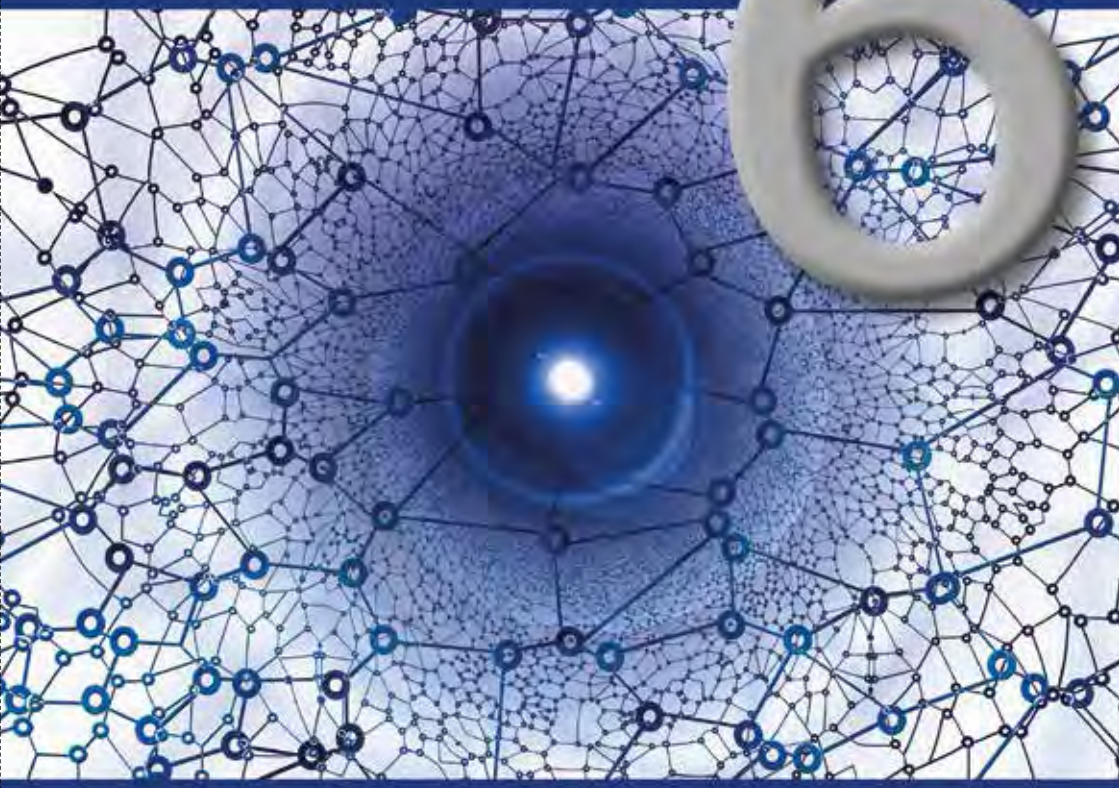
Quapos

Quality Standard for the
Oncology Pharmacy Service
-Commentary Version-

6



ESOP

QUAPOS 6

Quality Standard for the Oncology Pharmacy Service

– Commentary Version –

ESOP 2021

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The sixth issue of Quapos is now available. This version has been deeply updated and enriched. Obviously, Quapos is worldwide recognized as the best tool to find quickly all the information you could need in our daily practice, as oncology pharmacist. This English version should be easily accessible and understood by oncology pharmacists regardless of their native language. As editors, the German Society of Oncology Pharmacy (DGOP) and the European Society of Oncology Pharmacy have brought together invaluable experts in various fields to convey the latest advances in the practice of oncology pharmacy. The high level of this copious and complete book is suitable for fellows, residents, pharmacy students, graduate students and all experienced practitioners including medical doctors and nurses, who are interested in this exciting field.

Obviously, since the safe handling of anticancer drugs remains for all European countries the cornerstone of our activities and serves daily to demonstrate the role of pharmacists in the treatment of cancer patients, most of the chapters, subchapters and paragraphs are devoted to the organization of centralized units. This important part, largely technical, explains in detail all the updated requirements to ascertain that the preparation of drugs administered to the patient fully comply to the highest quality guidelines. This compliance to GMP or equivalent national guidelines is fundamental to be sure that the product furnished is of the best quality, but also handled in the optimal safety conditions to protect the manipulators and the environment. The chapter on pharmacy anticancer drug unit has been deeply optimized. Thus, a large part has been devoted to the organization of the pharmacy cancer drug unit, mainly to minimize the risks induced by anticancer drugs which are largely mutagenic and cytotoxic. Therefore, in several subchapters, emphasis was made on the risk of contamination of the manipulators and the environment and the means to avoid this. This concern is one of the main topics for ESOP with the development of research about contamination of the working areas at pharmacy and also at ward level (MASHA project).

The anticancer drug production chapter has been also largely enriched and benefiting of a new organization in subchapters and paragraphs, more rational and covering all the aspects of the process with special emphasis on quality control. The very detailed analysis of all the steps of the production process will be obviously very useful for beginners, but also for experienced pharmacists and manipulators.

However, oncology pharmacists should not be restricted only to technical roles, in the "underground of the hospital", but also be more and more implicated in clinical functions. Indeed, the clinical pharmacy in oncology is the most important challenge we will face up in the future. We have to be more visible at the patient's bed to improve the quality of care. Following the previous versions, several subchapters of this QUAPOS 6 are devoted to these aspects. As an example, dose adjustment in case of organ dysfunction is an important topic since pharmacist is well-trained in pharmacokinetics and drug metabolism and could play a key role to help prescribers to choose the adapted regimen for each patient.

The increasing use of anticancer drugs outside hospital, mainly linked to new oral formulations, is a major problem in terms of compliance, good use, management of drugs interactions and side effects. As widely developed in related chapters, the oncology pharmacist must be present and provide appropriate information and services, otherwise other health professionals such nurses will invest this competency on the drug which is normally his own. New interesting subchapters were devoted to special routes of administration and specific therapy such as HIPEC, which can provide new opportunity for pharmacists to exploit their unique competencies in pharmacokinetics, drug formulation and stability.

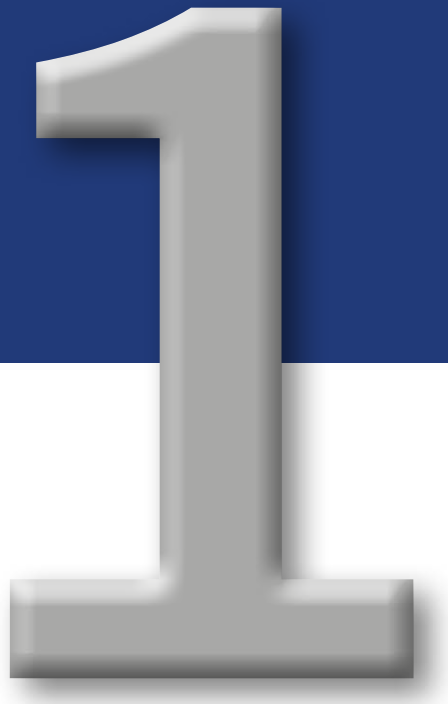
To take in account side effects of the treatment such as emesis, fatigue, mucositis or diarrhoea, it is critical to improve the quality of life of our patients. This approach is still inadequately addressed by physicians, but is a constant patient's request, and clinical oncology pharmacist may be very useful to propose and monitor adequate therapeutic protocols. Several very interesting and updated chapters should help some colleagues' wishing to develop new pharmaceutical services. Moreover, improving the quality of life of our patients is one of the best ways to push the role of oncology pharmacist as an important actor in cancer management, considering the increasing weight of patient's associations at political level.

As in the previous version, QuapoS 6 also includes several subchapters related to the unconventional approaches of cancer: herbal medicine or homeopathy. The courageous decision to present in this book also unconventional methods must be emphasized, recalling the care of a patient should be considered in toto, including as well pharmacological as psychological aspects.

Obviously, the role of the pharmacist in research and clinical trials is rapidly growing. Therefore, the subchapters devoted to the management of clinical trials in oncology and research are of a paramount importance for the present and the future since the handling of investigational drugs becomes more complex, implicating sensible molecules such as monoclonal antibodies but also viral-carried genes or cell therapies. Obviously, this is a great opportunity for the pharmacist to emphasize their skills and knowledge and demonstrate the real added value of their services to ensure the highest quality of clinical trials. Moreover, research should be a constant preoccupation for oncology pharmacists since it is the best way to be considered as a valuable partner by medical oncologist, especially in university hospitals. To convince some colleagues afraid by this word, it is critical also to explain that research is not only limited to very scientific areas which need expensive equipment, but also include well-designed studies to explore daily practices, organizations, added value services to patients or pharmacoeconomic. The corresponding results must be published to increase readability of our works, as an example in European Journal of Oncology Pharmacy, EJOP, which is supported by ESOP.

