Reasoning preparation

Yvonne Bouwman
Pharmacist,
Laboratory of Dutch Pharmacists,
Dutch Pharmaceutical Society KNMP, Den Haag

Disclosure

If any information about healthcare products or services will appear in my presentation, I declare that I have not had any financial relationship with the manufacturers of the products or provider of the services.

Preparation in this presentation =

Preparation from raw materials
Extemporaneous preparation
Manipulating dosage forms
Diluting and combining parenterals
Reconstitution in the pharmacy
Preparation at the bed-side

Look before you leap

Erst wägen, dann wagen!
Pensa antes de agir
Tænk dig godt om, før du handler
Bezint eer gij begint
Piensa antes de actuar
Najpierw pomyśl, potem zrób
Réfléchissez avant d'agir

a plea for joint decisions and transparency

This might be difficult if you:

- are eager to use your well-organized preparation facility
- are willing to help patients
- are expected to act immediately
- are subordinated to medical prescribers
- work in a rather closed/secluded community

Subjects:

- Position of preparation in society
- Unavailability
- Demonstration of quality
- Decision transparency

Position of preparation

Society (regulators): “you are making an unlicensed medicine.”
Responsibility and liability weigh heavier on you as a person than with licensed medicines.

Society (medical practice, patients and probably law): “the pharmacist (is a caregiver and) should make available the medicine which his patient needs”

In which countries is this second position laid down in law?

$Q_{patient}$. Why are medicines licensed?

A. The makers of medicines must ask the government for a license if they want to sell their medicines. They show the government that:

- their medicine works for the illness to be treated, does not have too many side effects or risks and:
- it has been made to a high standard

(from patient information on unlicensed medicines Royal United Hospital Bath, sept 2010)

Pharmacy preparations are unlicensed preparations.

'Unlicensed' can bring about doubts.

You should be able to account for preparation, offer transparency. Transparency about pharmacotherapy as well as about pharmaceutical quality.

In which countries is this a reality? Towards whom do you have to account: the patient or the inspector?

Position of preparation

$Q_{patient}$. How do I know that these (unlicensed) medicines are safe and will work?

A. This medicine will have been recommended by another doctor who is an expert, or by your own doctor who will have read information that says it is the best one for you. Your pharmacist is trained to make medicines and if you need a special medicine will make sure that it is made and will work properly"

(from patient information on unlicensed medicines Royal United Hospital Bath, sept 2010)

$Q_{patient}$. Why don't all medicines have a licence?

A "…… These may be medicines used for rare illnesses in which case it may be too expensive to have a clinical trial"

(from patient information on unlicensed medicines Royal United Hospital Bath, sept 2010)

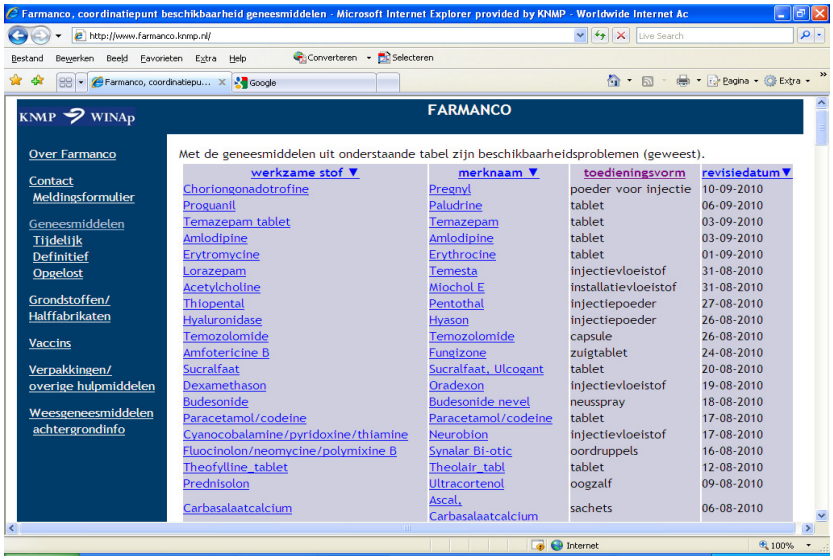
Why are not all medicines available as a licensed medicine?

