisory meeting. (see Chapter 4.42. "Decontamination after Inadvertent Release".)

3) Disposal

High-dose therapies normally do not play a role in the outpatient sector. Excreta from patients receiving cytostatic therapy can therefore be disposed of over the sewage system since it may be assumed that the fraction of carcinogenic and mutagenic substances is lower than 0.1%. If a patient vomits within two hours of taking a cytostatic, the vomit can either be disposed of down the toilet (flush several times; clean contaminated surfaces with household cleaner or an agent recommended by the pharmacy) or, alternatively, the vomit can be wrapped well in a waste bag and discarded with the normal household waste.

4) Disposal of Contaminated Materials

It must be stressed during the advisory meeting that it is essential to avoid contamination of upholstery and carpets, cushions, covers or mattresses (recommend protective mattress covers). Decontamination of such items is difficult, if not impossible. Contaminated clothing, bedding or towels should be replaced immediately and washed in the washing machine (if possible with a higher water level / intensive wash).

5) Cleaning Contaminated Surfaces

The surfaces should be wiped several times using a suitable agent for the decontamination of the particular substance. A suitable agent for the particular substance, or a household cleaner, should be recommended during the advisory meeting.

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Table 1:

Drug	Excretion rate after use	Recommended period for wearing protective clothing		Further Information
		Urine	Faeces	
Amsacrine	Urine: 20 % * in 8h, up to 42 % * in 72 h (1)	48 h (2)		
Bendamustine	Urine: almost completely* within 4 h (3)	6 h		only little elimination via the gall bladder (1)
Bleomycin	Urine: unchanged up to 68% over 24 h (2,7)	3 days (4,7)		
Busulfan		1 day (2)		elimination in the faeces negligibly small (6)
Carboplatin	Urine: 60 –80% * within the first 24 h (1)	1-2 days (5)		
Carmustine	Urine: 60-70% within 96 h in the form of metabolites (1) 4 days (1)	4 days (1)		1% of the dose in the faeces 10% of the dose is eliminated as CO_2 (1)
Chlorambucil	Urine: up to 67 % * in 24 h (7)	2 Tage (7)		
Cisplatin	Urine: up to 75 % * in 5 days (7)	7 days (7)		biliary elimination amounts to less than 10% (1)

Cyclophosphamide	Urine: unchanged up to 25% over 48 h; total up to 62% over 48 h (7)	3 days	5 days (after oral administration)	elimination of up to 4% of the dose in the faeces after i.v. administration, also elimination over sweat and saliva (contains up to 77% of the plasma concentration) -> protective measures over 3 days
Cytarabine	Urine: 71-96% in 24 h in the form of metabolites(1)	1 day (2)		
Dacarbacine		1 day (2)		
Dactinomycin	Urine: 20% unchanged in 24 h (1,2)	5 days (4)	7 days (4)	
Daunorubicin	Urine: elimination primarily during the 6 h after injection (6) possibly red coloration of urine over 48 h (1)	2 days (4)	7 days (4)	elimination via the gall bladder in the first 24 h approx. 20% * (6)
Docetaxel		1 day (6)	2 days (1)	faeces as main elimination pathway (1)
Doxorubicin	Urine: up to 15% * over 5 days, possibly red coloration of urine over 48 h (7)	6 days (7)	7 days (7)	up to 85% * eliminated in the faeces (7)
Epirubicin	possibly red coloration of urine over 48 h (1)	7 Tage (4) 4 days (7)	5 days (4)	
Etoposide	Urine: 40-60% mainly unchanged within 48-72 h (1)	3 days	7 Tage (7)	up to 15% eliminated in the faeces (7)
Fludarabine	**Urine : after i.v. bolus administration 60% in the form of metabolites in 24 h; after infusion 40% metabolised in 24 h and 60% metabolised in 72 h (8)**	2 days (7)		
Fluorouracil	Urine: after i.v. bolus administration 15% unchanged in 24 h, after infusion 4% unchanged over 24 h (7)		5-7 days (with oral administration) (7)	

Gemcitabine	Urine: almost complete elimination mainly in the form of metabolites in 24 h (1)	1 day		
Hydroxycarbamide	Urine: 50-80 % in 24 h (7)	2 days (7)		
Idarubicin		4 days (3,8)	7 days (3)	
Ifosfamide		2 days (5)		
Lomustine	50-66 %* in 24 h (8,9)	4 days (8,9)		
Melphalan	Urine: after oral administration 28%* in 24 h; after i.v. administration 56%* in 24 h (7)	2 days (7)	7 days (7) (after oral administration)	Faeces: 20 – 50% of the dose* over 6 days after oral administration
Mercaptopurine	Urine: 10–20% unmetabolised, 10-40% metabolised in 24 h (7)	2-3 days (7)	5 days (7)	
Methotrexate	Urine: at low dosage 40-50%* in 48 h, at higher dosage up to 90% * in 48 h (7)	3 days (7)	7 days (7)	Faeces: elimination of up to 9% of the dose after i.v. administration (7); after high-dose therapy the concentration * in the urine can reach up to 5 mg/ml (7)
Mitomycin		1 day (5)		Faeces: up to 18% *
Mitoxantrone	Urine: unchanged up to 6.5% over 5 days, metabolised up to 3.6% over 5 days (7), possible blue coloration of the urine over 24 h (7)	6 days (7)	7 days (7)	over 5 days (7)
Nimustine		4 days (8)		
Oxaliplatin	Urine: 40-50% of the dose* in 24 h (8)	3 days (8)		elimination of 40% of
Paclitaxel	Urine: up to 13% unchanged (2)			the dose in unchanged form via the gall bladder within 24 h (10) good absorption from
Procarbacine	Urine: 5% unchanged, 25-70% as metabolites in 24 h (7)	2 days (7)		the gastrointestinal tract (7), within 96 h 4-12% of the dose eliminated in the faeces (1)

Temozolomid	Urine: 5-10% of the dose unchanged in 24 h (1)			complete resorption (biliary elimination negligible) (1)
Teniposide	Urine: approx. 10% of the dose in 24 h (1)	3 days (2,8)		elimination of approx. 10% of the dose in the faeces (6)
Thioguanine	Urine: 1.5% unchanged	1 day (5)		
Thiotepa	in 8 h, 4.2% metabolised in 12 h (1)	3 days (5)		
Topotecan	Urine: 20 – 60 % * (1)	2 days (8)		
Treosulfan	Urine: 22% unchanged in 24 h (1), of which 90% within the first 6 h	1 day (8)		

5. Pharmaceutical Care of the Patient

The structured, quality oriented service of advising and caring for oncological patients by the responsible pharmacist should begin immediately before or during the first chemotherapy.

The content of advice given on the cytostatics used and the supportive measures includes the effect, location of the effect, type of administration, relevant side-effects and interactions. The advisory talk must include instruction on the action to take in the event of side-effects and a presentation of possible ways of avoiding side-effects in everyday life.

In addition, the pharmacy offers continuous care accompanying the medical therapy for the entire therapeutic interval. It is useful to provide the patient with written informational material and instructions on how to act. The contents of the talk are documented in the pharmacy. Efforts should be made to establish close cooperation with the doctors giving treatment, the nursing personnel and other professionals involved.

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The pharmacy is continuously striving to implement pharmaceutical advice and care as a component of the oncological service in practice. The aim is to seek direct contact with the patients being supplied with the drug and infusion solution. Development of the patient-oriented service takes account of the particular characteristics of the inpatient and outpatient sectors. Information can be imparted directly through contact with the patient, or indirectly by means of preparing and passing on informational material to the patient. In addition, the pharmacy provides technical advice for the doctors giving treatment and the responsible nursing staff; these activities are also part of a patient-oriented oncological pharmacy for cancer patients.

In order to implement an advisory and care service the employees of the cytostatics department must follow a structured procedure. A prerequisite for providing advice and care in accompaniment to therapy is that relevant data is conveyed through the doctor. (see Chapter 3.5.1. Requisition Form).

Direct advice and care is provided if personal contacts to the patient are possible.

Sequence of Structured Advice

First Contact with the Pharmacist

The first contact should be used to give advice about the current chemotherapy and the concomitant medication. The advice given must include the following important information about the cytostatics prescribed:

- Type of infusion solution and brief description of its quality-assured preparation
- How to care for pumps intended for ambulant use
- Details of taking / administration
- Location and type of effect
- Undesirable effects that may occur (explain the purpose of the prophylactic and necessary use of supportive medication and also aids, e.g. repeat reminder to be fitted for a wig)
- Interactions with other drugs already being taken, with foods and with unconventional treatments (CAM) if known to the pharmacy providing the care
- Give patient a written record of the talk or an information brochure about the chemotherapy prescribed
- Indicate possibility and benefit of continuous care (e.g. patient card, offer to answer questions over the telephone)
- Documentation of the content of the first talk.

First Follow-up Meeting at the Beginning of the Next Therapy Cycle

If after the first meeting the patient expresses the wish for care by the pharmacy during the therapy, a further meeting is useful at the beginning of the next cycle.

Possible content of follow-up talks:

- Brief referral to the first talk
- Discussion of open questions remaining from the first talk
- Enquiry as to how the patient feels
- Advice about new drugs if a change has been made
- Information about other medicines from the non-oncological prescribing sector
- Giving the patient a written record of the talk if necessary
- Additional record of the talk for the pharmacy.

Meetings Accompanying Therapy

If the patient has decided for a patient card or is being treated in a centre or clinic over a longer period, efforts should be made to establish continual pharmaceutical care. Meetings take place and contact is made, for example:

if the prescription is changed
- in this case advice is given about the drug and how it relates to the previous therapy, etc.

Brief routine contacts take place if the centre/clinic is revisited:
- short talks take place in the pharmacy or on the telephone as part of the pharmaceutical care.

Aims of the continuous care are:
- improvement in the quality of life of the patients being cared for
- promotion of compliance
- avoidance of side-effects
- detection of drug-related problems
- motivation of the patient to fulfil the therapy plan by explaining the effects of the drugs and avoiding or reducing side effects.