It is my privilege to strongly thank all the authors who contributed to this superb work and also the DGOP to have been the seminal initiator of the QuapoS series under the direction of its President, Klaus Meier. This brilliant and highly readable book will certainly meet the success it deserves to European pharmacists. Finally, this English version of QuapoS 6 will be an invaluable tool to promote oncology pharmacy, not only to MDs but also to national and European health authorities, politicians, pharmaceutical companies and patient organizations.

Professor Alain Astier
Pharm D, Ph D
Co President ESOP



QUALITY ASSURANCE

1.1 QUALITY MANAGEMENT FOR THE ONCOLOGY PHARMACY SERVICE

The certified quality management system (QMS) implemented in the pharmacy department is designed to produce anticancer drugs and/or offer counselling and care for cancer patients or oncology units:

- meet the minimum requirements of DIN EN ISO 9001 for a QM system,
- implement the current quality standards of the pharmacy oncology service and subsequently implementing guidelines for quality assurance,
- achieve systematic quality improvement, through regulated, conceptually coordinated and reproducible operational procedures,
- further develop the quality of patient counselling regarding the drugs used in cancer treatment as well as pharmaceutical care of cancer patients,
- increase drug safety in regard to user and patient protection and maintain 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.

► Dr Gisela Sprossmann-Günther, Berlin (Germany)

"The (German) National Cancer Action Plan already describes oncology centres as a 'network of qualified and certified interdisciplinary and trans-sectoral, sometimes multi-site facilities, which, wherever appropriate in terms of specialist requirements, cover as far as possible the whole supply chain for those concerned" [2]. "Evidence-based algorithms and guidelines are a crucial element in the quality-assured use of medical drugs in tumour and supportive therapy. Oncology pharmacists bring their specialist competence to the interprofessional formulation of guidelines for the health care practices and hospitals they serve. Their involvement in the therapeutic team extends to tumour boards and to expert working groups and quality task forces. Their work furthermore includes the individual monitoring of patients undergoing treatment and pharmaceutical interventions in a framework of interprofessional collaboration (e. g. clinical visits and chart checks). Part of this is to apply and refine quality management systems in their own work environment. The pharmacists who perform this role should in general, but in particular when supporting certified cancer centres, feel a commitment to establish a recognised standard for the oncology pharmacy service, building on the existing quality management system" [2].

As in Germany all pharmacies have been required by law to operate a quality management system pursuant to § 2a of the current code for the operation of pharmacies (Apothekenbetriebsordnung – ApBetrO), which came into force on

12 June 2012, they are assumed to be familiar with the contents of quality management systems. The pharmacy code itself, while the statutory basis, does not call for a certificate as evidence that the QMS has been implemented.

The legal provisions governing the technical rules for making up ready-to-use parenteral preparations are set out in § 35 ApBetrO [3], and the duty to provide information and advice by § 20 ApBetrO [4]. Reminder: The ApBetrO is a typical German document.

"Technical requirements for the care of oncology patients by all those involved in the servicing process are clearly defined by the Deutsche Krebsgesellschaft (German Cancer Society – DKG) when certifying Oncology Centres" [1].

In its survey forms the DKG recommends working with a pharmacist who has completed initial or further training in oncology and a pharmacy able to demonstrate its QMS/ technical quality in the form of an external certificate [5].

The Deutsche Gesellschaft für onkologische Pharmazie (German Society of Oncology Pharmacy – DGOP e. V.) has been certifying pharmacies and preparation units engaged in making up cytotoxic drugs since 2001.

Since February 2016, in keeping with its QMS Statutes of 31 January 2016, the DGOP has been offering certification, analogous to the medical certification performed by the Deutsche Krebsgesellschaft [6], for pharmacies/preparation units engaged in oncology, regardless of whether they prepare cytotoxic drugs or not. This permits specific oncology pharmacy certification of all pharmacies and preparation facilities engaged in oncological care.

"The DGOP certificate consists of a general section plus at least one of the following modules:

- Module 1 Preparation/Workplace safety
- Module 2 Pharmaceutical support for cancer patients
- Module 3 Oral cancer therapy – safe and effective
- Module 4 Patient safety/Risk management" [6].

Practice shows that it is useful to certify at least 2 modules, and the second module ought always to be Module 4 Patient safety/Risk management, as risk management includes components relating to all processes.

"As the DGOP certificate is a technical certificate specific to oncology, it can only be obtained if the general QMS operated by the pharmacy/preparation unit has been certified by an external certification body" [6].

For hospital pharmacies, this criterion for obtaining a technical certificate specific to oncology can be met either by the pharmacy obtaining its own certificate or if the hospital obtains certification that explicitly includes its in-house pharmacy.

The DGOP certificate demonstrates that an independent audit has been performed to review whether the quality standards applicable to an oncology pharmacy service/QuapoS are being implemented in the everyday working environment.

According to the QMS Statutes, the "purpose of a certified DGOP quality management system" is:

- to ensure seamless high quality in the proper public provision of ready-to-use cytotoxic drugs,
- to secure and enhance the quality of advice about the drugs used in oncology, in particular cytotoxic agents,
- to increase drug safety in terms of user and patient protection,
- to introduce, expand and develop pharmaceutical support for cancer patients, and
- to continue consistently developing a high technical standard of professional practice under the responsibility of health care professionals" [6].

Applicants who meet the current general requirements for QMS certification describe how they implement quality standards for an oncology pharmacy service in their working environment by answering the questions in the survey form.

Applications for the DGOP certificate can be made informally on the DGOP website. The applicant then receives a file containing the relevant survey form to fill in. Once filled in, the survey forms are submitted along with other required QMS documents (management review/organisation chart) and a copy of the basic certificate.

An on-site audit is then carried out to ensure that the replies in the survey form reflect practice and to review the resulting continuous improvements. If the theoretical statements are matched by practice, i. e. if the on-site audit is successful, the DGOP Certification Committee issues the QuapoS-based DGOP certificate. This certificate is valid for 3 years.

With respect to local laws and regulations, similar system may be implemented in any country. If pharmacies follow a quality management system, no matter if required by law or voluntarily, the local oncology pharmacy society may develop and provide a certifying system based on QuapoS, thus helping to increase the quality of care.

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1.2 RISK MANAGEMENT

Quality management represents the basis for a definitive control of the processes in the preparation of anticancer drugs and counselling and care for cancer patients. It is based on the risk analysis of the department. Controlled handling of the residual risk is connected to the analysis. Processes are continuously analysed, risks are identified and evaluated and solutions for risk control during drug preparation and/or during the process of pharmaceutical care are found.

► Michael Heymann, Siegen (Germany)

Starting situation of cytostatics preparation

"Human errors are unavoidable and can happen everywhere."
James Reason

The current risk situation in the cytostatics preparation can definitely be considered positive. The increased risks have been accompanied by establishing adequate protective mechanisms:

- Electronic storage of chemotherapy plans
- Checking the ordinances including the calculated body surface area on the basis of these plans
- Preparation according to the dual control principle
- Preparation regulated by scales and scanner
- Employment of experienced staff with updated advanced training
- Development of quality standards
- Local implementation of own SOPs and working instructions

But also the oncological treatment plans and associated preparation of cytostatics have developed in the past years in response to higher-quality requirements to an activity involving considerable risk potential. Hence the challenges to mastering the risks in this sector have risen, especially in the realm of high-dose treatments [10].

The analysis of errors, severe incidents and even catastrophes, independent from where they took place, shows that there are surprising parallels in the respective situations and preceding sequence of activities. The frequently diagnosed cause „human error" is often only the end point of an error chain in which technical and organizational weaknesses became apparent only after the errors of individuals. Defensive and protective measures restricted only to the level of the person doing the work often have a short-term preventive character [2].

The results of modern accident research show a high conformity among the causes of accidents, independent of industry and type of accident. For the cytostatics preparation sector, these findings can be used to establish a Risk Management System.

In general, error theory distinguishes between two forms of risk that contribute to errors. Human error, also a legal term, frequently concerns an active error on the execution and control level – for instance in the case of cytostatics preparation, by selecting a wrong cytostatic substance.

About a third of all causes of accidents can be ascribed to this type of error [7].

Apart from these individual errors, the examination of possibilities for errors within and between organizations is taken into consideration. Such errors are significantly more serious. Accidents in organizations caused by faulty chains of activities can be the cause of errors across job classifications and departments. The person doing the work in the preparation is frequently dependent on the preparatory work from previous process steps such as prescription of the treatment, test of the dose, correct concentration specifications, etc. This person stands at the endpoint of the chain of activities, where the specified requirements must be implemented, at the so-called „sharp end" of the process. In all of these precursor process steps, deviations and errors can occur consciously or unconsciously, and join to form an error chain. These potential possibilities of error can already start building up over longer periods of time, especially in complex organizations. This involves a latent error, when the persons involved are at the so-called „blunt end" of the process chain [8].

Specific occasions such as vacation substitutions or new employees with various information deficits trigger active errors that can lead to serious accidents in combination with these latent error structures.