- Orphan drugs
- Drug shortages
- Neglected patients (old, young, bad swallowers)

Import is still rather cumbersome in many countries

Drug shortages:
NL: 2004 – 2008:

- 340 drug products not on market anymore
  - 70% economical reasons
  - 6% production problems
  - 5% quality defects
- 41 were indispensable and had to be imported (24) or prepared in the pharmacy (17)



U.S. Department of Health & Human Services

U.S. Food and Drug Administration

[fda@service.govdelivery.com]:

http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm

You are subscribed to Drug Shortages for U.S. Food & Drug Administration (FDA). This information has recently been updated.

September 9, 2010

Drug Shortages: Current Drug Shortages: Calcium Chloride Injection (updated)

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Availability

Neglected patients:

A.T.Florence editorial Int J Pharmaceutics 2008:1-2. Neglected diseases, neglected technologies, neglected patients?

WHO-report Priority Medicines for Europe and the World 2004:
(...) there is a wide range of existing evidence-based, very often off-patent, technologies that are heavily underutilized. Such technologies could be used to improve the 'patient friendly' performance of a number of existing medicines, the use of medicines in paediatrics and geriatrics, and other areas where individualized timedosing of medicines is required, e.g., patients with impaired liver or kidney functions, or patients with compromised immune systems.'

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Availability

Why are not all medicines licensed? (proposal for an improved text)

Because:

Development and production of medicines has to be profitable.

To get a license there has to be done a clinical trial to show effect, effectiveness and harmlessness and there has to be an extensive quality system for the production.

A manufacturer cannot ask every price he needs.

So: for some medicines costs are less than benefits and they will not appear on the market. Therefore a patient (and thus society) has to accept the level of development of preparation by the pharmacy.

Any comments?

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We told the patient that although it is an unlicensed medicine:

- Our preparation is the best for him (better than a licensed medicine)
- We made it properly and it will work properly

How do we know and demonstrate it? Since we do not validate the product in the same way that is required for a licensed product and cannot share responsability with the authorities in the same extent as with licensed medicines.

Our preparation is the best for him =

- Pharmacotherapeutical advantages
- Better fit for use

We made it properly =

- Quality of design
- Quality of production

Demonstrating quality

Pharmacotherapeutical advantages (added value):

- There is simply no other drug, or
- the preparation is better than a licensed medicine

How much evidence is there for 'better'?

A licensed medicine is evidence based for a population. But there could be evidence for unlicensed medicines, for populations and even for individuals if you have "integrated individual clinical expertise with the best external evidence." (D.L. Sackett's definition of evidence based).

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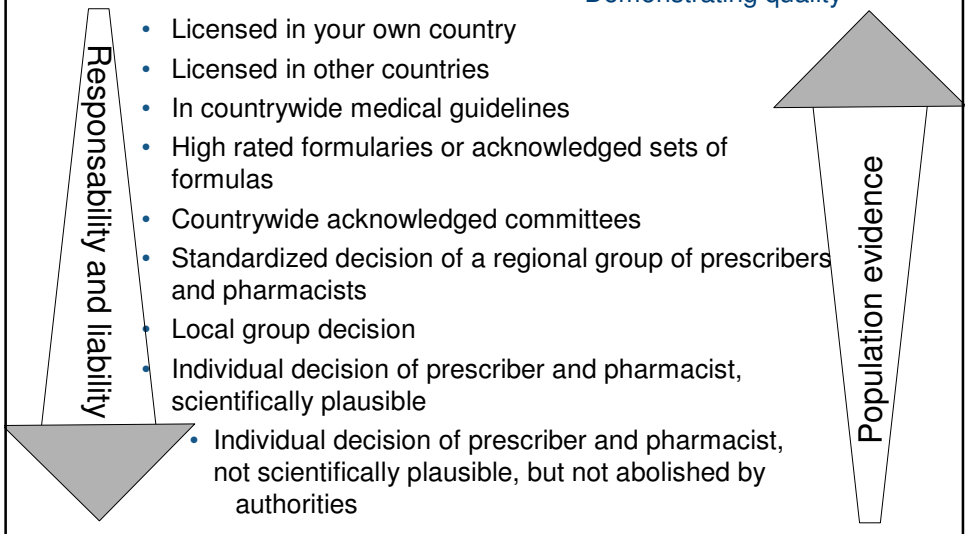
Demonstrating quality



