
Quality Standard for the Oncology Pharmacy Service

(QuapoS 5)

Quality Management for Pharmacies Producing Cytostatic Agents

The certified quality management system (QMS) implemented in the pharmacy department producing cytostatics is designed to

- meeting the minimum requirements of DIN EN ISO 9001 for a QM system,
- implementing the current quality standards of the pharmaceutical-oncological service and subsequently implementing guidelines for quality assurance,
- achieving systematic quality improvement through regulated, conceptually coordinated and reproducible operational procedures.
- further developing the quality of counseling regarding the drugs used in oncology as well as pharmaceutical care of cancer patients,
- increasing drug safety, including from the aspect of user and patient protection, as well as
- maintaining the existing QM system.

All aspects defining a consistently high level of quality are integrated in the QM system. These aspects are required for proper patient care and include, among other things, ready-for-application parenterals.

B Risk Management

The quality management represents the foundation for a definitive control of the processes in the preparation of cytostatics. It is based on the risk analysis in the department. Controlled handling of the residual risk is connected to the analysis. The processes are continuously analyzed and evaluated and solutions for risk control during drug preparation are found.

1. Personnel

1.1. Persons dealing with cytostatics

Persons dealing with cytostatics under the direct influence of the pharmacy include:

Pharmaceutical personnel:

- Pharmacists and persons being trained as pharmacists
- Pharmacy technicians and persons being trained as pharmacy technicians
- Pharmacy assistants
- Pharmacy engineers

Non-pharmaceutical personnel:

- Pharmacy auxiliary staff
- Professionals employed by the pharmacy
- Pharmacy sales staff
- Employees in the store
- Cleaning staff
- Transport staff

1.2. Persons in production

Categories of persons working in the cytostatics department include:

Pharmaceutical personnel:

- Pharmacists and persons being trained as pharmacists
- Pharmacy technicians and persons being trained as pharmacy technicians
- Pharmacy assistants
- Pharmacy engineers

Non-pharmaceutical personnel:

- Pharmacy auxiliary staff
- Professionals employed by the pharmacy
- Pharmacy sales staff
- Cleaning staff
- Maintenance personnel

Only pharmaceutical personnel may be employed in the production 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.

The employees are familiar with the quality management system of the department and actively involved in its further development.

1.3. Hazard evaluation, working rules and instruction

Before starting work in cytostatics production the hazard risks of cytostatics handling need to be evaluated and documented (industrial safety act, hazardous substances regulations). Based on these findings the employees must be instructed. In addition to the persons carrying out the production, all employees dealing with and using cytostatics must be instructed in the sense of s. 3 *GefStoffV* (hazardous substances regulations). This also includes, for example, the cleaning staff and persons employed in the transport service.

The instructions given must be appropriate to the different job categories. Depending on the respective requirements, it includes the following items:

- Effects of drugs
- Proper procedures for dealing with hazardous substances (cytostatics, latex, etc.)
- Hazards and protective measures
- Aseptic technique
- Disposal of contaminated materials and devices and of residues of cytostatics
- Occupational preventive medicine
- Action in the case of accidents

This instruction must be repeated annually (s. 20 (2) *GefStoffV*). In addition, written working instructions must be prepared specific to the particular workplace (s. 20 (1) *GefStoffV*). Cytostatics are classified according to their properties and are included in the pharmacy list of hazardous substances (s. 16 (3a) *GefStoffV*).

This list must be amended to accord with major changes and must be inspected at least once every year. If any changes have been made a new documented risk evaluation has to be performed.

Accidents must be documented in an accident protocol. In the case of personal injury, s. 1552 ff. *RVO* (statutory instrument) requires in addition 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 responsible statutory insurance body.

1.4. Permanent workplaces

Well-trained permanent employees must be available in adequate number for the scope of the production. Permanent workplaces should be avoided in the area of centralized cytostatics production. Pursuant to s. 36 (6) *GefStoffV*, however, the number of persons potentially exposed should be reduced to a minimum.

1.5. Occupational preventive medicine

Employees working in the area of cytostatics production in the pharmacy are dealing with potential carcinogenic, mutagenic and reprotoxic (CMR) drugs. They must be offered regular occupational medical check-ups taking into account all the relevant factors at the specific workplace. These check-ups include:

1. Initial examination before taking up employment.
 2. Follow-up examinations during the employment at intervals of 1 to 2 years.
 3. Examinations at the request of the employee if there is a suspicion of work-related impairment to health.
- It is recommended that the follow-up examinations include biomonitoring to test the effectiveness of the existing protective measures.

Exposure to cytostatics must be documented by the employer in a suitable form. This documentation must include the types and amounts of cytostatics used and the frequency of their preparations for each employee handling these drugs. Furthermore, a continuous use of technical and personal protective measures has to be ensured by implementing standard operating procedures regarding compounding, disposal, and clean-up of cytostatics as well as cytostatics-related accidents and their acute management.

1.6. Training, continuous education and professional specialization of employees

The goal of training, continuous education and professional specialisation is to provide personnel with theoretical knowledge and practical skills.

