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Abstract

Upon receipt of a request from a prescriber for a pharmacy preparation, the pharmacist must decide whether the request is appropriate and reasonable, and judge the level of risk associated with proceeding with the request. The pharmacist must also consider the risks of not supplying a medicine which may lead to the patient not receiving treatment. Further discussion with the medical team may be needed. This chapter approaches the risk assessment of the prescription in a structured way, referring to procedures and forms from different countries. The assessment also includes the feasibility of producing a preparation of appropriate pharmaceutical quality and with all necessary clinical information.

Pharmacy legislation defines the framework in which pharmacists can prepare medicines, however there are other legislative and quality frameworks that they must be aware of if other categories of products are requested, such as biocides, medical devices, or placebo's, or agents used for euthanasia. Veterinary and homeopathic medicines are also dealt with, as are raw materials, especially hazardous materials and precursors.

Keywords

Risk assessment • Prescription • Preparation • Reasoned assessment

Based upon the chapter Beoordeling recept by André Wissenburg en Frits Boom in the 2009 edition of Recepteerkunde.

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2.1 Pharmacy Preparation: Way Out or Unjustified

Case Suppositories with Hydrocortisone

Prescription states: Hydrocortisone suppositories
240 mg, 6 units

Dosage – Use 1 suppository when required as directed

(continued)

The parents of a 2 month old girl Klaartje come to the pharmacy with this prescription. The suppositories have been recommended by an endocrinologist at the hospital. Upon inquiry it appears that Klaartje suffers from a condition known as Prader Willi syndrome, a hereditary disorder which affects hypothalamic function; the adrenal cortex produces insufficient corticosteroid at times of stress.

An intramuscular injection with a licensed pharmaceutical preparation that contains hydrocortisone sodium succinate would constitute a major treatment option. However, the child's parents do not want to give an injection to their child. Klaartje drinks very reluctantly as all babies with the Prader Willi syndrome. The parents don't consider administration with the feeding of the contents of a capsule or of crushed tablets as a reliable option. Therefore, the doctor has suggested a rectal preparation.

This case is typical of requests for pharmacy preparations; in order to give tailor-made care, the doctor has prescribed an individual preparation instead of a licensed pharmaceutical preparation. When the oral route would have been an option, licensed oral solid medicines had to be adapted anyway because of the low dose required.

Before the pharmacist starts preparing the suppositories, he needs to perform a risk assessment to establish the likely safety, quality and efficacy of the product (in comparison with alternative treatment options).

Pharmacy preparation allows the doctor and pharmacist to provide individualised and tailor-made pharmaceutical care. The preparation of a medicine in the pharmacy fulfils a need when the licensed pharmaceutical preparation is not available (see also Sect. 3.2.2) or when a licensed pharmaceutical preparation does not satisfy a specific situation.

However, pharmacy prepared products are not subject to the same levels of scrutiny with respect to quality assurance and efficacy as licensed medicines; therefore prescribers and pharmacists cannot make the same assumptions of quality, safety and efficacy about these products as they do for licensed medicines.

This is due to the wide range of elevated risks associated with pharmacy preparation, including calculation and manipulation errors, formulation failures leading to overdose or underdose, possible toxicity from raw materials and microbiological contamination. The relative lack of

pharmacovigilance or monitoring systems for pharmacy prepared products also means that the likelihood of detection for any errors that lead to side effects is low.

Despite the relative lack of information about side effects related to pharmacy prepared products, there have been reports of catastrophic errors associated with them, including an error in the US that led to a 1,000-fold overdose of clonidine in a 5 year old child [1]. A high profile error also occurred in 1998 in the UK, when a baby died following a calculation error in preparing peppermint water in a community pharmacy [2].

Therefore, upon receipt of a request from the doctor, the pharmacist must examine the situation and decide whether the request is appropriate and judge the level of risk associated with proceeding with the request. Before proceeding, the pharmacist should review all other potential treatment options. The use of a licensed product in line with its approved indication should be strongly advocated unless there is a specific reason not to use such a medicine. However, the pharmacist must also consider the risks of *not* supplying a medicine which may lead to the patient not receiving treatment. In this context, it should be recognised that some patients do have special clinical needs which cannot be met by other viable options.

The pharmacist must make every effort to ensure that the medicine produced is of appropriate pharmaceutical quality and is fit for the intended purpose; an approved or authorised formula should be used wherever possible. Where such formulae are not available, steps should be taken to minimize risk where possible e.g. restricted shelf life, fridge storage (if applicable), use of licensed starting materials etc.

The same principles apply for reviewing prescriptions for pharmacy preparations as for licensed medicinal products.

2.2 Prescription Assessment

2.2.1 Alternative Treatment Options

Before a pharmacist decides to prepare a product, he must consider various alternative treatment options available.

Depending on legislative situation in the country and the relation between pharmacists and physicians, options may include:

- Use of a (licensed) medicine which is then administered by an alternative route or method e.g. use of a soluble or dispersible product or indeed rectal product in patients who have difficulty swallowing whole tablets.

- Use of an appropriate licensed formulation of an alternative medicine from the same therapeutic class (e.g. using a licensed liquid formulation of lisinopril rather than preparing a captopril oral suspension).
- Manipulation of a licensed medicine prior to each dose e.g. dispersing a tablet in a small volume of water or halving tablets (Note: the practice of dispersing a tablet in water and then using an aliquot of the liquid is associated with a high risk of inaccurate doses and is generally not recommended except in extraordinary circumstances). For the general approach of options when difficulties swallowing solid licensed medicines is the reason for the request, see Sect. 37.6.2.
- Use of a product intended for a different route e.g. use of an injection orally.
- Use of an imported product which bears a product license in its country of origin (a check should be made to ensure that the absence of a local license is not due to a revocation of a previous license).
- Purchase of a batch-manufactured unlicensed product from an alternative supplier (e.g. 'Specials Manufacturers' in the UK). Note that this practice is not allowed or highly restricted in some countries in Europe (see Sects. 3.9 and 3.12).
- Are the facilities and equipment appropriate and calibrated?
- Has a health & safety risk assessment been carried out?
- Are there systems in place to monitor the efficacy and safety of the product? Is the patient being monitored closely (if appropriate)?

2.2.3 Structured Assessments

Some pharmacists have suggested a structure approach to the decision-making process: e.g. Leeds approach, German reason check, Risk-benefit Form.

2.2.3.1 Leeds Approach

At Leeds Teaching Hospitals NHS Trust in England, the Pharmacy department has a 'catalogue' of authorised pharmacy preparations, which is periodically reviewed to ensure that other more suitable options are not available. Each of the approved preparations on the catalogue have been reviewed by a group of senior technicians and pharmacists to ensure that they have a sound evidence base and are backed by an authorised preparation instruction and agreed label.