Indirect Pharmaceutical Care

Preparation of written patient information material (content aligned on the matters discussed in the above talks) concerning the drugs prepared and the supportive medication prescribed. In most cases oncological patients do not see the package leaflets from the drugs used during an oncological therapy. The doctor explains everything to them verbally and the patient signs a patient education form on chemotherapy describing the general problems which may arise during treatment with cytostatics. The pharmacy should extend this with written information relevant to the patient about the drugs prepared in the individual case. This is then handed out along with the drug. The possibility is also mentioned of personal contact with the responsible person in the supplying pharmacy. This kind of drug information should be provided as a minimum offer within the framework of drug safety and, strictly speaking, is required by the *Apothekenbetriebsordnung* (pharmacy regulations).

Aims of the indirect service are:

- safe usage of drugs (drug safety)
- support for the therapy performed by doctors and for nursing work
- avoidance of side-effects and complications.

Documentation

In the outpatient sector the patient's decision in favour of pharmaceutical care is the start of the documentation. The written consent by the patient that personal data may be stored in the pharmacy follows with the decision for care. As far as possible the patient should be informed during the first advisory talk about the possibility of concentrated care through the medium of a patient card file. The documentation in the patient's file should be presented as an aid to ensuring the concentrated pharmaceutical service accompanying the therapy.

In the inpatient sector of drug supply the maintenance of a patient's file ensures that a mass of information already exists. In this case the oncological pharmacist, after agreement with the medical and nursing environment, can also make separate notes. It is recommended that a copy of informational material handed out be kept for documentation in the file and for informing the doctors and nursing staff.

The aim of comprehensive pharmaceutical care is improvement or maintenance of quality-of-life, promotion of compliance, dispelling anxiety by providing information as a team with doctors, nurses and other professional groups involved in the care of cancer patients and their relatives, and preventing medication errors. Lasting protection of the patient from the possibility of medication errors can best be achieved if the oncological pharmacy works in a patient-oriented way as part of a team with the other professionals involved.

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5.1. Preparing a Care Plan

The care plan is an essential component of the concept of pharmaceutical care. It serves for organising the pharmaceutical care of a patient in a way that is related to the problem and oriented on success. All care interventions are stated in writing in the plan. The result of these interventions is monitored at specific intervals using previously defined control parameters.

The care plan is the outcome of a systematic "SOAP" analysis of all medication-related problems of a patient.

The acronym SOAP stands for:

Subjective
The patient's subjective complaints and problems are ascertained and documented.

Objective
Measurable, objective parameters are determined and documented.

Assessment
The above objective and subjective problems are analysed systematically and different possible solutions are discussed with their advantages and disadvantages.

Plan
The care plan is prepared on the basis of the previous analysis. In this plan, therapeutic goals are fixed and the measures which will be introduced for achieving these goals are precisely defined. After an appropriate period, achievement of the goals is monitored using control parameters and the results are recorded in writing.

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5.1.1. Advantages of the SOAP Analysis

The high-quality pharmaceutical care of oncological patients is a very complex and time-consuming task. The recommended way of coping with this task as efficiently as possible is the preparation of a care plan according to the SOAP method. Some of the reasons in favour of this approach are:

- Working according to the SOAP method demands very precise formulation of the medication-related problems and therefore helps in distinguishing between medical problems (that the doctor must solve) and pharmaceutical problems.

- The care plan contains concrete measures intended to solve these problems and the success of these is regularly monitored; ineffective measures are therefore rapidly identified and can be modified.

- A care plan demands that patients become actively involved in dealing with their problems and complaints in the form of training courses, the keeping of records and evaluation of the results of interventions. Their personal responsibility is thereby strengthened and they have the feeling that they are themselves doing something to combat their illness. Studies at the Hospital for Tumour Biology in Freiburg have shown that patients with greater personal responsibility not only want to "take their fate into their own hands", but also live longer.

- The care plan can be used simultaneously for documenting the care provided.

- A written plan conforming with the SOAP method makes it easier for deputising colleagues to become familiar with the case and thus enables them to maintain continuity in caring for the patient.

5.1.2. Performing the SOAP Analysis:

Gathering Data

The SOAP analysis begins by gathering the subjective and objective data. If care is provided in a public pharmacy, most of the information is obtained during the talk with the patient. The medication profile and the chemotherapy protocols provide further important information. An attempt should always be made to talk to the oncologist or family doctor treating the patient.

In the hospital or care facilities much of the information needed is available in the form of patient files and the care report. Nonetheless, a talk with the patient is indispensable.

It is recommended that a standardised form be used in order to accelerate data collection and present the documentation clearly. This form can be developed by the pharmacy itself, or taken from a computer program for pharmaceutical care. This kind of form also helps to avoid important questions being overlooked, e.g. asking the patient about allergies.

The form should be constructed in the following way:

1. General patient data such as name, address, date of birth
2. Social background such as family status, children, domestic and accommodation situation, eating habits, consumption of alcohol and tobacco
3. Brief medical history with questions about functional disturbances and metabolic diseases, height and weight
4. History of drugs taken with current medication profile including OTC preparations, homeopathic medicines, "natural remedies" and "household remedies".
5. Space for notes on the patient's subjective complaints
6. Objective data such as weight, blood picture, creatinine and liver values are best recorded in tables and/or presented graphically in order to rapidly perceive trends.

Analysis

The aim of the analysis which follows is to investigate the problems individually in order of importance (for the patient!) from as many different aspects as possible. In doing so, all the factors causing or influencing the problem should be considered.

It is important not to take over any previous opinions relating to the origin or course of a disease, or to draw premature conclusions on the basis of a syndrome. All conclusions should be supported (e.g. by references to the literature).

The analysis is recorded in writing.

Preparation of the Plan

Based on the analysis, therapeutic goals are defined in the course of discussion with the patient, relatives involved, other persons providing care and/or the doctor giving treatment, and these goals are then entered in the care plan. Goals must be clear and formulated in a way the patient can understand. The steps necessary for achieving these goals are discussed with all participants and also written down. These steps must be understood and accepted by everyone in order to ensure compliance. It can be useful (e.g. for the handling of certain equipment) to prepare an information sheet for patient and relatives. If efforts are being made towards changes in behaviour (e.g. an increase in the quantity of supplementary nutrition drunk per day or per week), it can help if the patient is required to keep a diary or maintain a protocol.

Evaluation

The success or partial success of the measures introduced must be measurable (e.g. weight increase) or observable (e.g. reduction in the number of pain episodes recorded by the patient in the pain protocol - see 5.2.2. Management of Pain Therapy) within a period of time defined in the plan.

At the end of each control period every measure is evaluated. If a particular measure has not produced the desired result, it is important to explain the possible reasons to the patient in order to motivate for new measures and to maintain compliance.

Non-compliance is not the fault of the patient but indicates that the measures taken were not suitable for this patient.

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5.2. Supportive Therapy
5.2.1. Management of Nausea and Vomiting

As adverse effects of an antineoplastic therapy, nausea and vomiting are feared by patients and are perceived to be especially unpleasant. If these side effects are strongly pronounced, they may under certain circumstances lead to the therapy being discontinued prematurely. For these reasons, it is important to ensure an efficient antiemetic supportive therapy.

Account should be taken of the following points when choosing a suitable therapy:

- emetogenic potential of the therapy
- individual patient risk factors
- different phases of nausea and emesis
- therapeutic guidelines from official professional bodies following the principles of evidence based medicine (EBM)
- pharmaco-economic aspects.

Implementation of the selected therapy should be supported by
- cooperation of patient, doctor, pharmacist and other involved persons
- measures to promote concordance and
- information about additional prophylactic measures.

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In the course of an antineoplastic therapy the cancer patient is confronted by a range of systemic treatment concepts such as cytostatic chemotherapy, immune therapy and hormone therapy. These different approaches are buttressed by supportive therapy intended to maintain or improve quality of life.

Even after the introduction of the 5-HT_3 antagonists, the two effects feared most by patients and perceived as especially unpleasant are nausea and emesis [1]. In some cases, when these adverse effects are very strongly pronounced and poorly

treated, premature discontinuation of the therapy may result. It is therefore important to ensure an efficient antiemetic supportive therapy.

Emetogenic Potential of the Therapy

Choosing a suitable antiemetic supportive therapy is primarily oriented on the emetogenic potential of the substances being given. In this respect, not only the substances themselves but also the doses administered play an important role [2]. Table 1 presents an extract from this classification by Hesketh [1999].

Frequently, however, chemotherapy is not simply performed as monotherapy but involves a combination of different substances. Hesketh et al. (1997) therefore developed an algorithm by means of which the total emetogenicity of a combination therapy can be estimated [3]:

1. The most highly emetogenic substance in the combination is identified.
2. The contribution of the other substances to the total emetogenicity is estimated according to the following rules:
3. Substances at Level 1 make no contribution to the emetogenicity of a combination therapy.
4. Inclusion of one or more substances at Level Class 2 raises the emetogenicity of the most emetogenic substance in the combination by a total of 1 level.
5. Inclusion of substances at Level 3 and Level 4 increases the emetogenicity of the combination by 1 level per substance.

Examples for using this algorithm are presented in Table 2.

Individual Patient Risk Factors

In addition to the emetogenic potential of the chemotherapeutic agents, it is also possible to define individual patient risk factors (see Table 3) [4]. Although these have been demonstrated in clinical studies, they are mostly ignored in practice. However, they can serve to complete the picture of the patient and to provide clues for understanding better or poorer tolerance of the chemotherapy.

Different Phases of Nausea and Emesis

The different phases of chemotherapy induced nausea and vomiting must be taken into account for antiemetic supportive therapy since their occurrence is based on different mechanisms. The forms of nausea and vomiting that occur are divided between acute, delayed and anticipatory.

Acute vomiting occurs during the first 24 hours after the chemotherapy. In this case chemotherapy or radiotherapy leads to the release from the enterochromaffin cells of the small intestine of serotonin (and other substances), which then activates the vomiting process via specific receptors (5-HT3 receptors) located (for example) at vagus nerve endings. Further serotonin receptors are located in the chemoreceptor trigger zone in the area postrema, which in turn passes on information to the vomiting centre in the formatio reticularis. In addition to serotonin, dopamine (via D2 receptors) and neurokinin-1 (via NK1 receptors) are also involved in the induction of nausea and vomiting.