Theoretical knowledge:

- Quality Management
- Risk Management
- Rules and regulations
- Safe handling of hazardous substances
- Hazards and protective measures
- Accident prevention and acute management
- Disposal of contaminated material
- Drugs and dosage forms
- Stability and incompatibility
- Working in an aseptic area
- Drug effects and pharmacology
- Clinical pharmacy
- Pathology
- Departmental and organisational responsibilities

Practical training:

- Aseptic working techniques and their validation in simulations of work flow during compounding
- Handling of disposable articles
- Simulation of accidents and their acute management
- Checking cytostatic prescriptions
- Handling different documentation systems
- Packaging, quality management system for distribution and disposal
- Handling a spill-kit

1.6.1. Training of new personnel

Training of new personnel in cytostatic compounding needs to be performed with specific care since handling cytostatics bear significant risks for humans and product safety.

The training requires planning of time and content requirements and should be performed according to a predefined training program.

1.6.2. Continuous education and professional specialization of personnel

The goal of continuous education and professional specialization programs is to keep personnel informed about latest developments in science and technology.

Personnel that work in the cytostatic compounding need to undergo yearly training in hazardous substances regulations. They should also have the opportunity to participate in internal and external continuous pharmaceutical education programs.

A certificate should document participation.

Opportunities for professional specialisation in the oncology area should be taken if offered.

2. Central Cytostatics Department

The centralized preparation of CMR (carcinogenic, mutagenic and reprotoxic) drugs must take priority over distributed preparation.

2.1. Rooms and equipment

Preparation takes place in a separate, clearly designated cleanroom work area, which is separated from the remaining areas by one or more air-locks. The classification of the cleanrooms with regard to particle and microbial counts should be performed on the basis of the EU GMP guideline (attachment 1). Cross-contamination must be avoided by means of organizational and spatial measures.

The rooms used must not be combined with the remaining pharmacy rooms.

The configuration and fixtures of the rooms must be designed such that contamination by microorganisms and particles is reduced to a minimum. Along with technical fixtures, the rooms should be set up in connection with preparation, production and documentation.

The entire equipment of the preparation room must be defined in a fixtures plan and reduced to the necessary minimum.

2.2. Room air equipment

A cytostatics workbench of type H (or "other design, e.g. with isolated work room") must be used, type tested in accordance with DIN 12980 as laminar airflow (SWFC). SWFCs [safety workbenches for cytostatics] are equipped with an additional main filter that can be replaced free of contamination.

An exhaust air system as an additional security measure must always be installed.

Should an exhaust air system not be realizable for technical reasons, it is mandatory to use an SWFC with two HEPA filter stages. If a workbench is operated with recirculated air, and all regulations to the method recognized by regulatory and professional liability bodies **to the chosen method** need to be met.

In any 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 the currently valid GMP recommendations, without impairing the protective function of the safety workbench.

The velocity of the input air must not exceed 0.2 m/s.

3. Cytostatics Production

3.1.1 Requirements for drug manufacturers

The pharmaceutical company is responsible for its drugs and the information available for the use of these products. The particular properties of the active substances and the complex modalities of oncological therapy justify high expectations on the part of the users. User expectations often extend far beyond the legally stipulated minimum requirements.. The requirements for drug manufacturers are therefore more demanding in the area of oncology than in the majority of the other drug groups.

In the development of a drug the pharmaceutical company must take this into account when developing the drug. The finished drug and its various forms of packaging are to be designed accordingly to this

demand. In addition, the pharmaceutical company is to take special organizational measures into account with regard to distribution and storage. The information provided regarding the drugs must comprehensively cover all identifiable needs. The information should thus be prepared appropriate to the target groups for patients, physicians and pharmacists.

The pharmacist working in the oncology pharmacy must actively communicate its ideas and wishes for the design of drugs and its demands on the information provided

He/she introduces these quality aspects in the purchasing decisions in his/her facility and thus prevents a selection being made solely on the basis of the quoted price. He/she is available to the pharmaceutical company as a contact person who is familiar with the requirements in daily clinical practice.

3.1.2 Handling of cytostatic shipments

Only trained pharmacy personnel may be allowed to accept shipments of cytostatics.

Packages or shrink-wrapped cytostatics need to be opened in a separated location with personnel wearing a protective gown.

Notification of breaks, contaminations or other damages needs to be documented and reported to the manufacturer and the occupational safety department. The cause of the defect needs to be evaluated and eliminated as soon possible

3.1.3 Return of shipments to the manufacturer

Return of shipments of cytostatics to the manufacturer and wholesaler, respectively, have to be coordinated with the recipient.

The packaging container must allow for safe transfer and safe removal of the cytostatics.

The shipment has to be labelled according to the applicable rules and regulations

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 for the employees of a cytostatics department. The personal protective equipment must meet the CE (Communaute' Europe'enne) standards and needs to be specified in the hazard evaluation. Personnel assembling drug products for the cytostatic compounding process and personnel packaging the final product also need to wear personal protective equipment.