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Better fit for use:

The pharmacy prepares or manipulates to a different concentration, dose or dosage form. Reasons could be:

- Impossibility of getting the right dose with the licensed medicine.

Demonstrating quality

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The pharmacy prepares or manipulates to a different concentration, dose or dosage form. Reasons could be:

- Impossibility of getting the right dose with the licensed medicine.
- Patient unfriendliness of the licensed medicine (improving therapeutic adherence)

Better fit for use:

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- Impossibility of getting the right dose with the licensed medicine.
- Patient unfriendliness of the licensed medicine (improving therapeutic adherence)
- Improving quality and safety of the process (notably of parenteral mixing or reconstitution on the ward)

The UK National Patient Safety Agency (NPSA) have stated 'that it may be safer to use an unlicensed patient ready product rather than a licensed preparation that is complicated to make.'

Do the registration holder has to be informed about manipulation of his medicines?

Our preparation is the best for him =

- Pharmacotherapeutical advantages
- Better fit for use

We made it properly =

- Quality of design
- Quality of production

Pharmaceutical aspects

Quality of design:
Raw materials availability and quality.
Reasonable specifications have to be met.
Stability long enough for use by the patient

Quality of Preparation:
Validation
Quality management of the preparation process

Subjects:

- Position of preparation in society
- Unavailability
- Demonstration of quality
- Decision transparency

Decisions
(about preparation as such)
(about preparing certain dosage forms)

about specific preparations:

- how extensively will you found the quality of the design and preparation process of it?
- will you prepare it anyhow?

Risk of a possibly defective design or preparation process

How larger the risk for the patient(s) the better should prescriber and pharmacist search for a good design and quality of production.

or (limited budget):

Priorities are determined by ranging the risks.

A try to range the risks could be a kind of *failure mode and effect analysis* (FMEA), with the items:

- Frequency of occurence
- Detectability
- Severity
- Number of patients

Decision transparency

Frequency of occurence depends on:

- quality of the design (higher frequency to be expected with: an low-concentrated oral suspension due to inhomogeneity, or with a microbiologically vulnerable preparation with a high bioburden, with longer expiry dates)
- the quality of the preparation process (prevention of mistaking, clarity and unambiguity of the protocol, complexity of the preparation, functioning of apparatus, sufficient knowledgde and experience of the staff, adequate rooms and facilities).

Detectability depends on:

- monitoring with in-process controls, validation, assays (destructive assays are not always possible, but quality can be secured with non-destructive controls, experience and alertness of staff)

Severity depends on:

- Pharmacotherapeutic safety window, route of administration (parenteral is more risky than cutaneous)

Number of patients:

- Batch size
- Organization of recalls, which depends on area over which the batch has been spread, patients being known by name.

Just to prioritize the work on improving

Risk = (a × c × d)/b

a = frequency of occurence (1 = low, 2 = medium, 3 = large)
b = detectability (1 = low, 2 = medium, 3 = large).
c = severity (1 = low, 2 = medium, 3 = large)
d = number of patients (1 = few, 2 = some, 3= many)

Do you perform any sort of 'risk analysis' in order to prioritize your work on improving quality?

Decision transparency

Decisions
(about preparation as such)
(about preparing certain dosage forms)

about specific preparations:

- how extensively will you found the quality of the design and preparation process of it?
- will you prepare it anyhow?