Delayed vomiting occurs between 1 and 5 days after the therapy. The causes of delayed vomiting are not yet properly understood. It seems probable that this also involves participation by diverse neurotransmitters such as dopamine, serotonin and neurokinin-1.

Anticipatory vomiting already occurs for psychological reasons before therapy has begun. It is the result of conditioning by previous experience of nausea and emesis and can be triggered, for example, by the sight of the infusion solution or by the act of entering the hospital.

These different mechanisms must be taken into account during therapy and primarily influence the choice of drug (see below).

Therapeutic Guidelines from Official Professional Bodies Following the Principles of Evidence Based Medicine (EBM)

Therapy guidelines for optimal antiemetic therapy are issued by the different professional associations. They were drawn up and updated using the principles of evidence based medicine (EBM). Table 4 contains a selection of such therapeutic guidelines.

To summarise the content of the different guidelines, the combination of 5-HT_3 antagonists with dexamethasone has been objectively proved to be the most effective prophylactic against acute vomiting in the case of highly and moderately emetogenic regimens, and this is therefore recommended as the "gold standard". The most frequently recommended therapy for delayed emesis is the use of dexamethasone, combined if necessary with metoclopramide or a 5-HT_3 antagonist. On the other hand, the benzodiazepine group - primarily lorazepam - is indicated for anticipatory vomiting on grounds of its psychological nature. Exact dosages and the therapy for other emetogenicity levels are given in the guidelines listed in Table 4.

In addition to the established substances, new approaches to improving antiemetic supportive therapy are always appearing. Aprepitant (Emend®), the first substance from the neurokinin-1 receptor antagonist group, was licensed in the USA in June 2003. In clinical trials this group has demonstrated in particular a significant advantage in the therapy of delayed vomiting. In a multicentre, randomised, controlled, double-blind study, an antiemetic therapy with aprepitant, dexamethasone and ondansetron for the delayed emesis phase after chemotherapy including cisplatin achieved complete response for 75% of the patients. "Complete response" was defined as no incident of vomiting and no intake of rescue medication during this period. In the control group receiving only dexamethasone and ondansetron the corresponding figure was 50% ($p<0.001$). Further clinical studies are needed to demonstrate the benefits of this substance during therapy not containing platins.

Pharmaco-economic Aspects

As a result of the pressure of costs on the health service, therapeutic guidelines are drawn up not only on the basis of clinical trials but also with consideration of pharmaco-economic studies. The use of 5-HT_3 antagonists is the subject of particularly critical observation. Whereas the administration of 5-HT_3 antagonists in the case of acute vomiting is more cost effective than the administration of high doses of metoclopramide, 5-HT_3 antagonists should generally not be used for delayed vomiting. Compared with highly dosed metoclopramide, the use of 5-HT_3 antagonists would generate considerably higher costs of up to 30%. The particular 5-HT_3 antagonist selected, the formulation and many other aspects also exert an influence on the total cost of the therapy and should be taken into account in the therapy guidelines.

Interdisciplinary Cooperation

In addition to the preparation of such guidelines, their implementation in practice is particularly of central importance. The implementation demands close cooperation between doctor, nursing personnel, pharmacist and patient in order to ensure the best possible therapy. One way in which the pharmacist can provide assistance could be, for example, by supplying the doctor's office or the ward with the antiemetic support therapy for the particular patient together with the chemotherapy, and monitoring compliance with the guidelines by documenting drug usage. The creation of a "communication network" of all participants can contribute towards

improving the flow of information and thus ensure an optimal therapy for the patient.

In addition to the issues listed above, which primarily influence the collaboration between doctor, nursing staff and pharmacist, advising and informing the patient is also very important - above all in promoting compliance and concordance.

Concordance

Whereas the term "compliance" has a somewhat one-sided connotation ("the specialist prescribes, the patient obeys"), the term "concordance" also includes the wishes and needs of the patient. The term is defined as an agreement between patient and "expert" concerning the drug therapy - an agreement that respects the wishes and needs of the patient. Table 5 lists measures for promoting concordance [6].

Prophylactic Measures

The self-management of the patient is also of great importance within the supportive therapy and can be supported by the pharmacist. The main measure for promoting self-management is the provision of information about additional prophylactic measures. Within the context of treatment for nausea and vomiting, this primarily concerns advice about nutrition. Table 6 presents an overview of prophylactic measures.

The goal of supportive therapy is to ameliorate the adverse effects of the therapeutic drugs and thus to maintain the patient's quality of life during the therapy. This can be achieved in the field of antiemesis by observing the points listed above.

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Table 1: Emetogenic potential of cytostatic agents (from Hesketh 1999)

Level	**Frequency of vomiting** [%]	**Substance**
5	> 90	carmustine > 250 mg/m² cisplatin = 50 mg/m² cyclophosphamide > 1500 mg/m² dacarbazine
4	60 - 90	carboplatin carmustine = 250 mg/m² cisplatin < 50 mg/m² cyclophosphamide > 750 = 1500 mg/m² cytarabine > 1 g/m² doxorubicin > 60 mg/m² methotrexate > 1000 mg/m²
3	30 - 60	cyclophosphamide = 750 mg/m² cyclophosphamide (oral) doxorubicin 20 – 60 mg/m² epirubicin = 90 mg/m² methotrexate 250 – 1000 mg/m²
2	10 - 30	capecitabine docetaxel etoposide fluorouracil < 1000 mg/m² paclitaxel gemcitabine topotecan methotrexate > 50 < 250 mg/m²
1	< 10	bleomycin busulfan fludarabine methotrexate = 50 mg/m² vinblastine vinorelbin vincristine

Table 2: Examples of the emetogenic potential of combination therapies (from Hesketh et al. 1997)

Emetogenic potential of the individual substances		Level of the combination
2 + 2	=	3
2 + 2 + 2	=	3
3 + 2	=	4
3 + 2 + 2	=	4
3 + 3 + 3	=	5

Table 3: Individual patient risk factors

Factors for high individual risk
• Poor control in previous chemotherapy cycles
• Female gender
• Low alcohol consumption
• Young age

Table 4: Overview of the different guidelines on the treatment of nausea and emesis

Professional Association	Year	Title	Source
MASCC	1998	Prevention of chemotherapy- and radiotherapy-induced emesis: results of the Perugia Consensus Conference	Annals of Oncology 1998; 9:811-819
ASCO	1999	Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice Guidelines	Journal of Clinical Oncology 1999; 17:2971-2994
ASHP	1999	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery	American Journal of Health-System Pharmacists 1999; 56:729-764
ESMO	2001	ESMO Recommendations for prophylaxis of chemotherapy-induced nausea and vomiting (NV)	Annals of Oncology 2001; 12:1059-1060

Table 5: Measures for promoting concordance (modified from Reymond and Lennecke, 2003)

Measures for promoting concordance
Informing and motivating the patient in respect of: • benefits and necessity of the therapy • start of therapy • dosage, dosage interval • time of intake • interactions with foods • duration of treatment • common undesirable effects. Issuing dosage cards and administration plans

Table 6: Preventive measures in the case of nausea and emesis

Advice on prophylaxis against nausea and emesis
• Avoid large meals • Eat five or six small meals a day • Cold food is often tolerated better than hot; same applies to cooled drinks • Stimulate appetite with sharp-flavoured sweets, foods or drinks • Sufficient fresh air • Get through difficult phases with sleep, relaxing music or walking in the fresh air • Eat no sweet, very greasy, strongly spiced or fried foods • Avoid strong smells

5.2.2. Management of Pain Therapy

Most tumour patients suffer pain in the course of their disease. There are different causes of pain and different types of pain, which also occurs at different intensities. Pain must be recognised at an early stage and treated consistently and appropriately using all possible methods. This must be taken into account when preparing a therapy plan in which pharmacotherapeutic approaches can be combined with other possible kinds of treatment.

Thanke Mehrtens, Hannover
Annette Junker, Remscheid

Classification of Tumour Pain

Tumour-related pain occurs in 60 to 90% of patients as a consequence of the uncontrollably growing tumour infiltrating soft tissue, metastasising in bones, and compromising and infiltrating neural, blood and lymphatic vessels.

Between 10 and 25% of patients suffer therapy-related pain. This pain occurs as a result of operations (caused by neural lesions and scarring), radiotherapy (caused by neuropathies and mucositis) or chemotherapy.

Accompanying diseases or complications cause zoster neuralgia, bedsores, venal thromboses and fungal infections and
lead to so-called tumour associated pain in 5 to 20% of patients.

The treatment of existing pain syndromes which are not associated with the tumour, i.e. caused by migraine or arthritis, must naturally be continued.

Types of Pain

Nociceptor pain arises as a result of tissue damage. Stimulation of nociceptors in the skin, in connective tissue, in muscle and in bone leads to pain that is generally easily localised, is described as dull, boring, dragging or stabbing, and is intensified by movement or pressure (somatic pain). If the nociceptors of internal organs are activated by compression, infiltration, displacement or inflammation, the result is designated as visceral pain, which is frequently difficult to localise and is described as cramplike and deep.

Neuropathic pain arises as a result of damage or irritation to the nervous system (compression, infiltration). It is accompanied by sensory (e.g. paraesthesia and dysaesthesia) and motor disturbances (paralysis). Damage to the nerves is perceived by patients as permanent burning or tingling pain (deafferentation pain).

Breakthrough pain is the term used for pain that flares up from a stable level of resting pain. This can occur without any obvious trigger, but also under load (movement, coughing).

Recording Pain

A structured pain history encompasses the following questions:

• where?	localisation? radiation?
• how?	quality? intensity?
• when?	chronological progression? development?
• caused by?	trigger, amplifying, reducing factors?
• why?	causal relationship?
• accompanying symptoms?	nausea?

In addition, the chronological duration of the disease, the extent and localisation of the tumour, neurological disturbances, skin changes and measures taken so far are all recorded. The patient's circumstances, psychological situation and possibilities for care are also taken into account in developing a therapeutic strategy.