The personal protective equipment consists of:

- protective gown (possibly in combination with cuffs)
 - protective gloves
- and in special cases:
- respiratory protective equipment
 - protective eyewear
 - overshoes

The special cases are:

- 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 kind of personal protective equipment is chosen based on the hazard evaluation of the work environment

3.2.1. Protective gown

Protective gowns must be sufficiently long (covering the thighs) and closed up to the neck. They have long arms with close-fitting cuffs. They should repel liquids at especially exposed positions. For reasons of product protection they should at least be almost sterile and give off as few particles as possible.

3.2.2. Disposable gloves for protection during the production of cytostatic solutions

Suitable gloves or glove combinations must be worn, which are changed regularly and also in the event of contamination.

3.2.3. Breathing protection, protective eyewear, overshoes

In special cases the avoidance of contamination when dealing with cytostatics requires the wearing of breathing protection, protective eyewear and overshoes in addition to a protective gown and protective gloves. These additional measures are mandatory for cleaning the safety workbench, clearing up spillages of cytostatics and during filter replacement at the safety workbench. Breathing protection must consist of a half mask particle filter 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.

3.2.4. Applying the PPE

The proper applying of Personal Protective Equipment (PPE) is fundamental for safely and aseptically working with cytostatics; in doing so, the quality of the product is ensured and the greatest possible degree of safety is provided for all persons involved.

3.3. Equipment for production

3.3.1. Technical equipment for the production of cytostatics

In order to ensure minimum safety standards for the production of cytostatics, it is necessary to employ suitable technical equipment (*TRGS 525*). This must comply with the requirements of the *Medizinproduktegesetz (MPG)* (law on medical devices). In addition, the materials used must fulfil the special criteria associated with cytostatics production. All equipment must be sterile, or must be subjected to disinfection before use. The quality of the devices must be inspected at regular intervals. Technical equipment is also part of the hazard evaluation.

3.3.2 Technical Equipment for Application

Along with the legal regulations of the Medical Device Law, there are additional requirements for the selection of equipment for the administration of cytostatics: Protection from contamination, reducing the risk of extravasation, avoiding interactions and mix-ups and timely administration during intravenous and also local application must be taken into account.

3.3.2.1. Infusion pumps for the administration of cytostatics

Medical devices may be set up, operated and used only for their intended purpose pursuant to the "law on medical devices" and associated statutory orders, and in accordance with generally recognized technical requirements and occupational safety and accident prevention legislation.

3.4. Aseptic technique

Aseptic technique embraces all coordinated, necessary steps that lead to a sterile product by using optimal conditions for germ reduction and avoidance of microbial contamination.

Preparing for and going over the actual compounding process significantly influences the quality of the product.

The detailed planning, preparation and post-processing of the entire aseptic production process has a crucial impact on the quality of the product.

3.4.1. Measures for Avoiding Particle and Microbial Contamination

Validation includes evaluation of the entire work process and all aspects of the aseptic techniques.

Attention is to be paid in particular to:

1. the rooms in respect of cleaning and hygiene
2. the safety workbench (LAF - laminar air flow)
3. the work materials
4. the starting materials and

5. the aseptic production method.

The validation of the entire process includes all carefully planned and defined methods which ensure, during production and monitoring procedures, that the product thus produced meets all requirements set forth with regard to safety, identity, content, quality and purity and corresponds to the defined quality profile.

3.4.2 Aseptic Technique Validation

Cytostatics preparation in a cytostatics hood (**SWFC**) is an aseptic drug preparation process that must be validated.

Compliance with the requirements of the Ph. Eur. for parenteralia is fundamental.

Simulations procedures instead of in general prepared products have to be tested for the absence of reproduction-competent germs, using appropriate microbiological procedures. A testing plan must be compiled. Number and frequency depend on the possibilities of the individual pharmacy.

3.5. Requisition of ready-to-administer cytostatic solutions

3.5.1. Requisition form and plausibility check

Requisition of the cytostatics is submitted in writing or in electronic form through the physician within the scope of a prescription form.

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

- Patient name
- Date of birth of the patient and/or hospital chart number
- Body weight, height and/or body surface area
- Requesting ward, outpatient unit or practice
- Cytostatic prescribed (INN name)
- Dose (calculation according to body surface area, body weight or absolute dose)
- A required dose - reduction in the case of impaired organ function or other parameters must be indicated
- Pharmaceutical form
- Type and volume of carrier solution
- Start of therapy (if applicable, stage and time of application)
- Date and physician's signature or in the case of an electronic request, clear identification of the ordering physician by means of a password release

3.5.2-Stability of the preparations

- The shelf live of the preparations should be established from the informations of the manufacturer, from the publications of the international pharmaceutical journals or by using a stability study.
- The stability studies should be carried out according to the "Guidelines for the practical stability studies of anticancer drugs: A European consensus reference"
- The results of the stability studies published in the international journals should carefully compared with the conditions of the local production in termes of solvent, container, temperature, light, concentrations
- The extrapolation of the results should be justified

3.5.3 Dose adjustment

Cytostatics are drugs with a narrow therapeutic range. Reduced organ function can impair the excretion of these drugs. Owing to the resulting ant accumulation of cytostatics and their active metabolites, the toxicities can exceed an acceptable level.