This means that the clinical pharmacist has some assurance of the likely quality of the end product. They must, however, still judge if the individual formulae is appropriate for the intended patient. This is the difference between a product of high quality and one that is appropriate or 'fit for purpose'.

If a 'non-catalogue' (non-standard) preparation is requested, the requesting pharmacist must complete a form (see Fig. 2.1) to acknowledge that other options have been considered, along with the possible risks associated with the preparation. High risk products can still be authorised if the benefits outweigh the potential risks; however the authorisation must come from one of the senior management team in the department.

This process creates an appropriate barrier to pharmacists who might otherwise decide to authorise ad hoc or unusual formulations without considering the associated risks. The group of senior pharmacists and technicians then meet every few months to review the requests for non-catalogue preparations, and review whether other options should be pursued e.g. purchase of a licensed product from a foreign country, use of a batch-manufactured product rather than an extemporaneously-prepared product for an individual etc.

As a guide to help the risk assessment, the department provides a risk assessment matrix to highlight potential problems to the clinical pharmacist, see Fig. 2.2.

2.2.2 Considerations Upon Receiving a Request

When faced with a request for individualised pharmacy preparation, a pharmacist may find it helpful to consider the following questions in order to reduce or avoid risks:

- Has a risk assessment been carried out that has established pharmacy preparation as the most appropriate choice for this patient?
- Are there other more suitable alternatives, is a licensed product available, could a licensed product be adapted for each dose, are there other batch-manufactured products available, could you use an imported product that has a licence in a mutually-recognised country?
- What is the risk of not treating the patient?
- Does the active substance have a narrow therapeutic index?
- Can a peer-reviewed and evidence-based formula be used? If not, have the physico-chemical properties of the active substance been considered, and have steps been taken to minimise risk and complexity (e.g. reduce shelf-life, store in fridge, prepare a solution instead of a suspension, use commercially available suspending agents which have been tested with the active substance in question and pharmaceutical-grade raw materials)?

Document EXP01

Request Form for a Non-Catalogue Extemporaneous Product

Section A: Request Details

Patients Name:..... Consultant:
Ward: Weight:
Date of Birth: Hospital:
Pharmacist Name: Signature Date:
Requesting Doctor: Grade: Date:

Drug Requested:			Approximate Duration of treatment	Inpatient/ Outpatient
Name	Route	Dose		

Clinical Reason for use:

Section B: Points to consider (please circle)

Is an alternative formulation available? Yes/No
Is an alternative route available? Yes/No
Is an alternative licensed product available? Yes/No
Can the product be sourced from a licensed specials manufacturer? Yes/No
Is an alternative method possible? Yes/No
(e.g. tablet crushing & dispersing in water / oral administration of injection)
Is the medicine licensed for the indication? Yes/No
Could the prescription be changed to a catalogue presentation? Yes/No

Comments:.....
.....
.....
.....
.....
.....

Fig. 2.1 Request form for a non-catalogue extemporaneous product

Section C: Risk Assessment

Use the risk assessment matrix (EXP03) to assess risks for each category and overall risk. (Please attach evidence to form)

- Risks to Quality (Formulation & Stability) Low / Medium / High (Please circle)
Comments:
- Clinical Risks (Safety & Efficacy) Low / Medium / High (Please circle)
Comments:
- Health & Safety Risks (COSHH) Low / Medium / High (Please circle)
Comments:

Overall Risk Rating: Low / Medium / High (Please circle)

Section D: Approval

Decision to make product: Yes / No Signed: Date:

For Low and Medium Risk products obtain approval from CPTL. PRINT NAME
For High risk products obtain approval from LEVEL D PHARMACIST. PRINT NAME.....

Section E: Preparation

Notify dispensary and arrange for a blank worksheet and labels to be prepared. Authorize worksheet.
Note Worksheet authorization must occur before product is made.
Photocopy worksheet and retain copy in the dispensary. Attach form EXP01 to the original completed worksheet and leave in appropriate wallet in 'Green Extemp File' (found in LGIIP, LGIOP, CLA, SJIP, CDH, WGH, CKE, CAH dispensaries).
If this item needs to be added to catalogue refer to the 'Catalogue Request Pack' (found in dispensary Extemporaneous Dispensing File) Also refer to the Extemporaneous Dispensing Policy.
These documents will be reviewed periodically by the Extemporaneous Steering Group/Extemporaneous Review Group.

DOCUMENT EXP03 EXTEMP PRODUCT RISK ASSESSMENT MATRIX

Assessment of Overall Risk

- Assess risk for each category: Quality; Safety & Efficacy; COSHH.
- The highest individual rating gives the overall risk category.
- For high and medium overall rating contact:

- ❖ QC for quality issues
- ❖ Clinical Lead for clinical issues (categorisation of drug toxicity/ TI; patient monitoring measures)
- ❖ COSHH Team for COSHH issues

	SCORE			
Risks to Quality (Consider effect of preparative process on drug stability and uniformity of dose)	Validated formula and supporting stability data available. <ul style="list-style-type: none"> • Published papers • Pharmacopoeia • Developed by licensed manufacturer Rating: Low	Formula available, but not validated. No supporting stability data. <ul style="list-style-type: none"> • Evaluation of formula and shelf life from first principles by suitably experienced staff. • Experience of safe and effective use in NHS. Rating: Low	Formula available, but not validated. <ul style="list-style-type: none"> • No supporting stability data or evaluation. • No evidence of safe and effective use in NHS. • Reduced shelf life (max 7 days). Rating: Medium	Formula available, but not validated. <ul style="list-style-type: none"> • No supporting stability data or evaluation. • No evidence of safe and effective use in NHS. Rating: High
Risks to Safety/Efficacy (Consider effect of formulation on drug bio-availability)	Low Toxicity. Short term use Rating: Low	Wide Therapeutic Index (TI) Short term use Rating: Low	Wide Therapeutic Index Maintenance Therapy Rating: Medium	Narrow Therapeutic Index Maintenance Therapy Bio-availability could be significantly changed by crushing tablet Rating: High
H & S Risks (see extemp COSHH Guidance)	Full supporting COSHH data Control measures in place Rating: Low	Inadequate supporting COSHH data No control measures in place. No COSHH assessment carried out. Rating: High		

Overall Risk Assessment: HIGH MEDIUM LOW

Low Risk: Prepare worksheet & make in accordance with local SOP's. Use licensed or QC approved starting materials only.

Medium Risk: Make for short-term use only and monitor patient for clinical effect and ADRs. Consider outsourcing to a specials unit or alternative therapy for long term use.

High Risk: Consider all alternatives before making - only make as last resort. Monitor patient closely for clinical effect, toxic effects and ADRs.