This potential for error must be recognized and eliminated latest at the site of the cytostatics preparation. Otherwise they contribute (frequently unrecognized) to critical situations.

The systematic analysis of possibilities and causes of error as well as the alignment of the entire organization towards the given risk structure can create a sustainable positive effect.

Safety and the effective control of risks in organizations is influenced by their culture, regulations and rules as well as by economic pressure [3].

Contribution of so-called „non-technical skills" to the accident:

The investigation of accidents and catastrophes surprisingly revealed that defects in so-called „technical skills" such as education, knowledge, experience and training were not the leading reasons for such events.

The most frequent causes of accidents were deficits in the so-called „non-technical skills" such as attention, decision-making process, communication, cooperation in the group, the organization's culture and individual stress tolerance. Negative aspects and general conditions of the workplace such as high noise level, frequent malfunctions, interventions, heavy work load or time pressure also increase the probability of accidents.

Risks and the frequency of errors rise significantly in organizations characterized by a low level of these social skills.

Since these causes of accidents occur in constant frequency in practically all branches of industry, potential incidents and accidents in cytostatics preparation can also be attributed to these causes. At the same time, they provide starting points for preventing negative incidents [5].

Estimation as high-risk process

The cytostatics preparation with its possibly fatal consequences represents high-risk process in any case.

The various different therapy schemes with sometimes high doses amount to a considerable risk hazard for the patients. The patient-specific compounding of cytostatics takes place in complex structures within and outside the pharmacy. Thus the compounding of cytostatics is characterized by a close interdisciplinary, cross-departmental cooperation. The prescribing practice or hospital and the pharmacy producing the cytostatic preparations are two different organizational units that must work together. Especially this cross-departmental cooperation with the prescribing physician on the one hand, and then after preparation and provision of the drug, the drug application itself in the practice or hospital on the other hand, is an enormous challenge. The team responsible for the preparation has a key functional role for ensuring the authenticity and quality of the patient-specific products [6].

Any personal disturbances or malfunctioning within such a core group of the pharmacy considerably increase the risk of faulty actions. Apart from the professional qualification, non-specialist social skills are an important pillar supporting team success. Any risks and hazards that might arise are detected much earlier by a well-coordinated group and can be better managed by harmonized behavior than isolated single individuals.

Process deviations and „near misses" as opportunities to discover potential errors

The occurrence of process deviations, errors and „near misses" provides an excellent opportunity for scrutinizing the underlying mechanisms in their early stages and thus avoid the occurrence of a chain of errors with disastrous consequences. These faulty workflows are often caused by undetected latent potential for errors. By documenting and communicating these effects with all parties involved, the causes can be eliminated or appropriate protective measures taken [1].

Approaches to prevention through the system character of errors and accidents in highly technical organizations

Teams in organizations with high-risk situations, for example cytostatics preparation, contribute significantly to the minimization of accidents by using the following instruments:

- Open communication in the group
- Presentation of the individual possibilities of error
- Consideration of personal strengths and weaknesses in performance
- Development of sensitivity for unclear and unsafe workflows
- Early detection and evaluation of situations
- Exchange of different points of view
- Looking ahead at possible developments
- Control of the complexity
- Learning to understand the processes and workflows
- Development of Standard Operating Procedures (SOPs) and process instructions
- Building up a safety culture

Furthermore, teams in high-risk organizations show strongly above-average performance levels under consideration of the following principles:

- More attention on weak signals as early expression of dangers or risks
- Concentration rather on deviations and errors than on successes
- No roughly simplified interpretations or explanations

- Fine grasp of operational procedures
- Quest for flexibility to react to a changing environment
- Great respect for professional knowledge and abilities [9]

Procedures for setting up and maintaining a Risk Management System according to ISO 31.000

Creation of a risk framework by doing the following:

- Determination of valid risk criteria

  The organization defines risk criteria valid for itself, geared to the respective situation. With a high proportion of outpatients, there might be higher requirements on rapid preparation. High-dose treatments require a high level of knowledge about these forms of therapy.

- Explanation of methods and instruments to be used to identify risks and conduct risk analysis and risk assessment

  The preparation team preferably assesses the current risk situation in joint group meetings. The following methods can be used in a first step:

  - Risk audits, also to expose causes of error
  - Team discussions
  - Open communication of possible sources of error
  - Documentation of „near misses“ and process deviations
  - Exposure of fault-prone process flows
  - Exposure of conditions that provoke a violation of the rules

  Furthermore or in a later run-through of the risk management cycle, more extensive instruments can be used, such as:

  - Failure Mode and Effect Analysis (FMEA)
  - Scenario techniques
  - Root cause analysis
  - Fault tree analysis
  - and other methods

  These risk management instruments require a more intensive preparation and training and are sometimes very time-consuming.

- Embedding the creation of risk reporting into the existing management system of the organization

  The results of the Risk Management activities are frequently communicated internally along with the Quality Report, and possibilities for further improvements pointed out.

Risk management control loop

The risk management control loop is used to determine the existing risks and list them according to frequency and extent of damage, with detailed assessments. Depending on the degree of risk, possibilities of risk avoidance such as safety and protection measures are discussed and implemented.

- Risk identification
- Risk analysis
- Risk assessment
- Risk treatment

This provides a continuous loop from risk identification to risk treatment, that can be run through multiple times. The procedure reveals inherent principles concerning how errors arise. Furthermore, the monitoring and control of defined measures at least once annually is extremely important.

Risk types

- Technical risks
  - Risks for the patients
  - Risks for the staff
- Risks due to the cytostatics used
- Risks due to the medical devices used
- Risks due to processes
  - Right patient?
  - Correct dosing?
  - Matching prescription scheme?
  - Appropriate application?
  - Current level of knowledge of persons involved? [5]

Solution approaches of Risk Management

Decisive steps of Risk Management in cytostatics preparation are the identification and processing of existing risks, error process deviations, and „near misses“. It is very important to include influencing structures outside the pharmacy, such as prescribing physicians and nursing staff participating in the administration of the drug preparations.

Results from accident investigations and scientific projects show the following key elements of a risk-managing cytostatics preparation:

- Open communication, also across all interfaces

- Positive work environment
- Employee-oriented management
- Open culture of dealing with errors
- Intensive exchange in the group and with colleagues
- Sufficient process times
- Clear standards for action
- Compliance with the standard operating procedures and rules
- Open attitude about expectations
- Analysis of deviations and distinctive or unusual characteristics
- Consideration of personal strengths and weaknesses
- Knowledge and acceptance of the powers of recollection (human memory)
- Building and expanding a personal safety culture [4]

The cytostatics preparation is supported by a culture of open communication, in which unexpected and unforeseen situations can also be successfully managed. The individual creative commitment of the individual person, also as contribution to the group, contributes significantly to the successful management of risks.

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PERSONNEL

2.1 PERSONS HANDLING ANTICANCER DRUGS

As minimum requirement all personnel dealing with anticancer drugs must be qualified in understanding the local legal requirements connected to their activities.

Persons handling anticancer drugs (stocking, production, distribution, or oral dose packaging unit) under the direct responsibility of the pharmacy include:

Pharmaceutical personnel i. e.

- Pharmacists and trainee pharmacists
- Pharmacy technicians and trainee pharmacy technicians
- Pharmacy assistants and residents
- Pharmacy engineers

Non-pharmaceutical personnel i. e.

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

► Hannelore Kreckel, Gießen (Germany)

Before starting employment and at least once a year, all these members of staff must receive instruction in safe handling of anticancer drugs (see chapter 2.4 Hazard assessment, operating instructions and inductions).

Pharmaceutical personnel

see chapter 2.2 Persons in the production

Non-pharmaceutical personnel

Non-pharmaceutical personnel may only be entrusted with tasks that have a supporting function in production. Among these tasks are stock-keeping to maintain supplies of drugs and adjuvants, documentation, preparing delivery, including the packaging of ready-to-use cytotoxic solutions, and disposal.

The procedures used for documentation, labelling and delivery and for the disposal of the various materials must be defined in the pharmacy's quality management system (QMS) and communicated to employees in a comprehensible form.

Staff must be informed how to handle sterile disposables and how to calculate the quantities of all the materials and products kept in stock to supply both workflows and the department in general. Staff must be familiar with, respect and regularly monitor the required storage conditions.

Employees who do not have specific pharmacy-related training (e. g. stockroom staff) will find it easier to recognise ready-made products containing cytotoxic agents, e. g. when taking deliveries, if illustrations of the products concerned are prominently displayed and the places for storing cytotoxic agents are clearly designated as such.

Transport staff

Transport staff may only accept properly packaged, labelled and sealed containers that have been signed off for delivery and may do no more than pass them on to the requesting department. They are responsible for the correct and timely delivery of ready-to-use cytotoxic solutions.

Cleaning staff

Cleaning staff are responsible for cleaning and maintaining the floor, walls and surfaces of equipment and fittings. Cleaning staff must be instructed on the basis of the QMS about the special requirements relating to a clean room and about the particular risks and hazards of production zones where cytotoxics are made compounded.