For cytostatics which, to a large extent, are eliminated unchanged or as toxic metabolites, the need for a dose reduction must therefore be considered. This also applies to substances which have an organotoxic potential.

The criteria and principles which can influence the decision are shown subsequently.

3.5.3.1 Cytostatics dosage in case of impaired renal function

An impaired renal function may increase the toxicity of cytostatics and active metabolites through accumulation. A dosage reduction may therefore be necessary for substances, which are eliminated renally to a significant extent. Each decision should be made on the broadest possible base of information and the patient's individual situation. A condition for a proper recommendation is a measurement of the GFR approximation value (generally "creatinine clearance") that is as accurate possible.

3.5.3.2 Cytostatics dosage in case of impaired liver function

Decreased liver function may significantly influence hepatic clearance of cytostatics. Decrease of metabolic clearance leads to slower cytochrom P450 dependent and independent biotransformation processes, whereas reduction in biliary clearance decreases excretion via the biliary tract. Some cytostatics accumulate with decreased hepatic clearance. Therefore pharmaceutical services are very valuable in providing dosage modifications after evaluating patient specific clinical lab data.

3.5.3.3 Cytostatics dosage modification in case of blood count changes

One of many parameters that need to be evaluated when dosing cytostatics is differential blood count or bone marrow reserve. However, no fixed parameters currently exist for the evaluation of a patient's individual recovery time after cytostatic application or the bone marrow's capability of regeneration (in contrast to for example liver and kidney function, where parameters exist). The bone marrow may also be the cancer-spreading organ, which makes dosage adjustments even more difficult. In these cases, tight, individualized patient control is indicated (2-3 times per week after completion of chemotherapy cycle) in order to assess and monitor a 'real' myelosuppression.

When treating a patient it is necessary to consider the patient's age and if therapy should be palliative or curative. Based on the severity of myelosuppression, a nadir-adapted cytostatic dose modification will be performed in the subsequent chemotherapy cycle. It needs to be noticed that hematopoietic agents such as G- or GM-CSF may make cytostatic dosage adjustment unnecessary and the dosage intensity may be maintained. This is especially important when curative treatment is the goal. High dose chemotherapy or dose-intensified standard therapy with reduced cycle intervals can only be performed with support of hematopoietic agents.

Thus, dosage recommendations based on myelosuppression can only be considered as guidance instrument. If cure is the treatment goal and myelosuppression is a concern it is especially important to weigh the risks between using supportive measures or lengthen the interval between chemotherapy cycles.

3.5.3.4 Cytostatics during Pregnancy and Breastfeeding

Pregnancy during cancer treatment is always undesirable but also presents emotional and mental problems. The same applies to cancer treatment which occurs during a pregnancy. There are of course not any prospective studies with cytostatics during pregnancy, however there are countless case reports and some overviews as well as results from non-interventional registry studies. It can be established that the administration of cytostatics to pregnant women is not a no-go, per se.

3.6. Production

Production takes place on the basis of the working rules (s. 20 *GefStoffV* (hazardous substances regulations)) and the production specifications which integrates the results of the hazard evaluation. The work techniques defined in the working rules and production specifications are mandatory. Compliance with them must be regularly inspected.

3.6.1. Production specifications

Since the new version of the Ordinance on Pharmacy Operation [ApBtrO] in Germany and other European Guidelines (e.G. PICS) in 2012, the legislature stipulates production instructions created beforehand for cytotoxic formulations. To keep the workload as acceptable as possible, internal quality management should be used. In this way, the majority of the preparations can be represented via standardized, general, active-substance-based or medicinal-product-based production by instructions available in the production area. These should undergo regular review and updating within the scope of the QMS.

3.6.2 Aseptic Production Run

A detailed sequence of an aseptic production is described in summary. Articles in QuapoS already available are marked with cross-references.

Special attention is paid in particular to the safe handling of cytostatic solutions and equipment such as, for example, syringes, cannulas, spikes and ampules. Points such as order in the work bench and behavior during handovers and production are also examined.

3.6.3 Handling of oral Cytostatic

Oral cytostatics are only available in most cases as capsules or tablets. If there is a pediatric oncology department in a hospital, the question of other dose or pharmaceutical forms - in general, suspensions or solutions are desired since these are the easiest to handle during application and enable flexible dosing.

To produce such formulations, special precautions must be taken since the process may result in dusts from highly toxic substances. Employee protection is a key priority and must be ensured through appropriate measures and environmental conditions. Since this concerns oral preparations, product protection plays a less important role and thus aseptic production does not need to be ensured in most cases.

If drugs are turned into a new pharmaceutical form, it should additionally be ensured that the therapeutic effect is not impaired either through a lack of stability and incompatibility or through significantly altered pharmacokinetics, if drugs are turned into a new pharmaceutical form,

3.6.4 Documentation and Validation

Specifications on the documentation in the case of aseptic production of infusion solutions are indicated in section 7 (1c) ApBtrO. A production protocol is called for here for formulations;

The production protocol must contain the following information, at a minimum:

- the type and quantity of the finished drugs used and their batch designations
- special features of the production process
- the type and result of any in-process controls
- the name of the patient and the prescribing physician
- the name of the person who produced the drug

Additional information on the preparation is useful, however. In-process controls can be performed using weighing-based software and/or the "four-eye principle".