Document EXP03 Second Edition April 2009

Fig. 2.2 Extemporaneous product risk assessment matrix

2.2.3.2 German Reason Check

In Germany, pharmacists must perform ‘reason checks’ (Plausibilitätsprüfung) to establish the likely safety, quality, and efficacy of the product they want to prepare. The Pharmacy Practice Order (Apothekenbetriebsordnung, ApBetrO) specifies parameters of the preparation formula that must be checked, whether it is a doctor’s prescription or self-medication on patient’s request. Beyond that, the guideline recommends that the pharmacist considers the overall rationale for treatment.

A form has been developed (Fig. 2.3) for the performance and documentation of the reason check. Some parts will be dealt with.

Regarding “Qualitative and quantitative composition”: Substances used as active substance or as an excipient in pharmaceutical preparations have to be described in an individual monograph of the European Pharmacopoeia or comply with the requirements of the relevant general monographs (see also Sect. 23.1). Cosmetics and medicinal products may only be used if the required quality is documented. In Germany it is not allowed to change or add any active substances without permission of the prescriber. This does not apply to excipients that have no pharmacological effect.

Regarding “Compatibility”: if components of a prescribed preparation are not compatible (or there is a lack of evidence), it does not mean automatically that it should not be prepared. The preparation needs to show sufficient compatibility up to the in use expiry date; it may be possible to produce a preparation with a shortened but useful shelf life. Interactions between the active substances and excipients can however make it impossible to produce a preparation of sufficient quality. These incompatibilities can be visible or invisible during preparation. The attending pharmacist has to verify if incompatibilities are apparent. More information about incompatibilities is to be found in references such as Fiedler (Sect. 39.2.2), Handbook of Pharmaceutical Excipients (Sect. 39.2.3), Martindale (Sect. 39.2.4), Handbook of Extemporaneous Preparation (Sect. 39.4.6), Kommentar zum Arzneibuch (Sect. 39.4.8) and Trissel’s Stability of Compounded Formulations (Sect. 39.4.14).

Regarding “Stability and shelf life”: These items are amply discussed in Chap. 22 Stability. Stability is influenced by the solubility of all substances in the preparation, pH of the base, pH at which the active substances are stable, and the influence of oxygen and light. Shelf life is restricted due to:

- Chemical, physical, physico-chemical reactions
- Rheological changes
- Formations of toxic degradation products
- Microbiological growth
- Decrease in concentration of the active substance
- Incompatibilities or issues caused by the container

2.2.3.3 Risk-Benefit Form [4]

A risk-benefit form has been elaborated for extemporaneous and for stock preparation (Figs. 2.4 and 2.5). They enable the pharmacist to list and balance the benefits and risks of the clinical and pharmaceutical qualities of the required pharmacy preparations. The form follows the process for handling of requests for preparation, and defines decisive steps, levels of evidence of decisions, individuals concerned and responsibilities.

Possible benefits include:

- Unique therapeutic value if there is no comparable authorised medicine available
- Improved patient friendliness and therefore a better compliance with therapy
- Improved safety of health care processes (using preparations that don’t need any reconstitution steps on the wards or in nursing homes)
- Improved occupational safety and health (OSH) of health care personnel (by diminishing exposure from hazardous active substances)

- (Lower price)

Possible risks include:

- Uncertainty about therapeutic safety and efficacy
- Design failure causing quality defects, like poor bioavailability or poor content uniformity
- Preparation risk: if the actual pharmaceutical quality system cannot guarantee that the preparation will fully meet specifications
- Discouraging the marketing of authorised medicines

The forms for extemporaneous and stock preparation use the same benefits and risks. With extemporaneous preparations the balance refers to an individual patient. With stock preparations the balance results in the definition of the group of (anonymous) patients for whom, or care situation in which, the benefits may outweigh the risks.

Clinical benefits and risks are assessed on the front of the form by the attending pharmacist, who decides if the request adds enough value to be considered further. On the back the preparatory pharmacist assesses the risks of design and preparation. He also checks the feasibility: if necessary conditions are met such as availability of starting materials or sufficient control of the health and safety risk of the pharmacy personnel. Over-all it is the preparatory pharmacist who decides:

- In case of an extemporaneous preparation if he accepts the request(or not)
- In the case of a stock preparation on the conditions on which he will make this preparation available.

Balancing benefits and risks (see Fig. 2.6) is not a matter of mathematics but of professionalism, responsibility and transparency. The forms therefore are transparent about the decisions and show who made them.

Checklist for Reason Check			Actions Notes
1. Sufficiency and readability of the prescription			
Is the prescription complete?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Is everything readable?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Are there any perceivable mistakes?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
2. Safety and treatment concept, dosage and dosage instructions			
Are there questionable ingredients?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Is the treatment concept obvious?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Is the dosage sensible?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Are the dosage instructions sensible?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
3. Qualitative and quantitative composition			
Is the concentration of the active substances higher than the indicative concentration?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Is the concentration of the active substances within the normal dosage range?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Are all ingredients available in the required pharmaceutical quality?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Does the prescription conform to a standard formulation?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
If so, please specify the source:			
Are there any similar standard formulations?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
If so, please specify the source:			
4. Compatibility			
Are the ingredients compatible?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
If no, please specify the incompatibilities:			
5. Stability and shelf life			
Is there a need for an added buffer?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Is the microbiological stability sufficient for the targeted shelf life?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Is the prescribed preparation stable enough for the targeted shelf life?	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Additional assessments			
Date, Signature Responsible Pharmacist/Delegate			

Fig. 2.3 Form for German reason check ([3] translated). Further explanation about items 3, 4 and 5 is given in Sect. 2.2.3.2

Request for extemporaneous preparation	
Final formulation or action	
<input type="checkbox"/> Availability as authorised medicine checked	
Patient (name, details):	
Name physician or GP, specialism, date, discussion:	
Indication:	
Standard therapy:	
Reason of request	
<input type="checkbox"/> Non-availability authorised medicine <input type="checkbox"/> Unique therapeutic value <input type="checkbox"/> Improvement patient-friendliness <input type="checkbox"/> Improved health and safety health care personnel <input type="checkbox"/> Different:	Comments / references / literature / attachments:
Level of consensus about evidence	
<input type="checkbox"/> National (authorisation, guidelines, consensus), that is: <input type="checkbox"/> Regional: <input type="checkbox"/> Local: <input type="checkbox"/> Individual physician, GP, pharmacist: Experience with this therapy:	
Conclusion Request will (not *) be considered subsequently.	Assessed by attending pharmacist: (name, initials)

*) delete where not applicable

Design	
Design of formulation and of preparation process	<input type="checkbox"/> Analogous to <input type="checkbox"/> From literature: <input type="checkbox"/> Own design, based on: Attachment(s):
Is the design well-considered enough if balanced with the added value for the patient?	Yes / No*) Comments: Discussion with attending pharmacist:

Feasibility	
Raw materials available?	yes/no*)
Sufficiently stable for clinical use?	yes/no*)
Is the health and safety risk of the pharmacy personnel controllable?	yes/no*)
Other preconditions	yes/no*)
Another aspect:	
Conclusion: preparation is (not *) feasible	

Decision about request	
<input type="checkbox"/> To prepare for this individual patient (p.t.o.) <input type="checkbox"/> No preparation: no well-considered design available <input type="checkbox"/> No preparation: the request adds value for the patient indeed, the design is well-considered but the preparation is not feasible <input type="checkbox"/> Other:	
Result discussed with:	Attending pharmacist (name, date):
Signature: Preparatory pharmacist (name, date, signature):	

*) delete where not applicable

Fig. 2.4 Form for balancing risks and benefits of an extemporaneous preparation; front and back side (see Sect. 2.2.3.3)

Stock preparation (formula, strength, administration route, dosage form)	
Indication:	
Patient population:	
Standard therapy:	
<input type="checkbox"/> Availability as authorised medicine checked	
Reasons for preparation	Level of consensus about evidence
<input type="checkbox"/> Non-availability authorised medicine <input type="checkbox"/> Unique therapeutic value <input type="checkbox"/> Improvement of patient-friendliness <input type="checkbox"/> Improved safety of health care processes <input type="checkbox"/> Improved health and safety of care personnel <input type="checkbox"/> Authorised medicine available but not reimbursed <input type="checkbox"/> Different:	<input type="checkbox"/> National (authorisation, guidelines, consensus), that is: <input type="checkbox"/> Regional: <input type="checkbox"/> Local: <input type="checkbox"/> Individual physician, GP, pharmacist: Experience with this therapy:
Comments / references / literature / attachments:	
Conclusion Risk/benefit assessment is in*/sufficiently founded to continue the assessment.	Assessed by pharmacist: (name, initials)

*) delete where not applicable

Design Design of formulation and of preparation process <input type="checkbox"/> Analogous to <input type="checkbox"/> From literature: <input type="checkbox"/> Own design, based on: Attachment(s):		Is the design well-considered enough if balanced with the added value for the patient? Yes / No *) Comments:
Feasibility Starting materials available? yes/no*) Sufficiently stable for clinical use? yes/no*) Is the health and safety risk of the pharmacy personnel controllable? yes/no*) Other preconditions yes/no*) Another aspect: Conclusion: preparation is (not *) feasible		Comments:
Decision about suitability for stock preparation <input type="checkbox"/> To prepare only for patients from the own pharmacy <input type="checkbox"/> To prepare for patients nationwide <input type="checkbox"/> No preparation: no well-considered design available <input type="checkbox"/> No preparation: the preparation is valuable and the design is well-considered but the preparation is not feasible <input type="checkbox"/> Other:		
Result discussed with:	Signature: Preparatory pharmacist (name, date, signature):	

*) delete where not applicable

Fig. 2.5 Form for balancing risks and benefits of a stock preparation; front and back side (see Sect. 2.2.3.3)

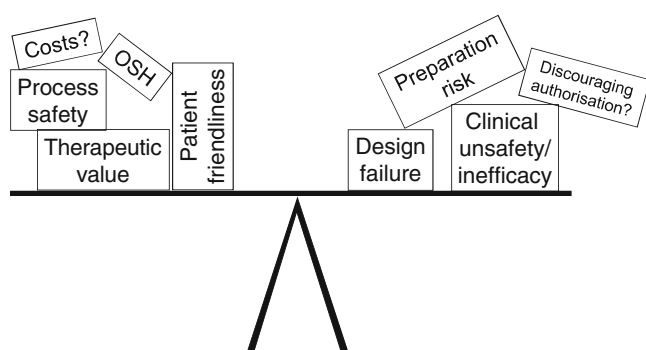


Fig. 2.6 Balancing benefits and risks of specific pharmacy preparations (see Sect. 2.2.3.3)

2.3 The Prescription

2.3.1 Legal Requirements

A prescription is a request from a prescriber (usually a doctor) to a pharmacist to dispense a medicine in the stated amount, strength and method of use. Each country has its own medicines law which will define the exact requirements of a prescription. However, there is a standard data set used with the European Economic Area (European Union plus Lichtenstein, Norway and Switzerland) as given in Table 2.1.

In some countries, the list of prescribers may include ‘non-medical prescribers’ such as nurses, pharmacists or chiropodists. These other prescribers may have limited formularies in some countries. However, the law varies

between different countries; the validating pharmacist must takes steps to assure themselves that the prescriber is appropriately registered to prescribe.

The pharmacist should consult the prescriber if it is possible or more appropriate to use a different medicine. A licensed medicinal product should be used in preference to a pharmacy preparation, if an appropriate product is available.

When a pharmacist considers that the delivery of a medicine carries an unacceptable level of risk, he can refuse to dispense the medicine to the patient, as pharmacists have a duty of care to the patient. In this situation, they must contact the prescriber to discuss possible alternatives.

2.3.2 Consultations with the Prescriber and the Patient

2.3.2.1 Consultation About a Prescription

When there are doubts about the pharmaceutical options, consultation between the pharmacist and the prescriber takes place. The pharmacist can advise on the options for treatment following consideration of the diagnosis and pathophysiology by the doctor.

A discussion between the pharmacist and the patient (or carer) may also be needed in order to make the most appropriate treatment decision. This is often the case in paediatrics, and the parent or carer may require some assurances about the need for medication, especially if the treatment is long term.

Table 2.1 Non-exhaustive list of elements to be included in medical prescriptions in the EEA [5]

Identification of the patient	Surname(s)
	First name(s) (written out in full, i.e. no initials)
	Date of birth
Authentication of the prescription	Issue date
Identification of the prescribing health professional	Surname(s)
	First name(s) (written out in full, i.e. no initials)
	Professional qualification
	Details for direct contact (email and telephone or fax, the latter both with international prefix)
	Work address (including the name of the relevant Member State)
	Signature (written or digital, depending on the medium chosen for issuing the prescription)
Identification of the prescribed product, where applicable	‘Common name’ as defined by Article 1 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
	The brand name if:
	(a) the prescribed product is a biological medicinal product, as defined in point 3.2.1.1.(b) of Annex I (Part I) to Directive 2001/83; or
	(b) the prescribing health professional deems it medically necessary; in that case the prescription shall shortly state the reasons justifying the use of the brand name
	Pharmaceutical formulation (tablet, solution, etc.)
	Quantity
	Strength, as defined in Article 1 of Directive 2001/83/EC
	Dosage regimen

Adherence to treatment regimens is influenced by a number of other factors, including the formulation (e.g. solid or liquid), administration route (e.g. rectal or oral), dosage size and frequency, and the organoleptic qualities of the medicine chosen (e.g. smell, appearance, flavour). By choosing a formulation that is easy to administer and by giving good information and instruction, the patient is more likely to comply with their treatment regimen.