Compliance with the hygiene and disinfection schedule must be documented.

2.2 PERSONS IN THE PRODUCTION

In the production and associated quality control laboratory units, only pharmaceutical personnel may be employed.

Before employees begin their work, they must be adequately educated and trained in aseptic working procedures and in the handling of hazardous substances.

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

► Hannelore Kreckel, Gießen (Germany)

All those with an active role in preparation have access to the preparation room, as do the employees engaged in cleaning and maintenance duties.

There are job profiles for all these groups of employees working in the cytotoxic drugs department.

Pharmaceutical staff

The preparation and quality control of ready-to-use cytotoxic solutions must be performed solely by pharmaceutical staff.

The staff entrusted with preparing cytotoxic drugs for administration must be equally well-versed in handling hazardous substances and in aseptic processes for reconstituting drugs. Staff must be adequately qualified for these tasks, attend regular refresher courses, be thoroughly trained and take part regularly in further education or continuous professional development [1, 2]. The training measures must be documented [1].

The initial training of staff to be deployed in the preparation of cytotoxic drugs requires planning, in terms of both time and content, so that the employees receiving this initial training are not overstretched but have every opportunity to acquire the preparation skills and the theoretical knowledge that is essential to understanding the process.

It is advisable to draw up a training plan where the requisite steps are broken down into units and the person receiving induction has an opportunity to work logically and systematically through the complex field of preparing cytotoxic compounds. It is essential that a competent senior staff member is available for them to contact (see chapter 2.7 Initial and vocational training).

Theoretical knowledge can be acquired in dialogue, in independent study or at further training courses. The fundamentals must be described, verified and distinguished from advanced knowledge.

The correct aseptic procedures must be regularly validated [2, 3] (see chapter 4.4.2 Validation of aseptic methods).

Non-pharmaceutical staff

See chapter 2.1 Persons handling anticancer drugs

Procedures to be adopted by both the preparation team and the support staff during the compounding process must be geared to the needs of preparation.

Any steps in this process that generate particles should be confined to an absolute minimum (see chapter 4.4.1 Prevention of particulate and microbial contamination).

The preparation process requires all employees to apply a high degree of concentration and precision during these complex workflows, and pressure of time

makes this a high-intensity operation. Any activities that might impair the concentration of staff must be ruled out during the preparation process. A survey of Australian colleagues identified isolation, the physical constraints imposed by temperature, noise and room size, and the ergonomic work station under a cytotoxic safety hood as key factors in the ability to concentrate [4]. Having a comfortable ergonomic work station enhances close concentration, as does complying with defined breaks, because working under a cytotoxic safety hood can be very isolating and limiting. Some standards suggest taking a break every two hours [3]. Staff must understand how and why the work environment and equipment are being monitored, so that no uncertainties arise. Safe, prudent action is the best basis for working effectively.

The quality of the work performed in a centralised cytotoxic drug preparation unit is crucially influenced by the staff who run the department. Well-motivated staff who are alert, focused, fast and targeted in their work are the most important key to departmental success.

Well-motivated employees are a great benefit, but they cannot be found and retained without effort. One promising approach is to provide each individual with plenty of information, to add commentary to the information, and to ensure it is well circulated. Staff must have enough time to absorb and digest this information. All employees working with the specific challenges faced by a cytotoxic drug department should feel that their questions and fears are taken seriously and that justice is done to their need for information and security.

This includes conveying to staff how the department fits within the overall pharmacy structure and also within the overall structure for treating and counselling patients. This knowledge of context is essential to evaluating, understanding and resolving the problems and expectations of the departments who submit prescriptions. To lay these foundations, it is advisable to offer employees the opportunity to spend a few days during their initial training getting to know the clinic(s) they will be servicing and to maintain their personal contacts with the units concerned while they are working.

Addressing the problems and expectations expressed by other departments calls for employees with clear-cut procedural and methodical competence and an awareness of their responsibility and specific powers in performing their tasks independently.

Employees must be familiar with their department's quality management system, as this will enhance understanding and sensitivity to the multi-faceted issues in a pharmacy oncology service.

References:

[1] ApBetrO § 35

[2] PIC/Ss Guide to Good Practices for the Preparation of Medicinal Products in Health Care Establishments, July 2018

[3] ISOPP Standards of Practice J Oncol Pharm Practice 2007:13, 1 – 81

[4] Roos I, Makela T. Human resource issues in cytotoxic drug dispensing J Oncol Pharm Practice 1997:3 200 – 218

2.3 PERSONS IN PHARMACEUTICAL CARE

- Pharmacists and trainee pharmacists
- Pharmacy assistants and residents
- Pharmacy technicians and trainee pharmacy technicians

Detailed information on this theme can be found in chapter 6 “Pharmaceutical Care”.

2.4 RISK EVALUATION, WORKING RULES AND INSTRUCTIONS

Before starting work in an anticancer drug preparation unit, the hazard risks of anticancer drug handling for that unit needs to be evaluated and documented. The employees must be instructed, based upon these findings. In addition to the persons carrying out the production, all employees dealing and working with anticancer drugs must be instructed in respect to relevant EU legal requirements (e. g. hazardous substances regulations) and/or national and local regulations. The instructions given must be aligned with the different job categories and responsibilities of the staff.

Depending on the respective requirements, they include the following items:

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

These instructions must be updated and documented annually. In addition, written working instructions must be prepared specifically to the particular workplace.

Drugs must be classified according to their properties and included in the pharmacy list of hazardous substances. This list must be amended according to major changes and must be inspected at least once a year. If any changes are made, a new documented risk evaluation has to be produced to accord with the changes made.

Accidents must be documented. In case of personal injury, the accident must be recorded (minor injuries, incapacity to work for a period of less than three days) and notified to the responsible statutory insurance body and local occupational physician.

Specific hazard evaluation must be conducted in respect to Advanced Therapy Medicinal Products (ATMPs) as defined by EU regulation 2007 – 1394.

2.5 RISK OF PERSONNEL WORKING PERMANENTLY WITH CENTRALIZE ANTICANCER DRUG PRODUCTION

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 anticancer drug production and organized on rotational basis. The number of persons potentially exposed should be reduced to a minimum.

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Hazard Evaluation

According to the provisions of the CM-Directive of the Euroepan Union [a] the employer must perform a hazard evaluation during which the dangers associated with the work are ascertained and appropriate protective measures are defined. The employer may delegate these tasks to persons who are capable, qualified and reliable as defined by the national law. Safety experts or company physicians 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 department, reception of goods, storage area, transport, laboratory, etc.
- *Ascertainment* of hazards and burdens, e. g. classification of the hazardous substances into the hazardous substances list (see above) using the material

safety data sheets provided by the manufacturers, but also mechanical dangers arising from equipment and physical and mental factors such as fatigue, stress, monotony, noise, light, etc.

- *Evaluation* of these risks, hazards and burdens
- *Decision* on the measures required. If possible, dangers should be countered at their place of origin. Technical protective measures have precedence over organisational measures and these in turn over individual staff-related measures. This approach is known as the occupational hygiene strategy.
- *Control of the efficacy* of the measures. Whenever measures have been taken, their efficacy is to be evaluated. The protective measures are re-evaluated to determine whether they are effective or may even produce new hazards.
- *Documentation:* The hazard evaluation must be documented in writing and signed by the staff working in the area.

the competent authorities may demand to view these documents:

For the classification of oncological substances and preparations, see the commentary on chapter 3.3

"Classification of oncological preparation according to CMR risk"

Operating procedures

Written standard operating procedures (SOPs) are demanded in every area where hazardous substances are handled.

These standard operating procedures must comprise:

- description of the workplace/activity
- name/class of hazardous substances
- labelling of the hazardous substance at the workplace
- hazards for persons and 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
- proper disposal of contaminated materials, devices, or residue drug products

The general remarks in the European directive clearly indicate that the employer shall be responsible for adapting the organisation and implementation of working procedures for any employee who can come into contact with hazardous substances, to the latest safety standards. Even if the exact hazard of certain substances is not known, but the substances are deemed to be potentially hazardous,

the employer must not wait until more scientific data become available, but install protection measures upfront. This is known as the "precautionary principle".

Instruction

All persons directly or indirectly handling cytostatics must be instructed. This includes not only pharmaceutical staff entrusted with the preparation of the cytostatics but also staff such as pharmacy assistants, pharmacy sales staff and other workers employed in the pharmacy who can perform auxiliary work in preparation and in maintaining stocks . The instruction process must also include the cleaning and maintenance staff responsible for cleaning and technically maintaing the rooms and equipment of the cytostatics department as well as the employees of the transport and delivery service. These employees must in any case be informed orally about the special hazards and told what action to take in the event of an incident.

Oncological practices and wards usually have a high need for consulting with regard to the legal basis for handling CMR drugs. Here support by the oncology pharmacist is desirable, even though responsibility will remain with the employer.