Prior to release, the production protocol is to be signed by a pharmacist or a person authorized as a deputy.

3.6.5 Label

Ready-to-use infusion solutions produced individually for a patient are labeled in accordance with the sections of section 14 ApBtrO and Labels should be applied directly to the primary container after completing the preparation in order to avoid mix-ups. Unambiguity with regard to the patient data and production number should be ensured, as should good legibility and long-term adhesion. Along with information on the active substance and the finished drug used, additional information is relevant like ward designation, units providing oncological therapy, amount and name of cytostatic contained e.g.. Supplemental information on the outer packaging regarding storage and application may be of use.

3.7. Delivery of the finished products to the entity providing oncological therapy

For "In-house" transport the finished products are delivered in unbreakable, liquid tight, closable containers labelled with the inscription "Caution Cytostatics". (TRGS 525 5.6) "

If the finished product will be transported out of the institution it needs to comply with hazardous freight regulations (*Gefahrgutverordnung GGVS*).

Cytostatic compounds partially belong to the group of hazardous freights. They have the UN number 1851 and need to be arranged under 'drug, liquid, toxic'.

3.8. Valuation

The costs of a preparation are divided between the following areas:

1. Material costs
 - medicinal product
 - carrier solutions
 - consumables
2. Personnel costs
3. Extra charges
 - The applicable contracts must be taken into account when billing the health insurance provider.

3.9. Information resources

The basis of an oncology pharmacy service is its resources to research and answer almost all questions regarding antitumor therapy. Essential information resources consist of a personal library with relevant print media as well as computer resources including access to relevant software. This particularly includes Internet access allowing for retrieval of scientific database information, use of search engines, available links, electronic mail, and other services.

Audio and video material for educational purposes should also be available.

4.0. The pharmacy as coordination center of cytostatic therapy

The pharmacy as central facility in the cytostatic therapy implements the quality management of the oncology pharmacy service and assumes responsibility for patients and staff in all areas of cytotoxic therapy.

The pharmacy records and processes all the medical and toxicological data relevant to the cytotoxic agent and, as far as possible, the accompanying and supportive measures as well.

The available information can be epidemiologically evaluated, documented with regard to clinical, pharmaco-economic and ecological aspects, integrated in advisory procedures and used for training the personnel.

4.1. Waste disposal

The principles of waste disposal are

- waste avoidance
- waste recycling
- waste disposal.

Disposal is to take place such that

- the health and well-being of persons
- the environment (air, water, ground, animals, plants and landscape) and
- public safety

are not jeopardized.

Hazardous wastes and objects contaminated with these are collected

- separately from other wastes
- at the place they originate
- in appropriate, labelled collecting vessels.

In general, cytostatic waste is considered hazardous waste. It should be collected in specific containers, which can be hermetically sealed after filling. Cytostatic waste needs to comply with hazardous freight regulations (GGVS) and applicable national and regional statutory requirements.

Handling waste materials containing cytostatics should be defined in the operating instructions (where to find).

4.2. Decontamination after inadvertent release

A decontamination kit must be permanently located in every area where cytostatics are dealt with. The responsibility for ensuring this is ideally carried by the pharmacy as a central unit.

The decontamination kit contains among other items:

- Instructions for the decontamination procedures
- Marking material
- Disposable gown
- Overshoes
- Breathing protection mask (P3)
- Protective gloves
- Additional pair of gloves providing adequate mechanical protection against glass splinters
- Protective eyewear with side protection, which can be worn over personal eyewear
- Disposable cloths or 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.

4.3. Extravasation (paravasation)

For cytostatic therapy, the accidental escape of cytostatic agents with necrotizing potential into the surrounding tissue represents a serious complication requiring immediate treatment.

Conducting cytostatic therapy absolutely requires knowledge of the risk factors and preventive measures. However, if there should be any extravasation, this must be immediately detected and treated.

Guidelines for prevention and an action catalogue and documentation sheet for the treatment of extravasation must be at hand in all wards and units providing oncological therapy.

A kit for immediate treatment of extravasation contains all the materials necessary for the specific therapeutic schemes of the substances used, and must be permanently ready for use in an open, accessible place in the ward or unit.

4.4. Chronooncology

Chronooncology is a method of treatment in which the times of administering cytostatic drugs are chosen with awareness of the existing biological rhythms of the patient, the therapeutic aim being to improve the bioavailability and efficacy of the cytostatics while simultaneously achieving a reduction in the extent of their adverse effects. Insofar as clinical results are available, the knowledge gained in the area of chronooncology is intended to be used in the sense of optimising the relationships between dosage, therapeutic effect and adverse effects, to the benefit of the patient.