Case – Vitamin ADEK Mixture

Pim is 14 years old and suffers from cystic fibrosis. Due to his illness, he cannot absorb fat-soluble vitamins well. The paediatrician recommends that Pim needs treatment with vitamin A, D, E and K in various oral preparations. The licensed pharmaceutical preparation consisting of 400 IU vitamin D is no longer available, meaning Pim potentially has to take even more tablets than previously.

The parents express concern to the paediatrician that Pim is unlikely to comply with his treatment. Therefore, the paediatrician requests a pharmacy preparation in which all vitamins are combined.

The pharmacist designs an oral liquid based on a standard formulation for an oral vitamin D solution. The mixture contains, per millilitre, 750 IU vitamin A, 250 IU vitamin D, 50 mg vitamin E and 0,25 mg vitamin K.

The pharmacist chooses an aqueous solution, because of the better availability of fat-soluble vitamins in patients with absorption disorders, such as cystic fibrosis patients. Due to a lack of data about the shelf life of the mixture and the absence of a stability-indicating analytical assay, a shelf life of 1 month in the refrigerator is assigned.

Pim now only has to use daily 4 mL of the oral solution that the pharmacy prepares for him every month.

Various national formularies exist and may be useful to consult during discussions with the relevant doctor e.g. the Dutch national child formulary (www.kinderformularium.nl) [6] contains various pharmacy preparations, which are included in the Dutch pharmacists Formulary (FNA, see Sect. 39.4.5).

Such national formularies are good starting points for formulations as they may have been tested or supported by published or validated formulae. A second example is the German Formulary (Neues Rezeptur-Formularium, see Sect. 39.4.2). In the UK, the Handbook of Extemporaneous Preparation (see Sect. 39.4.6) also lists a selection of 50 commonly used formulae, and the British Pharmacopoeia has a small number of formulations detailed. The existence

of validated formulae then allows for the potential for batch manufacture and suitable quality control testing.

Another advantage of using a national formulary is that it is kept up to date, with obsolete formulations removed or replaced regularly. This may be due to a change in recommendations (e.g. an excipient is no longer considered appropriate) or when a suitable licensed formulation becomes available.

Ferrous chloride oral drops had been removed from the Dutch formulary as there are now sufficient alternatives like Ferrous fumarate oral suspension 20 mg/ml as a licensed pharmaceutical preparation. That product however is so viscous that a small volume, which is necessary for young children, cannot be measured accurately. In the FNA therefore a Ferrous chloride oral solution 45 mg/ml has been reintroduced. This oral solution contains 20 mg iron (II) per ml which is suitable for children and it is not viscous. So the necessary small amounts can be easily measured.

2.3.3 Dose

The doctor writes the dose on the prescription and the pharmacist checks or 'validates' this dose. The validation process may take place with the help of a pharmacy computer system or electronic prescribing system. The usual support offered by pharmacy computer systems is limited if local formulae are used, and the pharmacist may need to consult a range of reference sources when considering the appropriate indications, doses, likely side effects and contra-indications. Extra care is required with some patient populations, such as children and the elderly.

2.3.3.1 Dosage Expression

The way in which the prescriber writes the dose is dependent on the administration form. Capsules and suppositories are given in an amount (usually milligrams) per dose unit followed by the number of units and the daily or weekly dose. For example:

R/ Folinic acid capsules 10 mg
x 10
1 capsule once a week

In the case of oral liquids, the doctor will write the strength in milligrams per millilitre followed by the amount and dose. In the case of electrolytes the strength is often written in millimol per millilitre because the dosages of electrolyte are based on blood concentrations. For example:

R/ Magnesium gluconate oral solution 0,1 mmol/mL
300 mL
1 mmol 3 times a day

For the preparation and the dose check, it may be necessary to convert the strength to milligrams per millilitre. In case of the oral solution in this prescription magnesium gluconate dehydrate is used. Therefore, the equivalent strength is 45 mg/mL. The above prescription can then be read as:

R/ Magnesium gluconate oral solution 45 mg/mL (Magnesium 2,43 mg/mL)
300 mL
10 mL 3 times a day

In the case of medicines for cutaneous use (e.g. dermatology medicines), the concentration of the active substance is usually written as a percentage. The prescriber writes the amount and the frequency with which the dermatologic medicine has to be applied. The doctor usually writes the part of the body on which the patient should apply the preparation. In this way the pharmacist can check whether the prescribed amount is sufficient. Furthermore it is also important to know whether the cutaneous medicine has to be applied thickly (liberally) or thinly. A practical device for dosing a cutaneous preparation is the fingertip unit (FTU), see Table 12.3. In Germany, the Neues Rezeptur-Formularium for doctors [7] contains a useful outline figure for the prescriber to mark the area of application (Fig. 2.7).

The pharmacist must look carefully at the chemical form in which the active substance (see Sect. 23.1) of the preparation is prescribed (or meant to be prescribed), because the active substance may be available in various forms such as a base, ester or salt. Also the amount of water of crystallisation in the raw material may vary. E.g. folinic acid is dosed as the calcium salt. The doctor may use a brand name in the prescription, in this case Leucovorine®. This contains 15 mg folinic acid in the form of calcium folinate.

2.3.3.2 Paediatric Population

Children regularly get prescribed medicines that are licensed only for adults or are licensed for use in other indications in children. This is called 'off-label' use and in this case the medicine is used in an 'unlicensed' manner.

Unlicensed medicines used in children are usually prepared by utilising raw materials or through adapting a dosage form designed for an adult population. Often there is limited data available about the dose and side effects in children. This means that consultation between the prescriber and pharmacist may be necessary.

In 2007 the Nederlands Kenniscentrum Farmacotherapie bij Kinderen (NKFK) was founded. It was established to help improve information available about medicines use in children. One of the activities of the NKFK is the compilation and publication of the national children formulary in the Netherlands [6]. In the UK, the Medicines for Children

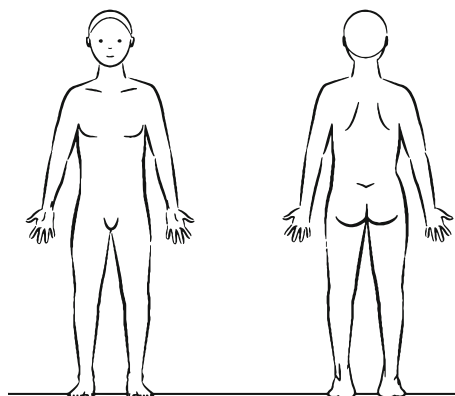
Gebrauchsanweisung für Rezepturarzneimittel



Patient:

Datum:

Rp.-Bezeichnung:



Wo genau wie anwenden?