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

- date
- name of employee
- training given by ...
- topics instructed, e. g:
  - effects of hazardous drugs
  - proper handling of cytostatics: acceptance of goods (see Chapter 4.1.1), store keeping, preparation (see Chapter 4.6), dispensing, and transport (see Chapter 4.7)
  - hazards and protective measures
  - aseptic procedures (see Chapter 4.4)
  - disposal of contaminated materials and equipment and of cytostatic drug residues
  - occupational preventive medicine (see Chapter 2.6)
  - action in the case of incidents or accidents, not only in theory but also practical simulation of possible exposure to hazardous substances should be trained

- proper use of the personal protective equipment (see Chapter 4.2)
- statutory requirements and working rules

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 Pregnant or lactating workers

According to the EU directive regarding workers who are pregnant, have recently given birth or are breastfeeding [b], there is no unrestricted prohibition of employment of expectant mothers in dealing with carcinogenic, embryotoxic or mutagenic hazardous substances. However, an employer may not enforce such work on a pregnant or lactating employee, and a hazard evaluation must be performed of all tasks that could have a potential risk for employees with 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. the employee must be transferred to a different workplace. If this is either impossible or unreasonable,

3. the employee must be exempt from work.

The result of the hazard evaluation and the protective measures must be available not only to the persons affected but also to all female employees (at least those performing similar work) and to the workers' council if applicable.

References:

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[2] The European Parliament and the Council of the European Union. Directive 1992/85/EC of the European Parliament and of the Council on the introduction of methods to encourage improvement in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding. Official Journal of the European Union October 19, 1992 Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31992L0085

2.6 OCCUPATIONAL HEALTH AND SAFETY

Employees working in the areas of anticancer drugs preparation in the pharmacy are dealing with potential carcinogenic, mutagenic and reproductive toxic (CMR) drugs. They must be offered regular (e. g. not less than annually) occupational health and safety medical check-ups, taking into account all the relevant factors pertaining to the specific workplace.

These check-ups include:

- Initial medical examination before taking up employment (i. e. full blood counts, chest X-ray).
- Follow-up examinations during the employment at intervals of 1 to 2 years.
- Examinations at the request of the employee if there is a suspicion of work-related health problems

It is recommended that the examinations include biological monitoring of occupational exposure, although it is of limited relevance.

Exposure to anticancer drug must be documented by the employer in a suitable form. This documentation must include the types and amounts of anticancer drugs used and the frequency of their preparation 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 anticancer drug as well as anticancer drug-related accidents and their management.

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The fundamental issues for occupational preventive medicine where staff are exposed to antineoplastic (cytotoxic) agents derive from the properties of these CMR drugs. It is fair to assume that these substances will remain a major pillar in malignant neoplasm therapies for at least the next ten years. Despite the growing use of targeted mechanisms in haemato-oncology, in quantitative terms the volume of antineoplastic agents used in treatment centres continues to rise. This is due to successful therapy outcomes and, as a result, longer treatment periods, permitting long-term tumour control for many tumour entities with fourth- and fifth-line therapies. From the perspective of occupational medicine, therefore, a preventive strategy is crucial. However many measures are taken after a person has been exposed to a CMR agent, they cannot ensure that the effect of damage is totally neutralised. The lack of reliable data on the chronic and sub-chronic toxicity of antineoplastic agents reaffirms the need to leave no gaps in the use of personal protective equipment, to train at-risk personnel regularly, and to install and regularly maintain the technical equipment as defined, for ex-

ample in EN 12980 for safety cabinets used in the preparation of antineoplastic drugs (see chapter PPE, instruction, safety cabinets).

Risk assessments for antineoplastic agents

The risk posed by antineoplastic agents derives from their genotoxic effect, and for this there can be no threshold. The absence of a scientifically founded limit value is due to the stochastic dose-response relationship of CMR drugs. In other words, damage follows a random principle. Moreover, this is not just an avoidable side effect of these substances, but the intended effect of the therapy. There has, therefore, been a long tradition of performing epidemiological and toxicological studies seeking to quantify the risk to which individuals are exposed through their work. Acute symptoms observed after skin contact are loss of appetite, nausea, vomiting, diarrhoea, coughing, shortness of breath, cardiac arrythmia and hair loss. [1]

Apart from these usually reversible symptoms, the literature includes a number of reports of serious long-term effects following exposure. Irreversible liver damage suffered by nurses after many years of exposure to antineoplastic agents has been classified as an occupational disease. [2]

Several studies have examined the question of higher spontaneous abortion rates among nurses, which still remains controversial (first reported by Selevan). [3]

Even the recent research into this issue has been unable to come up with unequivocal results [4] because interviewing exposed persons is not a suitable method for exploring these questions and the miscarriage rates generated in this manner are always an underestimate. Another factor that has been looked at is menstrual dysfunction. [5] As this can lead in extreme cases to infertility, the hypothesis was examined that an elevated infertility rate might be another long-term effect of exposure to antineoplastic agents and – to a small degree – this finding was confirmed. [6] For all the studies quoted here, there have likewise been studies that failed to replicate the results. A study of ward personnel established no link between (5 to 15) years of active service in oncology and levels of biostress. [7] This triggered a discussion still ongoing today about the effect of CMR drugs following low concentrations of chronic and sub-chronic exposure. The associated questions cannot be fully clarified in retrospect because the documentation of working conditions and consequently exposure is often fragmentary. From today's perspective, completely new conditions make new studies in this field essential, because the original working conditions encountered back then do not reflect current safety standards, as a direct comparison between different manufacturing standards compellingly demonstrated. [8]

Nevertheless, the exceptionally high risk potential that still emanates from antineoplastic substances remains beyond doubt.

The objectives of preventive medicine

Given the particularly toxic properties of antineoplastic agents, there are several important aspects to preventive strategies in occupational medicine:

- identifying risks that might result in disease in connection with possible workplace exposures (pre-cancerous conditions, immune disorders, allergies, skin complaints, ...);
- early detection of exposures which in the case of CMR drugs are linked to a high probability of health complaints;
- early detection of occupationally-induced levels that can be attributed to antineoplastic agents (allergies, skin complaints, genotoxic effects, ...).

Concentrations in the worker can be demonstrated by analysing the blood or urine for antineoplastic substances and their metabolites (biomonitoring). Analysis will additionally record any susceptibility to the unintended toxicity caused by antineoplastic agents due to their genotoxic effects (known as cytogenetic biomonitoring). If an occupational health check indicates any relevant concentrations or effects as a result of antineoplastic exposure, the medical officer will recommend biomonitoring so that the efficacy of protective measures can be observed on a continual basis.

Who? When? What?

Regular preventive check-ups should be offered to everyone working in an area where there are CMR drugs.

This includes:

an initial medical examination before taking up employment,

follow-up examinations every 12 to 24 months while the employment lasts,

examinations at the worker's request if occupational any health impairments are suspected.

It should be noted that these preventive check-ups are compulsory in, for example, Germany[1], but not in Austria[2]. In Germany, both the Berufsgenossenschaft for the health and welfare sector and the accident insurance association DGUV recommend these for all groups of workers entrusted with preparing and administering antineoplastic agents. This recommendation includes cleaning and waste disposal staff. It should be mentioned that persons exposed to radiation at work are subject to far more rigorous provisions. These workers undergo continual dosimetry monitoring and must undergo an annual occupational medical check-up, while in Germany the maximum interval for check-ups in the case of those working with carcinogenic substances is 5 years[3]. At the request of the insured person, a preventive medical examination must be arranged at any time in cases of justified suspicion in accordance with § 7 (1).

1 BGV A 4 (Occupational preventive medicine), § 3

2 Decree issued by the Federal Chancellery of Austria on protective measures for handling antineoplastic agents of 13 February 1990:

3 The nature of the occupational preventive medical examination

Particular attention is to be paid to the following:

- Medical history and occupational medical history with particular reference to previous exposures (initial check-up); a record must be made of the nature of the contact with antineoplastic agents, the quantity and nature of the substances, and any protective measures taken.
- Physical status
- Status of the skin and mucous membrane, as damage can be induced by direct contact with bleomycin, dactinomycin, dacarbazine, anthracyclines or vinca alkaloids; it is important to note any recurrent or therapy-resistant eczemas of the skin, which may open the gate to antineoplastic agents. Skin damage due to disinfectants and latex allergies are also important to note.
- Records of allergies that can be induced by bleomycin and cisplatin
- Immune status
- Record of respiratory disorders
- Record of functional disorders of the liver and kidneys
- Determination of lymph node status, e. g. lymph node swellings
- Clinical chemistry tests
- Erythrocyte sedimentation rate

BGV A 4 (Occupational preventive medicine), Annex 8

- Full blood analysis including reticulocytes
- Liver function parameters (gamma-GT, SGPT, SGOT)
- Creatinine
- Attention should also be paid to circumstances that can indirectly exacerbate working with antineoplastic agents, including e. g. intolerance of glove materials such as latex.