4.5. Handling cytostatics on the wards/units in the medical office

Nurses and physicians have the main responsibilities in handling cytostatics on the wards and units. These include accepting, storing, preparing for administration, and administering cytostatics as well as handling patient's excretions (patient's family members may also be involved) and managing accidental spilling of cytostatics.

The oncology-specialized pharmacist should support and advice the wards and units in the establishment of operating procedures for safe handling cytostatics and the correct use of personal protective equipment, so that safe working technique can be guaranteed.

4.6. Handling cytostatics at home

Certain cytotoxic therapy regimens demand that an active substance be administered over a period of 24 hours to several days. This type of therapy is performed both during hospitalisation and as outpatient treatment.

Patients, family members and personnel working in the home care setting need to be trained in the handling of cytostatics in this environment.

The following points should be specifically stressed during their training:

- Special handling of cytostatics
- Handling of application devices
- Management of spilling or other incidents
- Management of paravasation
- Handling patient's excretions
- Cytostatic waste disposal

An individual care plan should be established in cooperation with the responsible pharmacist (see chapter 5.1).

4.7. Management of clinical studies

Through his/her involvement in clinical trials in oncology, the pharmacist provides an important contribution to ensuring quality of the investigational drug and thus of the data collected in the clinical trial.

The pharmaceutical investigator is responsible for the proper receipt, storage, reconstitution (or production) and destruction of the investigational drug which he/she performs and documents based on valid legal regulations.

4.8. Management of excretions

Excretions of patients, who receive anticancer chemotherapy, may contain significant amounts of cytotoxic substances.

Health protection measures should be provided to all persons handling these excretions. In addition applicable disposal rules and regulations need to be followed.

4.9. Research and development

In oncology, research and development should preferably be conducted in interdisciplinary fashion. Pharmaceutical-oncological services make important contributions to research activities. Results from research and development improve efficacy, suitability and quality of the offered procedures and services. In any research environment including pharmaceutical science, qualified pharmacists should be involved in designing and conducting the trials. In research, scientific and ethic rules as well as the guidelines for the individual field of research based there upon must be complied with.

Prior to the study, a suitable and focussed goal must be defined in writing. All research activities including the rationale must be documented completely. The necessary resources as well as their efficient utilization must be determined in advance. Responsibility for scientifically and ethically acceptable performance must rest with one individual, as a principal investigator. For quality assurance, appropriately standardized methods and procedures must be used.

Confidentiality of clinical research data is essential. The results must be documented in standardized form and filed together with the corresponding original documents in a safe and easy to retrieve way. For electronic data, special approaches are required. The results must be assessed regularly with respect to their correctness and completeness. Records from clinical trials and public health studies must be archived in conformance with the applicable national regulations.

All research results, including negative ones, must be released for verification by scientific peers and made accessible to the general public. The person in charge of research shall authorize publication and release of information. Essential contributions to planning, performance and publication of the trial are prerequisites for authorship. Detected errors should be processed by the first author, and in cases of severe errors the person in charge must retract the work. Prior to inception, written contracts relating to intellectual property rights must be concluded with the sponsors.

5. Pharmaceutical Care of the Patient

The pharmacy team works in a service-oriented fashion in providing pharmaceutical consultations and care in the practice.

As a part of the pharmacological, oncological service, direct contact with the patients to be treated with the drugs and infusion solutions should be sought.

The patient-oriented service is developed while taking into account the special features in the inpatient and outpatient area. The Communication of information is possible directly with a patient contact or indirectly by creating and handing out patient information material. In addition, the pharmacy conducts specialist consultations with the attending physicians and responsible nursing staff. It is these activities that form a component of patient-oriented oncology pharmacy service for cancer patients.

The implementation of consultation and care services requires a structured approach by the employees of a specialized pharmacy cytostatic department in collaboration with the pharmacists working in the dispensary or on the ward. A precondition for performing consultations and care to accompany therapy is the transmission of relevant data by the physician responsible (for more information, see section 3.5.1 Dispensation and Plausibility Review).

Direct consultation and care take place if personal patient contact is offered in a fashion as part of the consultation service, taking legal regulations (e.g. Ordinance on Pharmacy Operation) into account.

5.1. Developing a pharmaceutical care plan

The care plan should be considered to be an important tool within the scope of patient-related care. In doing so, this procedure within consultation and care focuses on the patient's questions and problems and allows for results-oriented implementation.

The content of the care is recorded in writing, if possible, and thus allows the success to be verified using defined monitoring parameters.

The care plan that is created and agreed upon includes the systematic analysis of all drug-related questions within the scope of therapy and follows the widely used SOAP formula that has received multiprofessional recognition:

S=subjective: the patient's **subjective** complaints and problems are described or inquired about and then documented.

O=objective: identifiable and measurable, **objective** parameters and symptoms are determined and documented.

A=Assessment: the objective and subjective content is systematically analyzed according to the state of knowledge and various procedures for a solution are demonstrated and discussed.

P=Plan: A care plan with defined therapeutic objectives is created after a preliminary assessment and the necessary measures are precisely defined.

At appropriate intervals, achievement of the objectives is verified using the appropriate parameters and symptoms and the results are recorded in writing.