Standardised survey forms should be used for the anamnesis, the course of the therapy and its evaluation. In evaluating the intensity of pain, the recording process is also facilitated by one-dimensional scales (VRS = verbal rating scale) or VAS (visual analogue scale) or NRS (numeric rating scale). These scales are marked by the patient according to how strongly he perceives the pain.

A brief description of the scales follows:

Verbal rating scales (VRS) normally have a four- or five-level graduation:

- no pain
- slight pain

- moderate pain
- severe pain

The VRS is easy to understand and can therefore be used for most patients. It has the disadvantage that it is very coarsely graduated and slight changes are poorly registered.

The NRS (numeric rating scale) demands a greater capacity for abstraction from the patient but, in comparison to a VRS, provides the opportunity to record minor changes in sensitivity to pain. The number "0" describes complete freedom from pain and the number "10" describes the maximum imaginable pain.

0 1 2 3 4 5 6 7 8 9 10

The visual analogue scale (VAS) also requires a degree of abstractive ability and can therefore not be used for every patient. However, it does enable pain to be recorded precisely and changes to be documented.

no pain _____ strongest imaginable pain

The measurements should be taken several times a day and documented in the form of pain diaries in order to obtained a subtly differentiated picture. Multidimensional instruments for further pain recording are described extensively in the guidelines listed in the appendix. The BPI (brief pain inventory), for example, also records pain-related impairment of the activities of daily life and of the relationship to others, and also well-being and mood.

During the stabilisation phase the patient must visit the doctor frequently so that the therapy can be monitored and adapted as necessary. Later on, the periods between visits generally become longer.

Changes in Sensitivity to Pain

Since pain is perceived subjectively it is influenced by psychic factors. Worries and anxiety, sadness and depression can strengthen the sensitivity to pain and must therefore be accounted for and treated at the same time. Although psychotropic drugs raise the pain threshold, human affection also plays a very important role here.

Therapy

The initial approach involves the attempt to eliminate if possible the origin of the pain by means of surgical, radiotherapeutic and chemotherapeutic methods (causal therapy). The individual symptomatic pain therapy begins at the same time, focussing on oral medication. The medication is organised according to the stepped procedure suggested by the WHO and is given in accordance with a strict, needs-oriented schedule. Accompanying symptoms and side-effects must also be treated. Acute pain is treated with oral formulations with a rapid onset of action; occasionally intravenous or subcutaneous injections may also be necessary. Chronic pain is treated with long-acting drugs or sustained-release preparations, which are given according to a fixed, individual plan. Transdermal therapeutic systems (TTS) are also employed. For the treatment of attacks of pain, patients are prescribed additional, rapid release formulations. Regular monitoring of the pain medication is necessary in order to be able to adapt it frequently to actual needs. It may prove necessary to give co-analgesics to supplement the analgesics already being taken.

WHO Stepped Procedure

Level 1; non-opioids * and/or co-analgesics

These drugs given as basic medication inhibit prostaglandin synthesis and thus exert an analgesic and anti-inflammatory effect. Combining more than one NSAID should be avoided since the effects are not additive whereas the toxicities probably are. One problem is the delayed detection of infections as a result of the antipyretic active components in the NSAIDs. Paracetamol, metamizol, ibuprofen, diclofenac or naproxen are frequently prescribed at Level 1.

The term co-analgesics is understood to mean drugs that alter the perception of the pain situation without themselves directly exerting an analgesic effect. These are normally psychotropic drugs.

Level 2: Weak opioids* and/or non-opioids and/or co-analgesics

If the pain cannot be controlled using non-opioids or there are contraindications, weak opioids are prescribed. A combination of the two groups of drug is useful (additive effect). The weak opioids include codeine and dihydrocodeine, tilidine/naloxone or tramadol.

* Pharmacokinetics, dosages, side-effects and interactions of the drugs listed are described in the textbooks listed in the appendix, in the guidelines cited and in the prescribing information for the respective drugs. These aspects are therefore not dealt with here in any greater detail.

Level 3: Strong opioids* and/or non-opioids and/or co-analgesics

If the pain can no longer be sufficiently controlled at level 2, strong opioids - frequently controlled-release morphine - are prescribed. A combination with non-opioid analgesics and psychotropic drugs is useful. Morphine drops or rapid release tablets are suitable for break-through pain. An alternative is the use of oral levomethadone, oxycodone and hydromorphone or sublingual buprenorphine. Transdermal therapeutic systems (TTS) or opioids administered parenterally (PCA pumps) are primarily used for patients with dysphagia or suffering from severe vomiting. Pethidine is not recommended since this drug has only a short period of action and can lead to an increased excitability of the CNS with muscular tremor and spasms. Pentazocine is also unsuitable for treating tumour pain on account of its short period of action and its pronounced psychomimetic effects.

Parenteral Pain Therapy

Although drug treatment of pain should preferably be performed orally this is not always possible, for example in the case of a tumour disease that prevents oral intake of medication (oesophageal carcinoma) or of severe vomiting; in such cases a parenteral therapy is unavoidable. Further indications are pharyngitis or malabsorption, ileus, or the need to administer very high doses. Portable PCA pumps (patient controlled anaesthesia) make outpatient therapy possible. A continuous infusion of analgesics not only results in a stable concentration in the blood, but also enables the pain situation to be effectively titrated because the patient is able to initiate a bolus administration from the PCA pump in the event of breakthrough pain. Opioids and non-opioids can be combined (ensure compatibility!) The drugs used are metamizol, tramadol or piritramide. The preferred method of administration is subcutaneous since it is less invasive and less prone to problems while being just as effective as intravenous administration; it is therefore especially suitable for ambulant patients. The opioid is administered continually by means of a portable pump, subclavicularly through a subcutaneous needle in the anterior thoracic wall or in the abdominal region. The administration site is changed if there is pain at the site of injection, reddening, swelling or leakage. If the patient already has an implanted intravenous access, however, (Hickmann catheter, port system) this can be used for the i.v. therapy.

Most of the pumps described in Chapter 3.3.1.1. "Infusion Pumps for the Administration of Cytostatics" can also be used for pain therapy. Literature on the use, filling and compatibility of the infusion mixtures is available from the respective manufacturer. When choosing a PCA pump, the possibility of a bolus administration should be borne in mind.

Therapy Adaptation

It is often necessary to change the method of administration or the drug on account of difficult to control adverse effects (sedation, cognitive impairment, nausea, constipation). This applies not just to the anaesthetic but also possibly for the co-analgesic given at the same time. Conversion tables are available for the opioids, though these are based on results with patients not receiving long-term opioid therapy. The equivalent doses listed in these tables must be regarded only as a guide and the patient must be kept under close observation. At the changeover, a start is made with half the calculated necessary daily dose of the new active substance and this is accompanied by a fast-acting drug for times of need. The basic medication is then increased in steps and the drug for times of need is adapted accordingly.

Therapy of the Undesirable Effects of the Pain Medication*

The therapy of a few important side effects of pain medication are discussed in the following.

Nausea/vomiting

It is recommended that an antiemetic be given during the first 14 days of the opioid therapy. Several antiemetics can also be combined. If the nausea reappears spontaneously during the therapy the cause must be ascertained. The following drugs are available for this therapy: metaclopramide and domperidone, dimenhydrinate and haloperidol. If the effect is inadequate, it is also possible to resort to 5-HT_3 antagonists and/or glucocorticoids.

Constipation

The basic measures for preventing constipation, for example food rich in ballast, increased fluid intake and physical activity, are frequently no longer possible for tumour patients. Laxatives should therefore be prescribed according to individual needs and in good time. Available drugs include bisacodyl or sodium picosulphate, lactulose and salts exerting an osmotic effect.

Further Side Effects

The following undesirable effects frequently occur during therapy with opioids and must also be treated.

Special Pain Syndromes*

Treatment of neuropathic pain

Constant pain and burning pain respond to therapy with tricyclic antidepressants (e.g. amitryptaline, doxepin, clomipramine or imipramine). Anticonvulsive agents (carbamazepine, phenytoin, gabapentin, clonazepam) exhibit good effect against sudden attacks of pain. Baclofen is indicated for pain with spastic components and dexamethasone in the case of neural compression and increased cerebral pressure.

Possible side effect	Therapeutic possibility
sedation, confusion	check dose or change drug
sweating	anticholinergic agent, sage preparations, change opioid
itching	antihistamines, skin care, change opioid
retention of urine	reduce co-analgesics (especially tricyclic antidepressants) and anticholinergic drugs, give parasympathomimetics, check dose of opioid/change drug
dry mouth	oral hygiene, suck sweets

Treatment of pain in bone and soft tissue

Bone pain frequently depends on the load, i.e. pain at rest is easily treated but the treatment is insufficient for periods of loading. Bone pain responds well to NSAIDs and opioids; in the case of spasticity baclofen can also be used. In these cases biphosphonates (pamidronic acid, ibandronic acid, zoledronic acid) are also used frequently with success. Radiotherapy is often also indicated in the case of bone pain.

Treatment of visceral pain

In addition to the pain, accompanying vegetative symptoms (nausea, sweating, tachycardia, constipation) must also be treated. It may not be possible to administer the drugs orally because of severe vomiting or dysphagia in which case a different method of administration must be chosen. In these cases spasmolytic agents such as N-butyl scopolamine or NSAIDs with spasmolytic components (metamizol) and glucocorticoids are used.

* Pharmacokinetics, dosages, side-effects and interactions of the drugs listed are described in the textbooks listed in the appendix, in the guidelines cited and in the prescribing information for the respective drugs. These aspects are therefore not dealt with here in any greater detail.

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5.2.3. Management of Alopecia

Alopecia is a tiresome side-effect for the patient during many types of cytostatic therapy.

Although the possibilities for treatment are still very limited, this aspect must be taken into account in patient care and the preparation of therapy plans.

Michael Höckl, Hamburg

Hair cells divide very actively and are damaged by the administration of cytostatics; this has the following results:

In the case of moderate damage, a fraction of the hair follicles stops growing sooner. After a short transition phase they enter the resting phase and fall out more or less at the same time after two to four months.