Wann/wie oft anwenden?

Wie lange behandeln?

Sonstige Anmerkungen:

Fig. 2.7 Form for the instructions for use of dermatological medicines, © GOVI-Verlag Pharmazeutischer Verlag

Research Network [8] has been established to investigate formulation quality and the practice of manipulation of dosage forms before administration e.g. cutting tablets, opening capsules etcetera. It is preferable to use an active substance that has been used previously in a pediatric population, as information about the dose, pharmacological effect and side effects will already be available. Doses for babies and children are commonly expressed in mg per kg body weight. For medicines with a large therapeutic window, this approach is satisfactory. However, it must be recognised that during the growth and development of a child, the pharmacokinetic parameters change continuously. Children are not small adults and neonates are not small children. When considering active substances with a narrow therapeutic window, a dose in m² body surface may therefore be a more accurate basis for dose calculation and adjustment. This is because some physiological parameters, which are directly related to the elimination of medicines, are better correlated to body surface e.g. hepatic and renal function.

Various formulae for calculating body surface area can be found in literature [9]. For example, the Dutch kinderformularium [6] uses the Mosteller formula as below:

$$\text{Body surface (in m}^2\text{)} = \frac{[\text{length (in cm)} \times \text{weight (in kg)}]^{0.5}}{3,600} \quad (2.1)$$

Tables with length, weight and body surface of children of different ages with normal proportions [6] are convenient when one does not have the length and weight of the child. The British National Formulary (BNF) for Children in the UK also has tables for guidance, using the Boyd equation [10]. Finally the result has to be rounded to a practical strength for the product to be prepared.

Case Hydrocortisone Suppositories 240 mg

X 6

1 suppository when required

The pharmacist consults reference sources which suggest a rectal dose of 100 mg/m² body surface for stress situations in children with adrenal cortex disorder.

Klaartje is 2 months old and a girl of that age has an estimated body surface of 0.27 m². This means that the prescribed dose is too high. Discussions with the prescribing endocrinologist confirm that a prescribing error has been made. Hydrocortisone suppositories of 24 mg should have been prescribed.

In some cases, it may be necessary to estimate or derive a paediatric dose from a proportion of the adult dose, using a comparison of relevant body surface areas. However, this is a very approximate calculation, and further discussion with the prescriber will be needed to agree a final dose.

Usually the frequency of administration is similar to that of adults. However, this does sometimes require amendment. E.g. fluconazole dosing frequency varies with age, due to the changes in elimination.

2.3.3.3 Cutaneous (Dermal) Medicines Used in Children

Children and particularly babies have a large relative body surface area. Premature babies also have a thinner skin than adults, and lack the outer skin layer known as the horny layer or stratum corneum. In a young child with eczema, the skin may also be more damaged than in an adult with eczema. Therefore, the skin functions less well as barrier. Furthermore, application of any creams or ointments under a nappy or diaper prevents trans-epidermal water loss and leads to an increased absorption of the active substance.

Due to the larger risk of adverse effects and toxicity, certain medicines are not administered on the skin of young children. e.g. Salicylic acid is preferably not used on children younger than 2 years old and certainly not on large surfaces. Less potent corticosteroids are preferred as they are associated with a smaller risk of systemic adverse effects. Other options include a decreased dosing frequency to limit adverse effects e.g. application every other day rather than every day.

2.3.3.4 Elderly Population

Body composition, homeostasis, body tissues and organs change as people age. Therefore, this has consequences for the pharmacokinetic and pharmacodynamic processes associated with the active substance. E.g. due to a larger percentage fat tissue, the volume of distribution of lipophilic substances such as diazepam increases in elderly patients. The decrease of blood flow through the liver also has an effect with substances that have a high level of hepatic elimination e.g. morphine. Furthermore, two thirds of the elderly population has some degree of renal impairment. This has consequences for the dose of medicines with mainly renal elimination and a small therapeutic window e.g. digoxin, lithium. Skin also tends to be thin somewhat with advancing age.

The pharmacokinetic and pharmacodynamic changes usually become clinically more relevant over the 75th year of life. There are however large intra- and interindividual differences in aging of organ functions. Therefore, it is difficult to predict the exact pharmacological response of a given elderly patient. As with licensed medicines, it may be necessary to adjust doses of pharmacy prepared medicines carefully and cautiously in elderly patients.

Elderly patients are more sensitive to certain medicines and often use more medicines at the same time (sometimes called polypharmacy). This means that elderly patients are more vulnerable to adverse effects [11]. To avoid overdose and subsequent adverse effects, a lower starting dose may be used.

However, lower strengths are not available for every medicine and not every licensed pharmaceutical preparation is available as a tablet that can be divided e.g. coated tablets. In this situation, it might be necessary to produce a lower strength oral liquid that could be used for careful dose titration (see Sect. 5.4).

2.3.4 Contra Indications, Interactions and Intolerances

In addition to the validation of the dose, each preparation has to be reviewed in terms of possible contraindications, interactions and intolerances or allergies.

2.3.5 Narcotic and Psychotropic Substances

Based on United Nations conventions [12] most European countries have extra requirements or controls which are applied to medicines with narcotic and psychotropic substances. Requirements vary between countries but may include:

- Name, initials, full address and phone number of the prescriber
- Date of prescribing
- Name of the medicine and amount, written completely in letters
- Name, initials and full address of the patient or of the owner of the animal
- Clear description of the use, among what the maximal total drug use per 24 h, “use known” or “if necessary” is not correct
- If necessary: the amount of repeat doses

A prescription on which one or more raw materials fall under these regulations has to comply with these requirements.

In Germany the use of narcotic or psychotropic substances is not appropriate if the intended purpose can be achieved in other ways, e. g. with medicines with other active substances.

Some active substances falling under these regulations are exempted from the requirements associated with administration and prescribing, such as for preparations with codeine. However, for the raw material codeine, the administrative obligations mentioned in the law do apply in Germany.

2.3.6 Standard Amounts

The amount of a pharmacy preparation requested can vary widely, depending on the indication and area for use. The pharmacist should assess whether the amount is right for the use (see Fig. 2.7), the length of the treatment and the shelf life. In some countries, there are systems for standardising amounts used in order to improve consistency of products and maximise efficiency in the pharmacy setting. In addition in some countries the amounts are limited by the health insurance.

2.4 Special Categories of Prescriptions

Not every request for a pharmacy preparation is by definition a medicine. Examples include biocides, medical devices, starting materials and chemicals. It is important to make this distinction, because with that it becomes clear under which regulation the pharmacy preparation falls. The legal

requirements varies with the category. The relevant national regulations should be consulted before any such items are prepared.