The documentation and evaluation of the care plan according to SOAP is also suitable for presenting and discussing patient examples for optimizing care and multidisciplinary collaboration as a part of team discussions and continuing education/further education.

5.2. Supportive therapy

5.2.1. Management of nausea and vomiting

Nausea and vomiting are perceived by patients as frightening and particularly unpleasant adverse effects of cytostatic therapy. Their severity may even lead to premature termination of therapy. Thus, it is pertinent to provide efficient antiemetic supportive therapy.

The choice of an appropriate therapeutic intervention should be guided by the following aspects:

- Emetogenic potential of the cytotoxic therapy
- Individual risk factors of the patient
- Different phases of nausea and emesis
- Therapeutic guidelines of professional organizations based on evidence-based medicine (EBM)
- Pharmacoeconomic aspects

The implementation of the chosen therapeutic intervention should be supported by

- Cooperation between patient, physician, pharmacist and other involved professionals
- Compliance-supporting measures
- Additional prophylactic measures

5.2.2. Pain management

Most tumor patients experience pain during the course of their illness. Cause, kind and intensity of pain can be different. Pain needs to be diagnosed early and therapy should be consequent and appropriate including all different treatment options. It is important to include pain management in patient's care plan and it should include pharmacotherapeutic approaches as well as other treatment alternatives.

5.2.3. Alopecia

Alopecia is a for the patient burdensome adverse effect of many cytostatic therapies. in patients treated with cytostatic therapy. Alopecia can be very bothersome to patients. Although alopecia treatment options are still very limited, aspects and concerns about alopecia should be considered in the care plan and addressed during patient care.

5.2.4. Mucositis

Inflammation of the mucosa –mucositis- can be found in several locations. Examples are stomatitis, oesophagitis, or cystitis. Many tumor patients experience mucositis, because it is a very common side effect of cancer chemo- and radiation therapy. Mucosal lesions can be very painful and significantly impair the cancer patients' quality of life.

It is one of the pharmacist's responsibilities to give specific recommendations for individual patients regarding mucositis prophylaxis and treatment. As part of quality assurance the pharmacist also develops general prophylaxis and treatment guidelines in collaboration with other oncology healthcare professionals.

5.2.5. Management of diarrhoea

Diarrhoea is a serious complication of cancer therapy. Specific cytostatics as well as radiation therapy can cause diarrhoea as an adverse effect.

Immunological, infectious or cancerous processes can also cause diarrhoea and need to be included in the diagnostic evaluation.

Untreated diarrhoea may lead to weakness, electrolyte imbalance and exsiccosis, and may rapidly escalate.

It is one of the pharmacist's responsibilities to ensure implementation of early and adequate treatment of diarrhea.

5.2.6. Nutritional Advice and Therapy

Almost all oncology patients suffer from extreme weight loss. This not only leads to worsening of the patient's general condition, but cachexia also causes more therapy intolerance and an increased risk of developing adverse effects.

Nutritional therapy needs to focus on the patient's well being. Maintaining the patient's weight should not be the primary focus of attention, but some appetite and enjoys eating certain foods.

Part of nutritional counselling should be to discuss changes in taste sensation that may occur during cancer chemotherapy and the increased energy requirements. The pharmacist should also provide together with the physician and other members of the healthcare team guidance on how the patient might benefit from dietary changes.

Provision of related written information material and instructions is beneficial to the patient.

5.2.7. Management of Undesirable Drug Effects on the Skin

The pharmacist must be capable of recognising adverse drug reactions (ADR) on the skin and of offering suggestions for medical treatment. An important consultation task involves prophylaxis from drug reactions of the skin.

5.2.8 Fatigue

Fatigue is the most common and limiting side effects in cancer patients. Fatigue refers to both physical and psychosocial deterioration functions influence and affect very much the quality of life of the patient. Fatigue is also worsened with comorbidities and the occurrence and severity of other symptoms such as pain, insomnia, depression, anxiety, and diarrhea. Risk factors include female gender, and age. The

underlying formation mechanism is still largely unknown. as There is no general treatment recommendations for alleviating the symptoms are still, even if the co-treatment of symptoms and moderate physical activity can contribute to the improvement. The multidimensional symptom of fatigue thus takes a not inconsiderable influence on the quality of life as well as professional and economic aspects.

5.2.9 Tumor-Related Osteoporosis

Tumor patients develop osteoporosis more frequently than patients of the same age without any tumor disease. Tumor disease and its therapy disrupt the balance between bone generation and bone loss and thus cause increased bone resorption. Since oncology patients are able to be treated with increasing success and have longer survival times, osteoporosis is an increasingly significant long-term complication. A lifestyle change with a healthy diet, physical activity and supplementation with calcium and vitamin D can slow bone loss. Adequate screening, regular bone density measurements and early initiation of suitable therapy also help to prevent decreases in bone density and bone quality and significantly improve the quality of life of the affected patients.