If the damage is very severe, the hairs are poorly formed with the result that they break off prematurely. Loss of hair already starts two weeks after administration of the chemotherapy and all the hairs fall out within a few weeks, except for the hairs in the resting phase.

Not only the hair on the head is affected, but also eyelashes, eyebrows, facial hair and hair on other parts of the body. Not all cytostatics cause the same degree of hair loss and some substances hardly affect hair growth at all. Information is given in the respective prescribing information. After polychemotherapy, however, different levels of hair loss are very common.

Cool-caps are occasionally used at the patient's request. There is little scientific evidence, however, for the effectiveness and safeness of this measure. The reduced circulation of blood to the scalp results in a reduced local concentration of the cytostatic administered, but this may protect any metastases present in the scalp. Moreover, reducing the blood supply to the scalp only seems logical for substances with a short half-life and for administration as a bolus or short infusion.

After explaining the situation to the patient, the possibility of wearing a wig and the use of scarves should be discussed. A wig can be prescribed by the doctor. Providing information about the actual probability of hair loss during the use of the respective cytostatic agent is a central task of the pharmacy giving advice. It is important to stress the high regeneration capability of the hair follicles; new hairs are already visible one to two months after completion of the chemotherapy and hair begins to grow on the head at the same time. It should also be pointed out that the new hair may be different to the old; hair that was formerly straight may become wavy, and vice versa. There is no scientific evidence that hair growth after chemotherapy can be promoted by medication.

The pharmacist should provide information about the possibilities for covering the head and about the need to protect a scalp that is sensitive to sunlight. The patient should be told where wigs can be bought locally and should be given patient leaflets and an explanation of what they contain. If patients prefer to wear a scarf, brochures about tying techniques can be kept in readiness. If the patient wishes to wear neither a wig nor a scarf, advice must be given about the importance of protection from the sun since the exposed scalp is very sensitive to sunlight. In view of the loss of eyelashes and eyebrows, advice about make-up is helpful for women and should be offered in public pharmacies.

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5.2.4. Management of Mucositis

Inflammation of the mucous membranes - mucositis - is named according to its localisation: stomatitis, oesophagitis, cystitis, etc. It is a frequently occurring side effect in tumour patients being treated with chemotherapy and radiotherapy. Lesions of the mucous membrane can be extremely painful and impair the tumour patient's quality of life to a considerable extent.

The pharmacist works out proposals for the prophylaxis and therapy of mucositis for individual patients and collaborates with the oncology team in preparing recommendations for prophylaxis and therapy within the framework of quality assurance.

Hannelore Kreckel, Giessen

Inflammation of the mucous membranes, named according to localisation as conjunctivitis, stomatitis, gingivitis, periodontitis, glossitis, pharyngitis, oesophagitis, gastritis, enteritis, colitis or vaginitis, represents a burdensome situation for the patient, which can persist for several weeks if not treated. Typical symptoms are signs of inflammation with reddening, hyperthermia, swelling, pain, oedema, atrophy and ulceration. Between 15 and 40% of patients receiving chemotherapy suffer from mucositis, which can involve the formation of a wide diversity of outer layers (pseudomembranous, hyperkeratotic, lichenoid) but also haemorrhages. Patients treated according to high-dose protocols have a 60% risk of developing mucositis (1). This risk is amplified by combined treatment with chemotherapy and radiotherapy. The consequences of mucositis are taste disturbances, lack of appetite, speech difficulties, dysphagia, pain, sleep disturbances, anorexia, weight loss, dehydration and malnutrition.

Chemotherapy induced mucositis is a factor that negatively influences the patient's condition and can be dose-limiting for some substances of the antimetabolite group such as 5-fluorouracil, methotrexate, cytarabine and purine antagonists. Anthracyclines, vinca alkaloids, taxanes, alkylating agents and a few other substances such as bleomycin or actinomycin are further examples of chemotherapeutic agents that frequently induce mucositis. The consequences of mucositis are longer stays in hospital, the need for parenteral nutrition, the more frequent use of (opiate) analgesics and even discontinuation of the therapy. The administration of another oral drug meets with poorer acceptance on the part of the patient in many cases. The patient's quality of life is significantly impaired and the costs of the care increase.

Identification

In the hospital, identifying symptoms and problems of mucositis is the responsibility of the medical and nursing personnel. The pharmacist provides advice on the (drug) prophylaxis and therapy of the mucositis. He imparts the knowledge at his disposal by organising informational material for patients and by preparing guidelines and therapeutic notes for doctors and nurses.

In the outpatient sector the pharmacist is one of the primary contacts for patients and relatives. During the run-up he can bring possible risk factors to patients' attention, explain how to identify these and thus prepare them for the cytostatic therapy. The patient's age, nutritional status, oral and dental status (xerostomia, periodontal diseases) before the chemotherapy, and oral care during the treatment exert considerable influence on the occurrence of mucositis. It is important to identify mucositis at an early stage in order to be able to take appropriate measures for treating it. A simple and useful instrument for doing this is the classification system used by the World Health Organisation (Table 1). Careful examination of the oral cavity is necessary in order to perform the classification. During their stay in hospital patients should be given instruction on how to perform a self-examination, especially of the mouth and pharynx, and how to document the lesions. In order to carry out the examinations they will require an adequate light source and must be told to observe the colour of the oral mucosa, the moisture level, the surface of the mucous membrane, oedema and any lesions, and to document the result of the examination.

Table 1 Classification of mucositis by the World Health Organisation [modified according to (2)]

I	none
II	painful ulcers, erythema or slight reddening in isolated places
III	painful erythema, oedema or ulcers, patient can eat
IV	painful erythema, oedema or ulcers, patient cannot eat
V	patient requires parenteral or enteral support

Prophylaxis

There is currently no established regimen that can prevent the occurrence of mucositis (3). If drugs are used preventively, care must be taken that these do not make the situation even worse. The efficacy of using protocols for mucositis prophylaxis has been demonstrated (4, 5). General recommendations for prevention are:

- Keeping the mouth moist - recommendation to drink copiously
- Daily inspection of the mouth and pharynx in order to identify changes early
- Oral hygiene at least four times daily - after every meal and before retiring for the night
- Clean teeth with a soft toothbrush and fluoridated toothpaste; if necessary use cotton balls or applicators with cotton wool
- No alcohol - also not in drugs or mouthwash
- Avoid extremely hot, cold, sharp or strongly spiced food
  Soft foods as far as possible (see 5.2.6. Nutrition Therapy)
- No smoking

Involving patients as free and responsible partners attributes them with a higher level of independence and dignity.

Treatment

At the present time it is possible neither to prevent chemotherapy induced mucositis entirely, nor to treat it appropriately. Once mucositis has developed the main focus is on reducing the symptoms. The use of analgesics and good and adequate nutrition (see 5.2.6. Nutrition Therapy) form the basis for treating an outbreak of mucositis (3). Manifest infections must be treated adequately. The oral use of local anaesthetics is a standard procedure in units providing oncological therapy.

Classification of Substances

Personal experience and preference, traditions, and ecological and economic reasons are frequently decisive for the use of a particular drug. There is a paucity of conclusive studies. Small sample sizes dominate; the study design is rarely comparable and evaluation is made more difficult by the comparison of different methods. In some cases equivalent treatments yield contradictory results. Different review authors therefore also evaluate the same substance differently. Positive effects in smaller studies can frequently not be verified on a larger scale and even negative effects may be demonstrated. When one considers that a study is more likely to be published if the outcome is positive, there may well be other series of tests which were never published because of the negative results obtained.

Physical Methods:

Cryotherapy:

This involves pieces of ice from frozen fruit juice which the patient sucks during a bolus therapy with 5-fluorouracil over 30 min. The severity and extent of the mucositis is reduced. The mechanism of action probably involves a reduction in the local circulation of blood (6, 7).

Soft Laser Therapy:

The application of low-energy helium neon laser light reduces the occurrence of mucositis and improves the condition of the patient without major side effects (2). However, the necessary devices are not available everywhere.

Local Anaesthetics

Substances such as **benzocaine, lidocaine, tetracaine** and also **cocaine** belong to the standard drugs used for pain therapy. These are mainly applied as dilute solutions and recommended especially for use before meals. Because they impair both the feel for swallowing and also the sense of taste, they do, however, detract from the enjoyment of the meal - assuming this existed at all considering the pain from the mucositis. They are also a common constituent of mucositis cocktails (so-called magic mouthwash).

Local Antiseptics

Contradictory results have been obtained with **chlorhexidine**, ranging from slight worsening or no difference to the placebo, to significant improvement (2, 5). The substance induces additional taste changes, which are perceived as unpleasant (8).

Despite its broad spectrum of antiseptic activity, there are no controlled studies on **PVP iodine** used on its own (2). Acceptance of the substance is generally good.

Crystal violet and **silver nitrate** do exert antiseptic effects but also inhibit granulation and should therefore no longer be used (2). There are no controlled studies of these substances.

Hydrogen peroxide solution (3.5%) increases the risk of mucositis compared with 0.9% saline solution (9).

There are currently no study results available on the use of **octenidine** for rinsing the mouth. The solution is frequently perceived as having an unpleasant, burning taste (10).

Plant Remedies:

Camomile has slight antiphlogistic properties and is therefore used on an empirical basis. The results of an uncontrolled prevention study and a placebo-controlled study are contradictory, however (2, 11). In any case, care should be taken not to use an extract containing alcohol.

Sage, rhubarb, myrrh and **rathania** have astringent properties. Myrrh, rhubarb and rathania are supplied as alcoholic tinctures and should therefore not be used.

Eucalyptus oil and **peppermint oil** are mainly used for flavour adjustment.

No controlled studies could be found on the use of **tea tree oil**.

Pineapple (juice from fresh pineapple, frozen to ice for cryotherapy - q.v.).

Chemical Adjuvants:

Studies on the use of **allopurinol** in mouthwash solutions for the prevention and treatment of stomatitis induced by 5-fluorouracil produced different results. Whereas the first studies raised hopes of positive effects, these results were not confirmed by more recent investigations (2, 12).