The added value for the patient has to be balanced to the risks of:

- a possibly defective design or preparation process

but also to:

- health and safety of the pharmacy staff
- environmental impact of the chemicals
- the costs

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How to balance? Which options does a hospital have next to preparation:

- sending the patient to another hospital?
- ……..
- …….
- …….
- ……

if there are no other options, then…..

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Forms for checking and transparency

Beoordeling aanvraag apotheekbereiding (A)		Assessing the prescription for the preparation	
datum	patiënt en geb.datum Date of birth	Etiket of receptnummer	
Gevraagde bereiding Preparation wanted			
Indicatie/ beoogd effect: Indication/aimed effect			
Resultaat overleg Consultation result	*met arts* prescriber	*met patiënt*	*paraaf apotheker* signature pharmacist

Forms for checking and transparency

Toelichting (B) Details	
Standaardtherapie toepasbaar?	Is standard therapy applicable?
Geregistreerd middel beschikbaar en geschikt?	Licensed medicine available and fit for use?
Bereiding uitvoerbaar?	Preparation performable?
farmaceutisch as to pharmaceutical aspects	
Arbo health and safety	
Milieu environment	

Forms for checking and transparency

Reasoning preparation, Y.Bouwman, BEAM 24 September

Assessment of a prescription

Name/formula	*Flucloxacillin*
Dose	*Maximum 12 g/24 hr*
Route of administration	*intravenous*
Dosage form	*Infusion 250 ml with cassette*
Name prescriber	*Orthopedist Jansen*
Specialisme aanvrager:	*Orthopedist*
Datum aanvraag:	*Januari 2010*
Patient's name:	*Mr. B.*
Personal data	*13-01-1948*
Therapeutical indication:	*Osteomyelitis; intravenous home treatment with antibiotics*

Considerations about preparation yes or no:

Pharmacotherapy:	
Is there no better pharmacotherapy (separate form)	*no*/yes:... .....
Pharmaceutical substitution:	
Licensed medicine available?	*no*/yes: .....
Standard preparation formula available?	*no*/yes: ....
Pharmaceutical aspects:	
Raw materials available with sufficient quality?	no/*yes*
Is analysis feasable?	*no*/yes
Design of formulation:	
O according to literature	(add or give the reference)
O analogous to a published or existing formula	(add or give the reference)
O own design	(motivation)
Is the quality of the design of the formulation sufficient?	no/doubtful/*yes*
See annex (for instance an article about the stability of flucloxacillin)	
Health and safety:	
Is the health risk under control?	no/*yes*
Environmental:	
Is the added value for the patient larger than the	*no*/yes

Conclusion:	Start preparation/ no preparation	
Signature:	Prescriber	Pharmacist

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Decision transparency

With a given amount of money (time) a hospital pharmacist prioritizes his work on improving quality of the preparations for the patient's need. His decisions should be underpinned by risk analysis.

The quality level of the preparations is challenged by the inspection (or other auditors) and - should he decide not to prepare - the unavailability of necessary preparations is challenged by the board of the hospital.

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Informing the patient

In general about pharmacy prepared medicines, and/or specifically about this medicine

Always (even: informed consent) or:
only at high risk,
only if the patient is able to understand?

Who wants to share his/her experience?

Preparation because of:

- non availability (including: not fit for use)

other reasons may be:

- economic management of the preparation site
- price matters (countervailing power)

Price matters:

Insurance companies or Board of hospitals sometimes prefer preparation (or generally: unlicensed medicines or off-lable use) above licensed medicines because of lower costs. This is micro-logic.

The macro-logic is that preparation should never be an instrument for lowering costs of licensed medicines. The macro-logic would be in that case: easening of the registration process.

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We told the patient that although it is an unlicensed medicine:

- Our preparation is the best for him (better than a licensed medicine)
- We made it properly and it will work properly

And if necessary we tell him, the inspector or anybody else about our decisions.

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I hope I did not spoil your pleasure of preparation and you still feel good about making available valuable medicines.

Or even better: feel encouraged doing so