Depending upon the item in question, the pharmacist may be obliged to ensure that the product is suitable for use in humans, for instance does not contain any material of animal origin that may transmit any known diseases e.g. Transmissible Spongiform Encephalopathies (Creutzfeldt-Jacobs Disease), see Sect. 19.3.1.

2.4.1 Herbal Medicines

The regulation of herbal medicinal products is complicated and differs between countries¹. Roughly speaking, herbal products can be considered as medicinal products with medicinal claims, but also as food or dietary supplements without medicinal claims. The status will generally depend on the level of scientific evidence supporting their use. A detailed overview of the regulations concerning herbal medicinal products worldwide can be found in Herbal Medicines [13].

Herbal medicinal products are not explicitly mentioned in the Ph. Eur. but herbal raw materials are included. The reason is that any pharmacist should be able to judge the safety of herbal medicines but not the efficacy of the products. According to EC legislation [14], “a herbal medicinal product is any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.” Herbal medicinal products are also referred to in the international literature as herbal medicines, herbal remedies, herbal products, phytomedicines, phytotherapeutic agents or phytopharmaceuticals. The use of herbal medicinal products for the treatment and prevention of disease is called phytotherapy [13].

Few herbal medicinal products are on the market as authorised medicines in the EU, fulfilling the same stringent requirements that count for conventional medicinal products. This is largely due to the limited availability of randomised controlled trials to support the quality, safety and efficacy of herbal medicinal products. More often they are licensed as traditional herbal medicinal products, following an adapted and simplified registration wherein efficacy is made plausible based on available scientific data (well-established use) or long-term historic use in the EU (traditional use). Sufficient data to underpin the safety should be available in all cases and the quality of the herbal

¹ Contribution by Herman Woerdenbag, Groningen, The Netherlands.

medicinal product must always be demonstrated. A vast majority of herbal products however, are unlicensed (not medicinal products) despite the fact that they are frequently intended for health improving purposes [13, 15].

2.4.2 Agents Used for Assisted Suicide

In countries with legislation that allows for assisted suicide, pharmacists will be involved in preparing and dispensing the products. These pharmacists are then faced with ethical, moral, and practical questions. Is a pharmacist obliged to dispense these agents or is he allowed or even obliged to refuse in specific situations, and if so, based on which moral and ethical principles? How is professional information about pharmacologically effective agents and preparations distributed among pharmacists? These and similar questions have to be discussed in a social and legal context with the purpose of improving the difficult situation of patients and caregivers.

In the Netherlands a “Guidance for the management of euthanasia and assisted suicide” was developed by doctors and pharmacists and it covers the path from the patient’s request onto the arrival of the autopsist. The use of this Guidance is closely monitored [16]. This Guidance demands that any decision on dispensing the agents can only be made after oral consultation between the doctor and the pharmacist. The pharmacist must be ethically and morally independent in his decisions, like the doctor, which may eventually lead to the pharmacist refusing to dispense. The pharmacist has to be informed about all relevant backgrounds, in order to be able to make his decision and to be able to give the doctor or the patient relevant pharmacologic and practical information. The relevant products are prepared by the pharmacist and he will dispense them personally to the doctor, accompanied by oral or written information about their practical and technical administration. The standard advises pharmacist and doctor making general arrangements before an actual patient’s request will occur.

2.4.3 Homoeopathic and Anthroposophic Medicines

The law regarding the supply of homoeopathic and anthroposophic medicines varies between countries. In some countries, a pharmacist can refuse to dispense such an item and refer the patient to an alternative pharmacy.

In Europe the German Homeopathic Pharmacopoeia is available for the regulation of the quality of these medicines. If prescribed it usually is a licensed medicine but occasionally – mainly in cases of non-availability – a pharmacy

preparation may be requested. A general pharmacist will not be able to assess the efficacy of a homeopathic or anthroposophic prescription but he will be able to judge the safety, for instance following these recommendations:

- The pharmacist should only fulfill a request for a pharmacy preparation when the prescription comes from a homeopathic or anthroposophic doctor and relates to a single medicine of a non-animal or non-microbiological source and with dilution $\geq 1:10,000$, for oral or external use.
- When the medicine does not belong to these groups then the preparation is outside the competence of the regularly educated pharmacist. If that is the case it is recommended to get in touch with a pharmacy that specialises in preparing homoeopathic or anthroposophic medicines.

At all times, pharmacists should only practice within their sphere of competence.

2.4.4 Veterinary Medicines

In relation to the administration of medicines for animals, the pharmacological differences and local laws have to be observed. The pharmacokinetics of every active substance is different in each species. For animals, especially cats, the toxic concentration of many human medicines is lower than the therapeutic dose in humans due to differences in metabolism of medicines. For example, in cats, the administration of acetaminophen (paracetamol) very quickly leads to intoxication with methemoglobin formation, anemia, hemoglobinuria and liver damage, as they may metabolise the medicine poorly.

The European Commission (EC) has acknowledged that insufficient authorised veterinary medicinal products are available for the treatment of every clinical case in every species. Therefore, Directive 2001/82/EC allows, under Articles 10 and 11, veterinary surgeons to prescribe products that are not authorised for the relevant clinical case or for the relevant species, this provision is known as the Cascade. This is a derogation from the main requirement in the EU legislation to use authorised veterinary medicines. Therefore the Cascade increases the range of medicines that a veterinary surgeon can use [17]. The Cascade allows the veterinary surgeon to use medicines designed for other species, only if there is no licensed medicine for the species and the indication and the animal is critically ill. The use of medicines as part of the Cascade system has to be carried out in the order specified:

- Licensed Animal medicine, which has a different indication
- Licensed Animal medicine, which is licensed for a different species
- Licensed human medicine or EU licensed animal medicine
- Extemporaneous preparation

There are further regulations for animals bred for human food.

2.4.5 Medical Devices

As for the regulations which apply to medicines, the regulations for medical devices include consideration of the following issues: diagnosis, prevention, surveillance, treatment or relief of illnesses. However, the set-up of the regulations for medical devices differs essentially from the one for medicines. In the case of medicines licensing, the government is responsible for managing medicines regulation. However, in the case of medical devices, the company itself is responsible for risk assessing the product before it enters the market [18, 19]. Medical devices are classified in four different risk classes [18, 19].

The manufacturer has to decide in which risk class the device falls: I, IIa, IIb or III; the higher the class, the more risks are associated with the use. Therefore devices in class IIb or III have to be assessed in advance by a competent authority a so-called Notified Body. This is an independent organisation, designated by the national government. When the device belongs to class I or IIa, the producer only has to inform that authority of the device.