These tests, however, are not designed to establish a specific uptake or concentration, but to serve to provide general orientation. Nevertheless, they do have a firm role to play in preventive medicine, because problems at the workplace, be it with administering or preparing antineoplastic drugs, are frequently accompanied by non-specific symptoms. Often these take the form of an impaired sense of taste, headache, nausea, increased hair loss and a greater susceptibility to infection. If there are any grounds to suspect that there has been an exposure

to antineoplastic substances, biomonitoring must be initiated to determine the cause. In this event, the standardised rules for each work procedure should be consulted, as deviations from the protocol are often the reason for toxic effects.

The employer must document any potential risks to health arising from handling antineoplastic substances and describe the preventive measures taken. This includes notifying the regulator of the type and overall quantity of the antineoplastic substances in use and the frequency of preparation, carrying out training sessions and implementing the required protective measures (see chapter Hazard assessments).

Biomonitoring for uptake and concentration

In technical terms, the simplest form of monitoring is environmental monitoring, which detects workplace contamination by taking swabs. This type of test is very hard to standardise and should therefore be interpreted as semi-quantitative evidence. Swab sampling itself is easy to do, and the analysis can be contracted out to a laboratory. The parameters currently available are the antineoplastic agents cyclophosphamide, Ifosfamide and 5-fluoruracil. These substances are very often anchored in widespread treatment protocols.

Tests using this method on the above-mentioned pilot substances have shown that the body levels found in pharmacies where antineoplastic drugs are prepared are higher than in the wards where these therapies are administered. [9] Moreover, contamination has been detected not only in antineoplastic safety cabinets, but also on work surfaces, floors and personal protective equipment. While these findings flag up the problem, they only contribute indirectly to solving it. A concentration can be established, but the source cannot be identified in this way. Even with enhanced analytic procedures and detailed examinations in up to 15 different places, interpretations of the results of swab samples in the antineoplastic preparation zone are often unsatisfactory. [10] Even so, if used thoughtfully environmental monitoring can deliver valuable insights into the background to exposure, especially when no lasting improvement is achieved despite implementing the preventive measures and systematic effort still results in repeated spatial contamination.

The central role played by the interaction of personal protective equipment and technical equipment in the hands of well-trained staff, as reflected by the current state of debate, has been demonstrated in systematic exposure studies. The risk posed by the decentralised preparation of antineoplastic drugs, and a reduction in concentrations to below the analytical detection limit, were shown for methotrexate itself by investigating the case of high-dose therapy with the administration of 20 g doses. [10] This study documented a striking reduction in concentrations in pharmacists engaged in preparation once they had taken appropriate protective measures. After safety standards had been implemented everywhere, the situation

improved to such an extent that the burden was no longer detected in pharmacy staff. A longitudinal study in 21 hospitals with centralised preparation showed that accidental contamination during preparation led to measurable concentrations of anthracyclines in blood and a reversible elevation of exposure parameters. [11] This increase had a statistically significant impact on the rate of sister chromatid exchange (SCE), but produced only a trend for the micronuclei (MN) rate. The main conclusion of this study, however, was that over the representative period of two years no systematic increase in exposure or burden could be observed. Although these findings were confirmed by later studies [13], other research paints a more relative picture [14, 15], and this has recently revived the debate about safety in German-speaking countries. What is clear, however, is that current safety standards make it possible to work with as good as no exposure [16], highlighting the central importance in any preventive strategy not only of technical equipment must also of regularly training staff. This applies all the more to nursing staff who, because the patient is an "open system", do not start from such a strong position. [7]

Today there is an ever-expanding set of biomonitoring tools available to record exposure and genotoxic effects. At the same time, however, this approach reflects the inadequacy of existing test systems (for a summary of methods see [9, 17]). Even expanding this spectrum to include techniques based on molecular biology such as the comet assay or measuring DNA adducts induced by platinum compounds only offer a sporadic glimpse of the problem, as damage is often reversible and given existing sensitivity can at most be detected for a few weeks. The comet assay, for example, which can be used to monitor both double- and single-strand DNA breaks, is a welcome addition to the methodical repertoire, but usually it only picks up single-strand DNA breaks, while the rare occurrence of double-strand breaks indicates that exposure has already reached massive levels. Mucous membrane cells, which are considered to be especially sensitive in detecting chromosomal aberrations, have not yet been sufficiently researched as an alternative. [18] In the spirit of occupational preventive medicine, therefore, measurements should be conducted on a continuous, individual basis, as with dosimetry for workers exposed to radiation. One approach would be personal air monitoring, which means that the preparation worker wears a miniature pump on the body to collect air with the same composition as the ambient air (uptake measurement). With this technique, ambient air is continuously sucked through a filter to eliminate all the antineoplastic content. Approaches of this kind are made more difficult by the fact that antineoplastic agents evidently do not only spread through the air as aerosols, as originally thought, but can also disperse as molecules in gaseous form. [19] To enhance prevention, more attention has recently been paid to optimising surface cleaning and decontamination. These studies revealed that many antineoplastic agents actually rank among the substances which are difficult to decontaminate and there is no single detergent that can remove them all.[20] (see chapter Taking deliveries).

To ensure the transition from risk detection to genuine risk management, occupational preventive medicine must be firmly integrated and additional research is needed to gain more robust insights. In the complex process of preparing antineoplastic drugs, providing each individual member of staff with the necessary tools in addition to continuous training will ensure safety and motivation at the workplace. [21]

Conclusions

The instruments available for preventive examinations in occupational medicine today can be meaningfully combined with biomonitoring techniques. Accidental contaminations cannot be ruled out when all the safety measures are applied, although diverging findings on exposure in central European countries suggest heterogeneous standards. Longitudinal studies have confirmed the efficacy and high standard of existing protective measures, alongside regular staff training, as key to occupational preventive medicine. To enhance prevention, the consistent application of technical and personal protective measures should be supported by the implementation of standardised rules with a focus on storage, the preparation of antineoplastic drugs, disposal, cleaning, decontamination, accident measures and maintenance.

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2.7 TRAINING, 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- and Risk-Management System
- National and regional laws, rules, regulations and best practise
- Safe handling of hazardous substances within the facility
- Hazards and protective measures, equipment and disposal of contaminated material
- Accident prevention and management
- Hazardous waste handling
- Drugs and dosage forms
- Stability and incompatibility
- Production management
- Working in an aseptic area
- Technical equipment for the production and administration of anticancer drugs
- Drug effects and pharmacology
- Clinical pharmacy
- Cancer types and treatment options
- Pathology and impact on dose changes
- Management of Clinical Trials involving anticancer drugs
- Quality control laboratory

Practical training

- Aseptic working techniques and their validation in simulations of work flow during compounding
- Handling of disposable articles
- Simulation of accidents and their management
- Handling different documentation systems
- Packaging, quality management system for distribution and disposal of contaminated material
- Methods for practical training evaluation
- Handling a spill-kit
- Checking anticancer drug prescriptions including parenteral and oral drugs

Clinical pharmacy

- Training by simulation for medication reconciliation, therapeutic education, medication adherence evaluation

Team members with contact to patients and their relatives need to be trained to meet patients' needs in order to provide proper patient care. This includes knowledge about disease stages, factors influencing the quality of life of the patients including psychosocial circumstances and communication skills.

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Basic or initial education for pharmacists in university differs between countries depending on national regulatory frameworks and programs. Moreover, we can observe a diversity of subjects taught in universities.

In any case, additional or specialised education and training are needed to reach a level of specialization and practice hospital pharmacy. Specificities of oncology pharmacy are numerous as indicated above. These specific aspects must be taken into account in specialised education, as for example for radiopharmacy, or hospital pharmacy in pediatrics.

In order to practice safely and with independent competence, hospital pharmacists require a set of specific competencies that go above and beyond the basic education of 5 years for pharmacists [1]. These needs are evidenced and supported by the 2011 European Commission-sponsored Pharmine [2] project, the 2008 FIP Global statements [3] on hospital pharmacy, and the 44 European Statements of Hospital Pharmacy [4].

Most European countries have in place some form of post graduate qualification to raise the skills and competences of pharmacists to that required in hospital practice. Indeed, in some countries, possession of such qualification can be a requirement of practice. Qualification that comes with a hospital pharmacy qualification is an essential element of being able to continue to practice safely in an environment of high innovation and risk. However additional and specialised education is recognised for hospital practice, the terms of this training may differ between countries.

For example, in France this training takes place in the form of hospital residency even if this residence is not definitely recognized as a prerequisite for hospital pharmacy practice. The current format of French residency in hospital pharmacy is a 4-year specialized training which combines professional practice in several hospitals and university courses [5, 6].

In most of cases, specialised training in oncology pharmacy takes place after the qualification in hospital pharmacy. One of the reasons may be related to the heterogeneity of hospital structures. There are specialized oncology hospitals and general hospitals with oncology departments. Hospital pharmacists in oncology are recognised differently depending on the health system and country. ESOP is working with other organisations to increase the recognition of oncology pharmacy and to improve cross-border harmonisation of the requirements for oncology pharmacy.