Benzydamine as an antiphlogistic agent was less well tolerated by patients than chlorhexidine (13), but in a randomised study was evaluated as well tolerated and as safe and effective in comparison to a placebo (14). The study results as a whole are inconsistent.

Corticosteroids are used to control the local inflammatory reactions. They are frequently a constituent of so-called mucositis cocktails (2).

Doxepin improved tolerance to pain in one study but the substance is systemically absorbed (15).

Morphine mouthwash was compared with "magic mouthwash" (lidocaine, diphenhydramine and aluminium hydroxide) in a small study and positively evaluated (16).

Cytoprotective Agents:

Sucralfate has been tested in numerous studies. The mode of action is based on a protective layer that is formed as a result of ionic binding on contact with proteins and the stimulatory effect on prostaglandin E2 synthesis. The substance does not seem to be able to prevent the occurrence of mucositis (17) but the perception of pain was partly less pronounced (18, 19). On the other hand, a more recent study involving a comparison with a mouthwash solution containing salt and soda was unable to demonstrate any difference in the rate of healing or the perception of pain while swallowing (20). The substance is reasonably priced and has no serious side effects.

Misoprostol , a prostaglandin E2 derivative in tablet form that disintegrates in the mouth and is then swallowed, appears to have no positive effects. There is even a report of reactivation of herpes simplex viruses (21).

Growth Factors:

G-CSF and GM-CSF have been investigated in numerous studies. The available data do not permit a conclusive evaluation of its use in mouth rinse and - in view of the high costs - judgement should be reserved until results are available from controlled clinical studies (2, 3, 22).

TGF-ß (transforming growth factor ß) was tested in a Phase I trial (2); palifermin and repifermin as keratinocyte growth factors (KGF) are currently undergoing Phase II and Phase III clinical trials.

Vitamins:

Dexpanthenol is used on account of its granulation promoting effect. No study exists in which this substance has been tested as a sole agent (2).

Tocopherol as an antioxidant with membrane stabilising properties performed significantly better than a placebo when applied topically (23).

Salt Solutions:

Sodium chloride, Ringer's, Emser salt and salt and soda solutions were compared with chlorhexidine, "magic mouthwash" or water and demonstrated the same degree of efficacy as the active substances (24).

In a comparison of solutions with different **gels** (thin and viscous), thin gel performed better than the solution with viscous gel (25).

Antibiotics, Antimycotics:

Both groups of substance are frequently used in combination as pastilles. The goal is to decontaminate the potentially pathological flora of the mouth and to prevent fungal infections, especially candida infections (2). PTA pastilles (polymyxin B, tobramycin, amphotericin B) (not available commercially in Germany) produced positive effects in the sense of reduced occurrence of mucositis (26). It was also found, however, that the development of severe mucositis could not be prevented (27).

Imidazole antimycotics were shown to be superior to polyenes for local application (2).

Complex combined "mucositis cocktails" containing antimycotics are frequently used for mouthwashes. An example is the so-called Düsseldorf solution (dexpanthenol, amphothericin B, mepivacaine). The individual substances exert only limited effect in the diluted state.

The stability of nystatin was tested in a study for diverse solutions. The results showed a fall in the nystatin content over periods of four days to one week depending on the pH and the storage temperature (28).

Virostatic Agents:

Aciclovir is used successfully for treating oral herpes infections. Use of the substance for prophylaxis in comparison with a placebo showed no difference in the occurrence or severity of mucositis (2, 29).

"Household Remedies":

Glutamine as a non-essential amino acid showed positive effects in smaller studies (2, 30). Further studies are necessary before a final judgement can be made.

Glycerol serves as a sweet-flavoured means of conserving moisture but is known for its dehydrating effect.

Lemon sticks are principally used for refreshment and mostly contain glycerol and lemon aromas.

Lemon juice should not be used on account of its strongly acid pH.

Synthetic saliva is used for moistening the (dry) mucous membrane of the mouth.

Diphenhydramine has local anaesthetic properties and is therefore frequently a constituent of mucositis cocktails (2). No study could be found on the use of the substance alone.

The above list does not claim to be complete.

Systemic Measures:

The **biorhythm (chrono)-adapted administration of cytostatics** also reduces the rate of occurrence of mucositis side effects without affecting the efficacy of the active substances (see 4.4. Chrono-Oncology).

For **pain therapy** - including mucositis related symptoms - anaesthetics should be used according to the WHO stepped procedure (see 5.2.2. Management of Pain Therapy). The reduced consumption of anaesthetics was one of the methods used in studies to measure the efficacy of prophylactic and therapeutic measures against mucositis (14, 31).

When measures such as adequate drinking, avoidance of drinks containing caffeine and alcohol, possible discontinuation of medication associated with dry mouth as a side effect, chewing cinnamon- or peppermint-free chewing gum, sucking sugar-free sweets or the use of synthetic saliva are not sufficient, xerostomia can be treated with low, single doses of **pilocarpine** (32). Drugs causing this side effect include: analgesics, antipsychotics, antihistamines, diuretics, anti-arrhythmics, antiemetics, spasmolytics, expectorants, anti-Parkinson drugs, muscle relaxants, coronary drugs, tranquillisers, antidepressants, anticonvulsives, antibiotics, antihypertensives, anti-vertigo drugs, appetite stimulants, MAO inhibitors, lipid lowerers and acid blokkers.

The role of the anticholinergic agent **propantheline bromide** (not commercially available in Germany) in reducing etoposide elimination with the saliva (31, 32) needs to be examined in larger-scale studies.

Summary

The search for effective substances for the prevention and treatment of mucositis is difficult. A wide diversity of protocols and regimens exists for the prophylaxis and

therapy of mucositis induced by chemotherapy and radiotherapy. It is not possible to give a single, evidence based recommendation on the basis of the available data. The pharmacist with his specialist pharmaceutical knowledge should be involved in the design of protocols within a unit providing therapy. These protocols should be applied consistently in order at the very least to enable statements describing the situation in the department to be made and to ensure comparability within the unit. The instruments used to record data, and therefore the documentation, should also be used in a uniform way.

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5.2.5. Management of Diarrhoea

Diarrhoea during the treatment of tumour diseases is a complication that must be taken seriously. It can occur as a side effect of certain cytostatics or of radiotherapy.

In addition, tumour associated, immunological or infectious processes must also be considered as possible causes.

Untreated diarrhoea leads to weakness, loss of electrolytes and exsiccosis. There is a danger of rapid escalation. The pharmacist should therefore strive to ensure that treatment is early and thorough.

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As a side effect during the treatment of tumour patients, mucositis induced by chemotherapy and radiotherapy must be taken seriously (see 5.2.4. Mucositis). Mucositis of the gastrointestinal tract frequently leads to diarrhoea. If the diarrhoea symptoms worsen despite treatment, this can mean the dose limiting toxicity of the chemotherapy. Moreover, the chronological sequence of the therapy may be delayed. The compliance of the patient is reduced and severe diarrhoea is potentially life threatening for tumour patients receiving treatment (1). It is therefore essential to begin treatment at the appearance of the slightest symptoms of diarrhoea.

According to estimates approx. 10% of all patients with an advanced tumour disease suffer from acute or persistent diarrhoea (2). Typical substances which initiate chemotherapy induced diarrhoea are capecitabine, cisplatin, cytosine arabinoside, cyclophosphamide, daunorubicin, docetaxel, 5-fluorouracil, interferon, irinotecan, leucovorin, methotrexate, oxaliplatin, paclitaxel and topotecan. Combination therapy with fluoropyrimidines and irinotecan increases the risk of suffering from diarrhoea to 50 - 80%. Therapies following high-dose protocols also increase the likelihood of diarrhoea symptoms (2).

Diarrhoea is generally classified according to the National Cancer Institute Common Toxicity Criteria (3):

Grade 0	no diarrhoea
Grade 1 (mild)	up to 4 - 6 stools per day or moderate spasms that do not impair normal activities
Grade 2 (severe)	increase to 7 - 9 stools per day or severe spasms and in continence; everyday activities impaired
Grade 3 (life-threatening)	10 or more stools per day or bloody diarrhoea with the necessity for parenteral therapy

Triggers of Diarrhoea

In addition to the chemotherapy, consideration must also be given to other circumstances which can trigger diarrhoea. These include the use of laxatives (also large quantities of sugar substitutes), antacids with high magnesium content, the use of antibiotics or prokinetics and drug side effects of cardiac glycosides, potassium salts, misoprostol, propranolol or theophylline. Past operations, infectious diseases, stress, neuroendocrine tumours, metastases in the abdominal cavity, radiation therapy and graft-versus-host reactions after bone transplantation are also capable of inducing diarrhoea. Pseudomembranous colitis induced by Clostridium difficile, which is normally associated with longer-term antibiotic therapy, has also been observed in chemotherapy patients who are not receiving any antibiotics (4).

Prophylaxis and Treatment

It is desirable for tumour patients to be warned before the start of treatment about the possibility of diarrhoea. They should be given comprehensive information about possible treatments and supportive measures. During the run-up they they should also be provided with written instructions on measures for symptomatic therapy and a prescription for the corresponding medication. Within the framework of pharmaceutical care and in collaboration with the doctor, the pharmacist can ensure that the patient is informed and educated about which measures are appropriate among the catalogue of possibilities.

Dietic Measures

Patients should be instructed to favour mildly flavoured, easily digestible food with a low proportion of insoluble roughage as the main constituent of their solid intake, and at the same time to compensate the loss of sodium and potassium by drinking large quantities of liquid. Preparations analogous to the "WHO rehydration mixture" (e.g. Elotrans®, Oralpädon®) may be used for compensating fluid deficits. Low-acid fruit juices, preferably mixed with non-carbonated mineral water, are also suitable. Very hot and very cold drinks should be avoided just as strictly as fried, roast and fatty products. Foods rich in potassium (e.g. bananas, peaches, apricots,

mashed potatoes) are useful for potassium replacement and are generally easily digestible.