How does one handle the request of a hospital ward for the preparation of sodium citrate solution 30 % in ampoules? Concentrated sodium citrate solutions are used as catheter locks on dialysis wards of hospitals. By filling the lumen of the catheter with such a solution the formation of blood clots is prevented and the flow is maintained. Sodium citrate solution is an alternative for a concentrated heparin solution and should be preferred because of the anti-microbiological effect [20]. Citra-Lock® is available as a medical device. This product contains 46,7 % sodium citrate and is CE registered class IIb. Are there justifiable reasons to prepare the solution? This could be for example when the marketed product is associated with more side effects due to the higher concentration, or is delivered in a container that is hard to use in practice. If those reasons are absent, then the marketed product is to be preferred.

Information about medical devices is not as accessible as about licensed medicines. If a pharmacist has to decide about a medical device being used in a way that is not included in the instructions for use, he has to contact the manufacturer.

The European Commission has made proposals for new guidelines in September 2012. This means that all medical devices will have to undergo thorough, independent assessment of safety and performance before they can be sold on the European market. Also new rules on traceability are proposed and public information on products available on the EU market [21].

2.4.6 Biocides

Biocides (also called disinfectants) are active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means. A pharmacy may get a request for the preparation of a disinfectant. This may be difficult to handle because different laws are appropriate.

Disinfectants for the skin of patients, such as chlorhexidine in alcohol, are regarded as medicines for humans. When the same preparation is used in the hospital for disinfection of the hands of nurses and other staff, it is considered as a biocide and falls under the applicable EC legislation [22]. Disinfectants that are used in combination with specific medical devices fall under the regulation for medical devices and should have a CE identification mark. Disinfectants for inanimate surfaces fall under the legislation for biocides. When delivering such a disinfectant the pharmacist has to comply with this regulation, that is with the following requirements.

1. Generally only registered products should be used. This is indicated by a number or registration code on the packaging.
2. Registered biocides products must be delivered in the original package with the approved legal instructions and with the relevant danger symbols and safety recommendations.
3. A pharmacy preparation is allowed 'if necessary' but uses an allowed disinfectant and excipients.
4. Operations such as diluting, addition of a buffering agent or dispensing should be executed in accordance with the instructions and with due regard for the required precautions for preparation and labelling.

Practice Example: Sodium Hypochlorite

When the pharmacist obtains a request for the preparation of a sodium hypochlorite solution 2 %, the indication for use must be clear. A dentist may use such a solution for root treatment as a disinfectant and because of the tissue-dissolving effect. The prescription is from a dentist and therefore it is a medicine, so falling under Medicine law. When using a sodium hypochlorite solution for the disinfection of the floor, the biocides legislation applies. The pharmacist firstly has to examine whether there is a registered product which could be used instead. If this is not the case, then he is allowed to prepare the solution on the condition that there is a recognised use. That is to say that the use is described in guidelines or other reliable sources. In case of doubt, consultation with the authorities is recommended.

2.4.7 Raw Materials (Chemicals)

2.4.7.1 General

Chemicals only become recognised as medicines if they have been incorporated into a dosage form or when a medical indication is claimed. Chemicals can, if handled inexpertly, become dangerous to the health and in that case have to be labelled as hazardous substances (see Sect. 26.3). It is the responsibility of the pharmacist to assess whether he will supply raw materials. When delivering to members of the public (without a doctor's request) he should know the potential dangers, assess the intentions of the person who requests the item, and inform that person about the possible dangerous qualities. It is recommended to document such supplies via a request form. Data recorded on this form should comprise the identity of the person who makes the request, data about the delivered starting material (name and amount) and the indicated use. For the delivery of some raw materials separate legal regulations apply if the risk of abuse is considered to be substantial, such as with precursors. See further down.

Two Examples of Requests

Strong hydrochloric acid

A request for a bottle of strong hydrochloric acid for hobby purposes will raise doubt about the intended use. When the use seems to be acceptable, this raw material may be delivered but robust documentation of the request is strongly recommended, also to prevent problems in the context of the precursor legislation (see further down). Furthermore, the legally obliged safety information has to be present on the package (see Sects. 26.3.2 and 26.6.3). By supplying Concentrated Hydrochloric Acid Ph. Eur. the quality is guaranteed.

Sodium sulfate

Sodium sulfate may be delivered on request of a citizen. Delivery is analogous to the hydrochloric acid example. The situation is different when sodium sulfate is required on a doctor's prescription. Supplying a measured quantity of sodium sulfate in a bottle on prescription renders this raw material into a medicine and it has to be labelled as such.

2.4.7.2 Hazardous Substances

Hazardous raw materials are chemicals that provide a hazard to safety or health because of the chemical characteristics. Substances are defined as hazardous if at least one H(azard) statement (see Sect. 26.3.2) is attributed. They must only be delivered in a container that is labelled with the legal safety

information such as Hazard and Precautionary statements. A Material Safety Data Sheet (MSDS) must accompany delivery.

2.4.7.3 Precursors

Precursors are raw materials that may be used at the synthesis of narcotics and psychotropic substances ('drugs'). For this group of raw materials, the EC regulations [23], lay down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances. These regulations recognise 3 categories of substances of which only category 1 has a practical significance for pharmacy preparation. That category contains ephedrine, ergotamine and ergometrine. Pharmacies require special licences for ordering and possessing these substances. This special licence is only valid for the use of precursors "within the scope of the official duties of the operators". A licence is not required to supply pharmacy preparations that contain such substances.

2.5 Essentials

Pharmacy preparation allows the doctor and pharmacist to provide individualised and tailor-made pharmaceutical care. The preparation of a medicine in the pharmacy fills a need when the licensed pharmaceutical preparation is not available or when a licensed pharmaceutical preparation does not satisfy a specific situation.

Upon receipt of a request from the doctor, the pharmacist must examine the situation and decide whether the request is appropriate and judge the level of risk associated with proceeding with the request. However, the pharmacist must also consider the risks of not supplying a medicine which may lead to the patient not receiving treatment. Further discussion with the medical team may be needed.

The pharmacist must make every effort to ensure that the medicine produced is of appropriate pharmaceutical quality and is fit for the intended purpose. An approved or authorised formula should be used wherever possible. Where such formulae are not available, steps should be taken to minimise risk where possible e.g. restricted shelf-life, fridge storage (if applicable), use of licensed starting materials etc.

The usual support offered by pharmacy computer systems is limited if local formulae are used, and the pharmacist may need to consult a range of reference sources when considering the appropriate indications, doses, likely side effects and contra-indications.

Whether the request is for a medicine or other type of preparation, the pharmacist is responsible for ensuring that the final product supplied is of acceptable quality and backed by the best possible evidence base.

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Practical Pharmaceutics

An International Guideline for the Preparation, Care
and Use of Medicinal Products

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