It is also essential to maintain knowledge during the professional exercise. That's the goal of **Continuing Pharmacy Education.** EAHP defines Continuing Pharmacy Education as per the ACPE definition* which states that "Continuing education for the profession of pharmacy is a structured educational activity designed or intended to support the continuing development of pharmacists and/or pharmacy technicians to maintain and enhance their competence. Continuing pharmacy education (CPE) should promote problem-solving and critical thinking and be applicable to the practice of pharmacy" [7].

** Accreditation Council for Pharmacy Education [8]*

2.7.1 TRAINING OF NEW PERSONNEL

Training of new personnel in anticancer drug compounding needs to be performed with specific care since handling anticancer drug bears 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.

Training of persons counselling patients includes the knowledge of the special needs of cancer patients in order to provide individual pharmaceutical care.

► Dr Christophe Bardin, Paris (France)

Example in Germany (Ruth Hangen, Germany)

The specialised knowledge demanded by the AOLG (association of the highest regional health authorities) is given in the guidelines on the preparation of ready-to-administer cytostatic solutions in pharmacies [9]. They should be acquired in the course of training events and a safety training course. Thüringen is the only state in Germany whose Chamber of Pharmacists requires staff to hold a Cytostatics Preparation certificate [10]. The rules governing the award of this certificate state that obtaining it "forms the individual basis for staff active in the field of cytostatic preparation". These rules set out the number and nature of the training events to be acquired, as well as requirements for training establishments and head instructors. The holder of a certificate must attend further training in order to extend its validity.

Knowledge and skills can be imparted using a diversity of methods:

Human aspects for practical training:

The employee being trained must be allocated a competent contact partner – a mentor – for all the questions that arise during the training period. The mentor should be performing the same activity as the new employee and must feel responsible for him/her during the training phase.

The training plan should set out the content in modules, which are then imparted to the employee in stages. This will enable him or her to get to know the complex field of cytotoxic preparation in a logical, systematic manner. A plan 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. One way to encourage this is, for example, to discuss the process during each module.

Theoretical knowledge:

- during discussions with the mentor or with colleagues
- by private study of suitable materials: scripts, computer programs, e-learning
- by attending beginners' courses/lectures/workshops/seminars.

Knowledge of preparation in practice (including aseptic procedures):

- written instructions, SOPs
- watching videos
- demonstrations by colleagues.

Practical skills:

The work described or demonstrated is performed using dummy material that should be as realistic as possible; 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 cytotoxic preparation facility.

Evaluation of training

Evaluation will include theoretical knowledge and practical skills. In this case, it can include:

- wearing protective clothing
- clean room conducts
- 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 [11, 12, 13]
- 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.

Participants should be "tested" on what they have learned after completion of every individual training module and at the end of the entire training phase; this must be documented and confirmed by the employee. 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.

Scientific societies may also be involved in education process

Training offers by these societies is more about continuous education, but initial training is also concerned. **For example, in France, a pharmaceutical working group, GERPAC,** is an association to promote the techniques and skills needed for the development of biological and physico-chemical protection in the hospital pharmaceutical environment where toxic drugs are prepared [14]. In this perspective, GERPAC intervenes in the training of pharmaceutical staff and intends to provide a training and information Platform covering different themes: congress workshops, training oriented **Quiz** space , A **space Simulation** with the presentation of digital tools dedicated to the training of the operators in immersive virtual environment (training operators by making them evolve in a virtual environment) and intuitive and publications.

The French Society for Oncology Pharmacy, SFPO, also organizes every year since 2013, a 2-day Masterclass in Paris: *"Stability studies in Oncology."* This training helps young pharmacists and residents to perform a stability study, to read, and to use stability data. The objectives of this workshop are to give the participants the scientific basis on the degradation of drugs, the methodology to carry out a stability study, and the regulatory environment. The program is partly based on the European guidelines published by SFPO [15]. Knowledge assessment is implemented. An extension to a European level is being implemented in collaboration with ESOP.

Another mission of SFPO is to centralize and make available the regulatory texts and guidelines in relation with topics for education. In the thematic "anticancer drug production", there are some examples of important regulatory texts and documents for specialized training: "the Good Manufacturing Practices for hospitals", "Good Practices in Hospital Pharmacy" and also some guidelines from SFPO "Adaptation des ressources liées à la Pharmacie Oncologique" [16, 17, 18].

Training in clinical Pharmacy

Training clinical pharmacy shows a more heterogeneous situation due to different ways to implement clinical pharmacy recommendations. Clinical phar-

macy in oncology is very well developed but depending on the type of hospital and number of staff available to take actions. Training of persons counselling patients includes the knowledge of the special needs of cancer patients in order to provide individual and optimal pharmaceutical care.

The two concepts of clinical pharmacy and pharmaceutical care are closely related. The European Society of Clinical Pharmacy (ESCP) defines clinical pharmacy as a health specialty that describes the activities and services of the clinical pharmacist in developing and promoting the rational and appropriate use of medicinal products and devices. In the Clinical Pharmacy Survival Guide [19], clinical pharmacy is described as a name for a series of patient-related services, including prescription monitoring, therapeutic drug monitoring and patient counselling. Whatever definition is adopted, it is clear that clinical pharmacy is not synonymous with hospital pharmacy. There are two reasons for this. First, hospital pharmacy encompasses a much wider range of activities, such as manufacturing, quality control, supply, procurement, and system-management. Second, clinical pharmacy can also be practiced by community pharmacists. In the field of oncology, they may play an important role for oral targeted therapies depending on the country healthcare system.

In any case, clinical pharmacy is a key activity in oncology. Considering initial training in clinical pharmacy, two prerequisites must be included:

- knowledge of pharmacological aspects of anticancer drugs and drugs used in supportive care (including pharmacokinetics, pharmacodynamics, drug-drug and drug-food interactions, pharmaceutical particulars as handling of different dosage forms)
- knowledge of different types of cancer and medical terminology in cancer.

Pharmacists interact with patients, physicians, and nurses in a wide variety of situations. It is essential that practical training may include simulation-based training to reflect real life. That's the case for pharmaceutical consultations, medication reconciliation but also activities such as active participation to multidisciplinary tumour boards or multidisciplinary patient rounds [20, 21, 22].

Examples of clinical pharmacy trainings in France

Most of the trainings in clinical oncology pharmacy in France are university trainings. There are 4 to 5 university degrees or inter-university degrees for this topic in various regions. Most of the participants are young pharmacists or residents in hospital pharmacy.

Example of a teaching program (Lyon University clinical oncology pharmacy degree)

- **Course module 1: therapeutic strategy and main pathologies (22 h)**
  Cancer overview and epidemiology
  Leukaemia, sarcoma, lung, breast, urological, melanoma, head and neck, gynaecologic, digestive, pediatric cancers, geriatric oncology
- **Course module 2: anticancer drugs and supportive care (32 h)**
  General principles: polychemotherapy, radiotherapy, hormone therapy, immunotherapy, nuclear medicinePain management
  Medical devices in oncology
  Therapeutic drug monitoring
  Mechanisms of action of anticancer drugs: alkylating agents, antimetabolites, antimitotic drugs, topo-isomerase inhibitors, anthracyclines…
  Protein kinase inhibitors and monoclonal antibodies.
  Immunotherapy
  Chemoresistance
  Toxicity management of toxicity of anticancer drugs: pharmacovigilance, neutropenia, hypercalcemia, digestive, cutaneous and cardiac toxicity, tumor lysis syndrome
- **Course module 3 (28 h):** Centralised production of anticancer drugs and quality management
  Technical equipment and aseptic working techniques
  Occupational health and safety
  Stability of the preparations
- **Course module 4 (31 h): multidisciplinary organization**
  National and regional regulatory aspects for cancer management and cancer centers
  Oncology clinical pharmacy:
  Prescription analysis and check
  Medication errors and iatrogenic risks
  Drug-drug interactions
  Therapeutic education
  Pharmaceutical consultation, medication reconciliation, patient counselling
  Pharmaceutical care with nursing staff

The degree includes practical sessions with simulations, visits to sites, and workshops

Training and professional specialization of pharmacy technicians

It is also important to offer appropriate and specialized trainings to pharmacy technicians. Status and responsibilities of pharmacy technicians are very heterogeneous according to regulatory frameworks of the countries. The first basic principle is to offer an adequate training to work in hospital pharmacy.

Example in France

Once the initial and first degree "pharmacy technician" is completed, a complementary training and diploma is required to become "hospital pharmacy technician". This is a 10 months training course including and combining 660 hours of teaching (theoretical knowledge) and 700 hours of practical periods in hospital pharmacy [23].