Milk products present a general problem for patients with lactose intolerance. Moreover, damage to the intestinal villi in patients undergoing chemotherapy can lead to a reduction in the enzyme lactase so that patients may also be affected who previously had no problems (5). These patients should therefore reduce or discontinue their consumption of milk products. Lactose-free milk products can still be used as an alternative. Buttermilk and yoghurt are often tolerated as a result of active lactic acid bacteria. Cheese products are suitable because the lactose is fermented during the production process. Numerous industrial supplementary foods based on milk are free of lactose and can therefore be used to good effect (see 5.2.6. Nutrition).

Drug Treatment

If patients with diarrhoea seek advice in the pharmacy, the possibility should also be considered that an infection is causing the problem. In this case drugs that hinder motility are contraproductive and an ("empirical") antibiotic therapy is indicated. Symptoms such as fever, blood in stool and exsiccosis necessitate consulting a doctor immediately. The following circumstances and symptoms should be taken into account when using drugs: diarrhoea, exsiccosis, malabsorption, loss of electrolytes, neurological symptoms, immunological problems, nutritional status and age of the patient, gastrointestinal and rectal symptoms.

Selection of Drugs and Substances Used:

Medicinal charcoal is frequently recommended for treating diarrhoea because it increases the consistency of the stool. However, it hinders the absorption of orally administered drugs. The swelling substance **pectin** (e.g. in Aplona®) - also in combination with **kaolin** (Kaoprompt H®) - does increase the consistency of the stool but has no influence on its frequency or water content. There is no definite proof that either of these agents are effective against chemotherapy induced diarrhoea (6).

Cholestyramine has proved to be effective against radiation induced diarrhoea. The substance is used in doses of one sachet at every meal and one before retiring for the night. However, side effects are common, especially flatulence and constipation, and the substance interacts with numerous other drugs.

Loperamide, a synthetic opioid, is one of the most commonly used drugs for chemotherapy induced diarrhoea. In Germany it is licensed for a maximum daily dose

of 16 mg. Symptom oriented, a high-dose therapy with 2 mg every two hours is also recommended (7). Within a study, this two-hourly administration was not discontinued until the patient was without a bowel movement for 12 hours. The patients received an average of 21 capsules of loperamide (8).

Diphenoxylate, another synthetic opioid, is recommended - also in combination with atropine - in numerous publications and also used, but because it is potentially addictive it is no longer commercially available in Germany.

Tincture of opium is used only rarely, primarily in the case of diarrhoea accompanied by spasms.

The alpha-2 receptor agonist **clonidine** stimulates absorption and reduces the secretion of the intestinal tract. Because of its hypotensive effect clonidine must be used with caution. The recommended dosages give 0.1 mg twice daily with a daily increase of 0.1 mg up to an interval of 0.4 to 0.6 mg twice a day (4).

Octreotide, a long-acting somastatin analogue, is licensed in Germany for treating endocrine active tumours of the gastrointestinal tract (and for other indications), but not for treating chemotherapy induced diarrhoea. Nevertheless, the substance is used to treat severe diarrhoea and is licensed by the FDA for the treatment of severe, loperamide resistant diarrhoea. Generally commercially available are a preparation that is administered subcutaneously several times a day, and a depot formulation for administration once a month. Use of the depot formulation must be preceded by subcutaneous testing for efficacy and tolerance in accordance with the FDA license. An expert group (including a pharmacist) recommends that in the case of Grade 1 or 2 diarrhoea after high-dose treatment with loperamide, 100 -150 µg octreotide s.c. be given every 8 hours (7). For more severe diarrhoea (Grade 3 - 4) dosages of 500 - 1500 µg s.c. or i.v. as bolus every 8 hours are recommended as first-line therapy (7). A study performed by Meropol et al. was unable to demonstrate any prophylactic effect (9). Side effects, which occur with a frequency of approx. 15%, include burning and pain at the injection site and abdominal symptoms (10). Before using octreotide the advantages of the treatment should be weighed against the possible side effects and the cost-effectiveness of the therapy (11).

N-butyl Scopolamine, an anticholinergic/spasmolyitic, is used to relieve cramplike symptoms. As necessary, a dosage of 1 to 2 tablets every four hours is recommended. The bioavailability of the substance is low after oral administration.

The parasympatholytic **atropine** with the same mode of action but corresponding central side effects is commonly used to treat acute diarrhoea occurring under irinotecan therapy.

Racecadotril (synonym "acetorphan") is an orally administered selective encephalinase inhibitor and is used to treat acute diarrhoea. The substance is a prodrug that is converted to the active metabolite thiorphan. This prevents the breakdown of endogenous encephaline. The result is reduced secretion of water and electrolytes into the lumen of the bowels. The substance is used in dosages of three times 100 mg daily (12). Prophylactic administration proved in a Phase II study to be ineffective (13). Racecadotril is not commercially available in Germany at the moment but can be imported.

Budenoside as a steroid with local activity was tested in a small study for therapy of irinotecan and 5-fluorouracil induced diarrhoea after failure of loperamide treatment. The authors were able to establish a reduction in the symptoms by at least 2 levels (NCI toxicity grade) (14).

The symptoms of proctitis could be reduced with a **rectal foam containing steroid**.

The use of **narcotics** has proved to be useful as supplementary medication for pain relief.

In the case of patients with tumour of the pancreas who develop diarrhoea during a radiation therapy, the possibility should be considered of **pancreatic enzyme** replacement since a deficiency of these enzymes can lead to diarrhoea.

Substances currently undergoing clinical trials include **TJ-14**, a **ß-glucuronidase inhibitor containing baicalin**, which a Japanese group has tested successfully against irinotecan induced diarrhoea (15). Inhibition of the ß-glucuronidase of the endogenous intestinal flora prevents conversion of a metabolite of irinotecan with no antineoplastic activity back into the active substance and thus reduces the duration and severity of the diarrhoea.

Summary

The immediate and intensive treatment of chemotherapy and radiotherapy induced diarrhoea can improve the patient's quality of life and reduce the overall costs of therapy. It is the responsibility of the pharmacist to assist in avoiding the effects of diarrhoea such as weakness, electrolyte loss and exsiccosis.

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5.2.6. Nutrition Therapy

Almost all oncological diseases are accompanied by extreme loss of weight. In addition to a worsening of the general condition, this cachexia leads to lower tolerance of the therapy and to a higher incidence of side effects.

Nutrition therapy must focus on the patient's welfare, which is expressed by appetite and pleasure in eating rather than by maintaining weight at all costs.

The patient must be given nutritional advice pointing out the changes in taste perception and the increased energy consumption; possible changes in eating habits should be indicated in collaboration with the patient, the doctor and other persons affected.

It is useful if informational material and instructions on what to do are kept in readiness for giving to patients.

Svenja Sander, Hamburg

Many cancer diseases show very non-specific symptoms in their early stages. Thus considerable loss of weight is often the first indication of a tumour and is the reason for consulting a doctor. Cachexia is also a problem during the advanced stages of a tumour disease. It worsens the prognosis of the disease, diminishes the response to chemotherapy and increases mortality in the case of an operation. There is no clear connection, however, between the severity of tumour associated cachexia and the size, extent or degree of differentiation of the tumour itself.

In addition to the increased energy consumption as a result of the tumour situation, the therapy can also be the cause of malnutrition. In this connection tumour patients suffer:

- sensation of repletion 60%
- modified perception of taste 46%
- anorexia 40%
- nausea or vomiting 27%
- swallowing or chewing disturbances

- inflammation of the oral cavity
- depressive moods.

Many patients wish to take active supporting measures in combating their tumour disease. Nutrition represents an excellent possibility to do this. Changing eating habits in the direction of healthy, fully adequate nourishment can exert a positive influence on the condition of the patient. A radical change of diet is inadvisable, however, because this is mostly associated with eating less. An explicit warning must be given against most of the so-called cancer diets. There are forms of nutrition that have been proved scientifically to offer protection against cancer - this applies in particular for intestinal carcinoma. One example is the widely supported "5 A Day" regimen. Once a tumour disease has broken out, however, there is no diet that has been proved by scientifically recognised studies to exert a positive effect on the progression of the disease. On the contrary: many forms of nutrition are one-sided and can exert a negative influence on the progression of the disease. If patients wish to go on a diet it is useful to acquire information about this diet. If it is oriented on healthy, whole food products it can be implemented; if, on the other hand, it is very one-sided advice must be given against it. In such cases it is absolutely vital that patients be given sound advice.

The following tips can help motivate cancer patients to eat under the changed circumstances due to therapy:

- wish fulfilment, i.e. involve the patient in the choice of diet, no drastic changes, decisive is that patients eat at all, retain their appetite and take in enough nutrients; orientation on the patient's protocol
- many small, varied meals distributed throughout the day
- food prepared in an appetising way
- mildly flavoured, little aroma, possibly prefer cold meals
- eat and cook in different rooms
- diversion during meals (music, entertainment)
- avoid fixed mealtimes, eat according to appetite, also at night
- many different foods in stock
- bowls with small snacks which tempt patients to eat.

If the calorific intake with normal nutrition is inadequate, resort can be made to the range of supplementary or exclusive drink and tube-feeding products. These can not only be consumed undiluted, but can also be stirred into warm and cold foods. If necessary the manufacturing firms can be asked for recipes to stimulate appetite.

Maltodextrin is a neutral flavoured product from maize starch and contains readily absorbable carbohydrate. It can be stirred into drinks, desserts and soups and is suitable for providing additional calories to patients who develop a dislike of fatty foods.

The increased calorific requirement is only one aspect of nutrition for tumour patients. A systemic inflammatory process develops, that is probably generated by tumour products and by substances released by the body's own defence mechanism, e.g. cytokinins. Omega-3-fatty acids exert a positive anti-inflammatory effect. They occur primarily in oily types of fish such as mackerel, herring, tuna and salmon, and also in cod-liver oil and linseed oil.

There is also an increase in the requirements for vitamins, minerals and trace elements - for example, the selenium requirement is two to three times the normal value.

The daily requirement for micronutrients is best covered by a varied diet that focuses on wholemeal products, fruit and vegetables (raw or cooked). Foods rich in selenium include nuts (especially coconut), eggs, offal and fish.