5.2.10 Thrombosis Prophylaxis and Treatment in Tumor Diseases

For a long time, it has been known that cancer patients are at increased risk for thromboembolic complications. Along with the type of malignant underlying disease, specific cancer therapies such as surgery, hormone or chemotherapy also play a significant role in the pathophysiology of the tumor-associated venous thromboembolism (VTE). Since a VTE significantly reduces the probability of survival of cancer patients, adequate primary prophylaxis and therapy and secondary prophylaxis are crucial. Clinical studies have shown that in drug therapy for tumor-associated VTE, long-term treatment with low-molecular-weight heparin (LMWH) is superior to therapy with vitamin K antagonists. However, it has not been definitively clarified which cancer patients benefit the most from primary thrombosis prophylaxis with an LMWH. For some patient groups with special risk factors such as, for example, hospitalized tumor patients, recommendations on primary prophylaxis have been made.

5.2.11 Prophylaxis and Therapy of Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) describes a metabolic disturbance triggered by rapid tumor cell disintegration with a massive release of intracellular material over a short period of time. TLS is a potentially life-threatening complication of tumor therapy due to acute renal failure or cardiac arrhythmias.

5.2.12. Adherence in the case of Oral Cytostatics

Oral cytostatic therapy has significantly increased in recent years. Many patients must take these drugs for several weeks to months, sometimes for years. This requires a significant degree of

adherence to and understanding of the therapy by the patient in order to achieve the desired therapeutic effect.

Adherence is affected by various factors and improved by collaboration in a multi-professional team. The pharmacist should be involved in this task in order to support the patient via consultations, comprehensible information and/or medication plans.

5.3. Unconventional methods of cancer therapy

The oncology specialised pharmacist should be knowledgeable about complementary and alternative medicine (CAM) regarding cancer treatment. If requested he should be able to give advice about unconventional treatment methods which are not approved or accepted by the school of medicine. However, some scientific evidence of those unconventional treatment methods is mandatory. Products and methods need to be assessed from a professional standpoint. Furthermore, it is necessary to evaluate if the patient's health is at risk by applying these methods. Many unconventional treatment methods are blunt charlatany and the patient needs to be protected from them.

Any Interactions between alternative medicines and currently applied therapy regimes need to be assessed and ruled out.

During patient counselling the pharmacist should respect the patient's views regarding alternative medicines and take his opinions seriously. However, it is also the pharmacist's responsibility to stress the importance and safety of evidence-based medicine and to inform the patient of the risks involved when using alternative medicines.

5.3.1 Homeopathics

Homeopathy is a **holistic** form of therapy which was established about 200 years ago by the physician Samuel Hahnemann.

According to the **law of similars** "Similia similibus curentur," a **potentiated** agent (= diluted and mixed according to particular specifications) is administered which could cause symptoms in a healthy person that are as similar as possible to the patient's condition (Simillimum).

The patient's symptoms of the disease are considered to be a manifestation of his/her imbalanced **vital force**. In this case, not only are the physical symptoms but also the emotional, psychological and mental condition of the patient in particular and especially unusual ("peculiar") symptoms crucial for the selection of the appropriate homeopathic agent and assessing the healing process.

The administration of the potentiated agent returns the vital force to a state of equilibrium and activates the body's own **self-healing powers** to overcome complaints on all levels.

Homeopathy is an **energetic** form of therapy and the mechanism of action cannot be proven with currently available methods.

For many people, it is not conceivable that a homeopathic agent can be effective at a potency in which, purely arithmetically, no molecule of the starting substance is present any longer. Only those who can let go at this point of the notion of an effect on an exclusively material basis can accept homeopathy.

In the case of so-called "**classical homeopathy**" in which the simillimum (see above) is given as a single agent, a differentiation is made between between

- **constitutional treatment:**

The homeopath (physician or practitioner) records the patient's various symptoms in their entirety in a comprehensive **initial history** (lasting several hours) and subsequent elaboration. He/she administers an agent at the suitable potency (generally only as a single administration in the case of high potencies). The reaction of the patient on a mental, emotional and physical level (= effect of the agent) is evaluated in subsequent meetings and the healing process is further supported homeopathically.

- **acute treatment:**

When treating acute illnesses, the past history is much shorter and a proven, frequently prescribed homeopathic agent is used for the respective illness. This procedure is also described in many self-help guidebooks.

"**Complex homeopathy**" should be differentiated from this. Here, various established low-potentiated acute agents are mixed together. They are used according to usual conventional medical indications and are administered frequently.

5.3.2 Anthroposophic medicines

Anthroposophy is translated as "human wisdom" and goes back to Rudolf Steiner (1861-1925). It refers to an ideology incorporating the human spiritual world and human emotional perception. It is dedicated to the states of consciousness (waking, sleeping, dreaming), states of living (perceptions) and the external form (physical visibility) of people. This triple division is also seen in all spheres of anthroposophy, such as in Waldorf education, special education, biological-dynamic agriculture, the eurythmics expressionist dance, the Christian community religious groups, in finance, in the social field and in anthroposophic medicine.

The drugs involve a "composition agent". They include various active substances which act on the functional systems (triple division) or on the organization systems (entities) which are connected together by means of a pharmaceutical process. By contrast, allopathics only act on the physical body.