Teaching program includes 8 modules:

- **UC1:** analyse drug request and contribute to prescription check with respect to regulatory requirements of hospital pharmacy. This module includes basic knowledge for therapeutic classes
- **UC2:** analyse medical device request
- **UC3:** know and apply quality procedures in hospital pharmacy
- **UC4:** organize process and produce all kinds of pharmaceutical preparations with respect of Good Manufacturing Practices. This module includes handling of anticancer drugs, knowledge of technical equipment for the production of anticancer drugs and aseptic working techniques (laminar airflow and isolator).
- **UC5:** organize process and produce all kind of radiopharmaceutical preparations
- **UC6:** organize and execute sterilisation processes of medical devices
- **UC7:** manage drug flows; drug management and inventory tracking according to hospital and national regulatory framework.
- This includes module includes management of specific drugs as biosimilars or oral anticancer drugs. It includes also drug process with transition points between community pharmacy and hospital and benefit to include medication reconciliation to reduce errors risks
- **UC8:** communication module. Process and transmit information, work in a team, and mentor personnel.

2.7.2 CONTINUOUS EDUCATION AND PROFESSIONAL SPECIALISATION OF PERSONNEL

The goal of continuous education and professional specialization programs is to keep personnel informed about the latest developments and innovations.

Personnel working in the anticancer drugs compounding unit as well as the staff providing pharmaceutical care and patient counselling should also have the opportunity to participate in internal and external pharmaceutical education programs.

A certificate should document participation.

Opportunities for professional specialisation and continuous education should be taken if offered.

► Dr Christophe Bardin, Paris (France)

Example in Germany (Ruth Hangen)

The BAK guidelines [24] 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. The general principles governing the training of pharmacists adopted by the federal association of pharmacists [25] likewise apply to the field of oncology pharmacy. Internal training can be organised as practice days or the presentation of innovations in the form of talks and demonstrations by the employees themselves. Continuous training on innovations in cytostatic therapies are provided and/ or offered all around the country by associations of pharmacists, specialist societies and the pharmaceutical industry. Points are awarded for accredited continuous training events. These can be collected, and most regional associations of pharmacists will issue a certificate of further training upon request. This certifies that the participant has attended continuous training over a defined period. The follow-up courses required by the Thuringian certificate in "Cytostatic Preparation" [26] refer specifically to further training in the field of cytostatics. The Deutsche Gesellschaft für Onkologische Pharmazie (DGOP) regularly holds courses in "Aseptic Procedures", for which a certificate is issued. In addition to the events already mentioned, external training also includes visiting other pharmacies in order to learn about their methods of working. Although this is relevant for pharmacists, it applies much more for pharmaceutical technicians who are generally the persons carrying out the preparations.

For pharmacists, the federal pharmacists association (BAK) drew up a curriculum for further training in oncology pharmacy in 2004, in collaboration with the pharmacists associations of all the Länder [27]. Some sections of the association have since been offering an additional strand of further training in Oncology Pharmacy. The DGOP (German association for oncological pharmacy) offers the "Onkologischer Pharmazeut DGOP" with an identical curriculum, and this can be obtained by members of all sections of the association. The practical requirements are broader than in the BAK curriculum, but this title can then be used as an independent qualification [28].

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 [29] require that cytotoxic solutions be prepared in accordance with recognised pharmaceutical practice and at state of the art. This automatically generates a duty to undergo continual training and further training.

Continuing training – Christophe Bardin, Paris

Most of continuing education programs are implemented by university or scientific societies.

Continuing education reinforces the knowledge already acquired but above all to keep knowledge possessed by the personnel constantly up to date with the latest scientific and technological developments. This is particularly important in oncology where many new drugs become available with evolving therapeutic guidelines.

Some examples:

- Production: automation for the preparation of cytotoxic drugs in centralized preparation unit, evolution of dose-banding
- Pharmacotherapy: CAR-T cell therapies and other advanced therapy medicinal products (ATMPs), new therapeutic combinations with immunotherapies
- New designs in clinical trials: adaptive trial designs, BASKET and UMBRELLA trial designs.
- Clinical pharmacy: implementation of pharmaceutical consultations with increasing responsibilities for pharmacists
- Increasing use of Complementary and Alternative Medicines (CAM)
- Digital health and devices to maintain patient's medication adherence in oral chemotherapy
- But also: cost management in cancer care and drug shortages in oncology.

French Society for Oncology Pharmacy SFPO has launched a continuing training program called Oncoteach®. The Oncoteach® program is intended for hospital pharmacists in oncology. Some parts are specifically intended for community pharmacists or pharmacy technicians. The training program consists of livel sessions of 1 or two days:

- Clinical pharmacy activities focused on oral chemotherapies in oncology and haematology *(2 days),* this includes medication reconciliation, pharmaceutical consultation, prescription check, management and prevention of drug toxicities
- Clinical research in oncology *(1 day):* how to read clinical trials, understand methodology, evaluation criteria, basics for statistics interpretation, regulatory and ethical aspects

- Phytotherapy and Complementary and Alternative Medicines in oncology *(1 day):* terminology, pharmacological aspects, epidemiology, interactions, management and toxicity detection, psychological aspects.
- CAR-T cells therapies and other Advanced Therapy Medicinal Product (ATMPs) *(1 day):* terminology, regulatory frame, how to involve clinical pharmacist, specific aspects of safe handling and preparation
- Evolution of Good Manufacturing Practices in hospital *(1 day):* impact on chemotherapy preparations
- Anticancer drugs production *(1 day):* basics for working in aseptic working zone, correct handling of hazardous substances, dangers and protective measures, automation and robotics, pediatric formations
- Management of patients with cancer – pharmacological and clinical basis (intended for community pharmacists) *(1 day)*

National and international congresses of scientific societies are also an interesting opportunity in order to propose continuing education. That is the case for workshops during SFPO congresses.

EUSOP program

Education and continuing training in oncology pharmacy is a priority for ESOP and this theme is considered as prerequisite for a high value involvement of oncology pharmacists in hospitals and optimal pharmaceutical care. Continuing education at a European level is a major and strategic goal for oncology pharmacy development across Europe, fully reflecting national and regional realities. It's an opportunity for the development of competency-based education and training programs, especially in those countries where formal structures of this kind may be under developed. It's also an opportunity for cross-border cooperation in the oncology pharmacy field.

ESOP has launched an education program called **EUSOP, European Specialization in Oncology Pharmacy.** The 100 hours program consists of webinars (e-learnings), national trainings, and an international workshop (Excellence Course for Oncology Pharmacy – ExCOP). The Program divides in 50 h of e-learning, 12 h of National Training and 38 h of International Training (ExCOP). National trainings take in account national specificities and local regulatory frameworks. After passing the whole EUSOP program, the title "European Pharmacist in Oncology Pharmacy" will be conferred.

The full program with a total of 100 h contains,

- **Basics of Oncology Pharmacy (18 h)**

  Main learning targets: understanding classification and mechanism of action of antineoplastic drugs; handling of anticancer drugs and aseptic working techniques; environmental and personal protective equipment (PPE)

- **Oncology Pharmacy in practice (11 h)**

  Main learning targets: understanding the role of pharmacists in clinical trials, have information on topics such as medical errors, risk management and pharmacovigilance; formulations and pharmacokinetics of anticancer drugs; specificities and challenges of oral chemotherapy and targeted therapies; knowledge about the nutrition approach of cancer patients

- **Clinical Oncology Pharmacy (46 h)**

  Main learning targets: to be able to use clinical pharmacy skills in oncology pharmacy; to understand the importance of patient communication in oncology pharmacy and to provide patient consultancy service; to be able to prevent/reduce drug interactions and side effects; to be able to create pharmaceutical care plan; to understand the role of the oncology pharmacist in patients with organ dysfunctions; to learn about the common types of cancer in the society, to understand their classification, diagnosis and treatment methods

- **Biologics in Oncology Pharmacy (25 h)**

  Main learning targets: understanding the importance and importance of biologics in cancer treatment; to understand the characteristics of proteins and monoclonal antibodies, stability and factors of instability; to learn biosimilars, their development and production; to understand the current practice and regulations about biosimilars, switching, implementation and management of biosimilars in hospital.

The bi-annual European Conference in Oncology Pharmacy (ECOP) represents also a great opportunity for continuing education.

Accreditation of continuing education

Accreditation of training is an important point since it can be considered as a formal, regional or national recognition of the training. This is also a major asset in the career path of the pharmacist. Depending on the country and regulatory framework, continuing education may be a regulatory obligation, at national or regional level for health professionals. For all these reasons, accreditation may be a strong incentive to participate in continuing training.

Continuing education evolves independently in each European country and the collection of continuing education points or credit may be more important in some European states than in others.

Due to the heterogeneity of healthcare and academic systems across different countries, European accreditation of continuing education is a difficult topic and represents a real challenge. In the longer term, an enhanced agreement between countries would present an opportunity for labour mobility.

For example, the Accreditation Council of Oncology in Europe (ACOE) provides accreditation to Continuing Medical Education (CME) providers (including Member Societies of the European Cancer Organisation) for the benefit of participants receiving education in oncology. Accreditation by ACOE provides CME credits to participating delegates, recognising the high quality of the education delivered [30].

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