For most people enjoying a meal is a very important factor in their subjective joy of life. It is therefore essential when giving advice on nutrition to take into account the patient's wishes and eating habits.

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5.2.7. Unconventional Remedies in Cancer Therapy

The oncology pharmacist also provides information about complementary and alternative medicine (CAM) for treating persons with cancer and gives advice on unconventional remedies if requested to do so. These are medicines or methods which are not recognised by orthodox medicine, but which must be capable of undergoing scientific investigation.

In order to protect the patient it is essential to assess whether using the products or methods involves a health risk for the patient and/or whether a quack treatment is involved.

Interactions with existing therapeutic regimens must be examined and excluded.

It is the duty of the pharmacist to take patients seriously who "want something extra", to inform them of the importance of the orthodox treatment of their disease, and to analyse the wish for alternative remedies.

Michael Höckel, Hamburg

Unconventional remedies in cancer medicine - also known as methods for cancer treatment with no proven effect - are summarised by the term "complementary and alternative medicine" (CAM). In this context "complementary" means the additional use of unconventional remedies and "alternative" means using these instead of orthodox medical treatment. There is a considerable dearth of information about complementary medicine among patients, their relatives and the doctors giving treatment. An increasing number of patients want to combine orthodox medicines and methods with unconventional remedies. Only the pharmacist with access over the Internet to the relevant literature and sources of data will be in a position to provide competent answers to questions concerning the use and safety of such remedies. The decisive issue in giving advice is to segregate, on the one hand, unconventional but reputable preparations for which the therapeutic process appears logical to the pharmacist, from dubious remedies (quackery) on the other. Some examples of unconventional remedies are:

1. mistletoe
2. enzymes
3. organ preparations
4. plant remedies
5. vitamins, minerals and trace elements

These remedies must be distinguished from products and methods which, for example, can be recognised by the lack of information provided by the producer or seller/supplier of these products. Individual reports of outstanding therapeutic results are often used in advertising. The doubtful information about the alleged success of the remedies or methods is disseminated via newspapers and magazines. Some products are even offered as alternatives to conventional therapy. Particular caution is necessary in these cases because of the risk that patients become confused and may refuse or discontinue orthodox medical treatment. As a general rule, advice should be given not to use remedies and methods associated with uncertain or a complete lack of data. The pharmacist giving advice should analyse the wish for unconventional remedies and in the advice proffered should strengthen the patient's confidence in orthodox medical treatment. In answer to specific questions by the patient about unconventional remedies, the pharmacist gives advice and recommends that the patient discuss the matter further with the doctors giving treatment. With the patient's agreement, consultation with the responsible doctor may be useful. After approval by the doctor giving treatment, the pharmacy takes care that the remedy prescribed is used safely, e.g. in the case of subcutaneous injection of a mistletoe extract. The sequence of advice is aligned on the consultation concerning conventional, orthodox drugs.

Internet addresses as sources of information:

- Alternative treatment methods, Munich Tumour Centre
  http://www.krebsinfo.de/ki/alternativ/kialtoo1.html
- Working group for biological cancer therapy at Nuremberg Hospital North
  http://www.agbkt.de/
- Resource of Alternative Medicine, Complementary Therapy and Natural Health Care, Great Britain
  http://www.internethealthlibrary.com/
- Medline plus Information
  http://www.nlm.nih.gov/medlineplus/cancergeneral.html
- Information on unconventional medication, also interactions with chemotherapy, Stanford Center for Integrative Medicine
  http://www.cancersupportivecare.com/complementary.html

- Office of Cancer Complementary & Alternative Medicine, National Cancer Institute, Bethesda, USA
  http://www3.cancer.gov/occam/information.html
- MD Anderson Cancer Center Complementary & Integrative Medicine, University of Texas
  http://www.mdanderson.org/departments/cimer/

Literature Sources:

1. Bopp, Annette: Die Mistel als Heilpflanze in der Krebstherapie (Mistletoe as a plant remedy in cancer therapy), Rowohlt Verlag 2000

2. Irmey György et al.: 110 wirksame Behandlungsmöglichkeiten bei Krebs (110 effective ways of treating cancer), Haug Verlag 2001

3. Rostock, Matthias: Unkonventionelle Mittel in der Krebstherapie (Unconventional remedies in cancer therapy). In: Krebspatienten in der Apotheke (Cancer patient in the pharmacy), Deutscher Apotheker Verlag, in press

4. Sauer H. et al.: Krebsbehandlungsmethoden ohne nachgewiesene Wirkung (Cancer treatments without proven effect). In: Supportive Maßnahmen und symptomorientierte Therapie in der Hämatologie und Onkologie (Ssupportive measures and symptom oriented therapy in haematology and oncology), Zuckschwerdt 2001: 257 - 264

Appendix A.
Requests to the Drug Manufacturers

Drug manufacturers are an important source of information about the medicinal agent and drug.

Their duty to provide essential information about safe handling (safety data sheet) and safe use (prescribing information) must be extended to include more information and, especially, more measures. There is particular inadequacy in respect of precautions for ensuring safe handling by persons involved in preparation and both the oncology pharmacist and the person responsible for purchasing must demand improvements in this sector.

Gerhard Carstens, Hannover

The special role of the pharmaceuticals manufacturer as a source of information derives from the fact that only it knows all the constituents of the composition - i.e. medicinal agent, inactive ingredients and packaging - and, if needed, has direct access to relevant data via the suppliers.

The first consideration is therapeutic safety: obvious items such as dosing accuracy, correct labelling and batch conformity are expanded by information on stability and compatibility. If the information given is insufficient, the information about the active substance and the inactive ingredient(s) can enable a wider search for information to be carried out.

The second consideration involves issues of work safety. Thus it is explicitly stated in TRGS (technical rules for hazardous substances) 525 that advice on dangers can be provided by pharmacists and doctors on the basis of information for use, specialist information and, if necessary, safety data sheets. In practice, however, safety data sheets vary considerably in the information they contain. As a rule it is difficult or impossible to discover whether the information in safety data sheets comprises general recommendations, or whether it applies specifically to the medicinal agent, the ready drug, the solvent added, or even the ready preparation of stock solution. In particular, information about cleaning agents after contamination of surfaces or persons must be specific and must take into account the chemical/physical proper-

ties of the toxic constituents. The same applies for notes on protective garments, especially protective gloves. Formulations such as ”suitable protective gloves” or ”protective gloves of latex are preferable to PVC gloves” are of little help in choosing suitable gloves (see also 3.2.2. Single-Use Gloves for Protection during the Preparation of Cytostatic Solutions). It must be demanded that every manufacturer make concrete statements about suitable protective products for its drug formulations. Taking over results for other drug formulations or simply naming protective materials (latex, nitrile, etc.) is not acceptable. Excellent information is available! Since the information involved may be applicable for only a short time, a reference in the safety data sheet to an accessible source of the latest data is perfectly adequate.

A further point in which environmental and work safety are by no means covered satisfactorily involves the contamination of primary packaging. After the contamination of primary packaging had been demonstrated in a number of different studies [1, 2, 3], this topic was taken up with manufacturers of cytostatics. None of the manufacturers approached felt able to guarantee the delivery of non-contaminated primary packaging. In the meantime the first types if protective packaging are available that make handling possible without contact with the primary packaging. This does nothing toward solving the intrinsic problem, but it is an aid to increased work safety. Last but not least, our behaviour on the market will decide whether, and if so how quickly, manufacturers will devote themselves to finding a solution to this problem.

References:

1. Wilken A.: Beobachtungen zur Außenkontamination der Primärverpackungen von Zytostatika (Observations on the outside contamination of primary packaging of cytostatics). Krankenhauspharmazie 1997;18(7):37-9

2. Hepp R, Gentschew G.: Untersuchungen zur Außenkontamination der Primärverpackungen von Zytostatika (Studies on the outside contamination of primary packaging of cytostatics). Krankenhauspharmazie 1998;19(1):22-7.

3. Delporte JP, Chenoix P, Hubert Ph.: Chemical contamination of the primary packaging of 5-Fluorouracil rtu solutions commercially available on the Belgian market. European Hospital Pharmacy 1999;5:119-21.

Appendix B.
Return Consignments to the Manufacturer

Returns of cytostatics to the manufacturer or wholesaler must be agreed in advance with the recipient.

The packaging must ensure safe transport and safe removal of the contents. The consignment must be labelled in accordance with statutory requirements.

Ludwig Metz, Munich

The manufacturer must be notified of return consignments, above all in the case of complaints. This is best done by telephoning directly and clarifying the details with the person responsible.

It is also possible that the Web page of the individual manufacturer includes an icon for complaints which leads to information about the steps to be taken in processing a complaint and about which persons should be contacted. It would be desirable if every manufacturer made this information available on its homepage.

Once the contact at the manufacturer is known, this person should be asked what information is required by the manufacturer for processing a complaint. Many firms already provide an appropriate complaints form.

After the procedure has been established, the drug that is the subject of the complaint must be safely packaged.

Special care is necessary in the case of liquid cytostatics:

Liquid cytostatics, e.g. vials that are not leaking, are sealed in plastic film and then packed in a box; they must also be secured against jolts and impact.

Liquid cytostatics, e.g. vials that are leaking, broken vials, etc., should no longer be returned to the manufacturer since this is too dangerous both for the sender and for the recipient. If the manufacturer insists, however, that such materials be returned,

a precise and safe packaging procedure must be mutually agreed in order to ensure that neither the sender nor the recipient is exposed to danger.

Packages containing returned cytostatics must be addressed to the person responsible, carry sufficient postage, and bear the inscription "Caution Cytostatics". If the package involves a complaint, the word "Complaint" must also appear on the outside of the packaging. This ensures that the manufacturer can process the package as quickly as possible taking the necessary safety precautions.

Letters of complaint should be affixed to the outside of the package so that there is no possibility of the letter being contaminated. A few firms already provide return kits for cytostatics. These return kits include both instructions for the return consignment and suitable packaging materials. Ask the manufacturer whether such return kits are available.