

European Cooperation & Synergy in Quality Standards beyond the European Pharmacopoeia

Session 2

EDQM Symposium

15-16 June 2007

Strasbourg, France



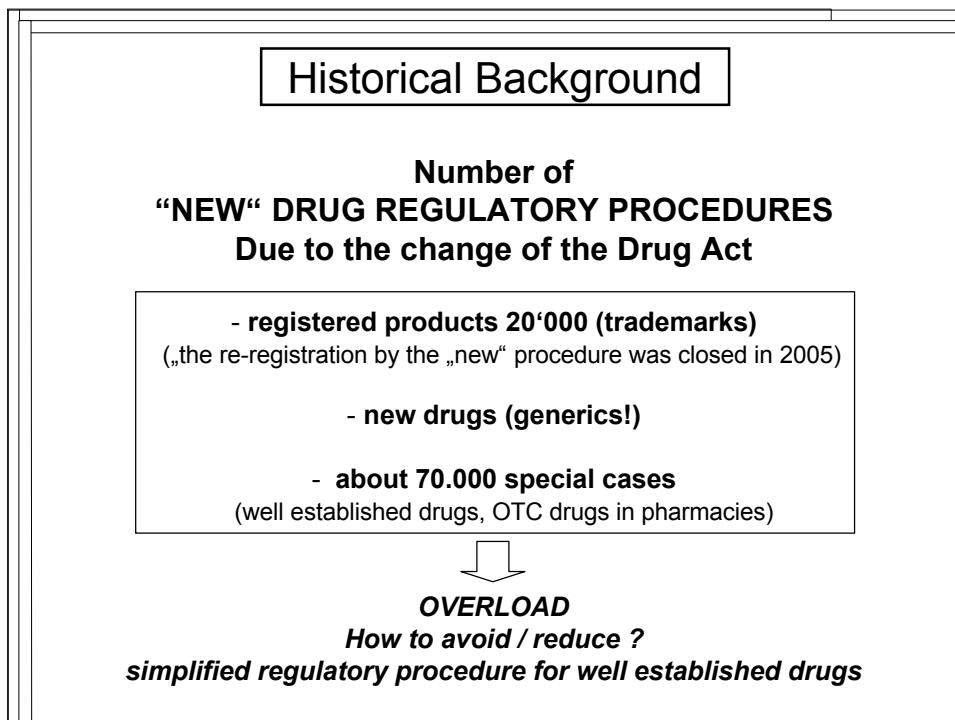
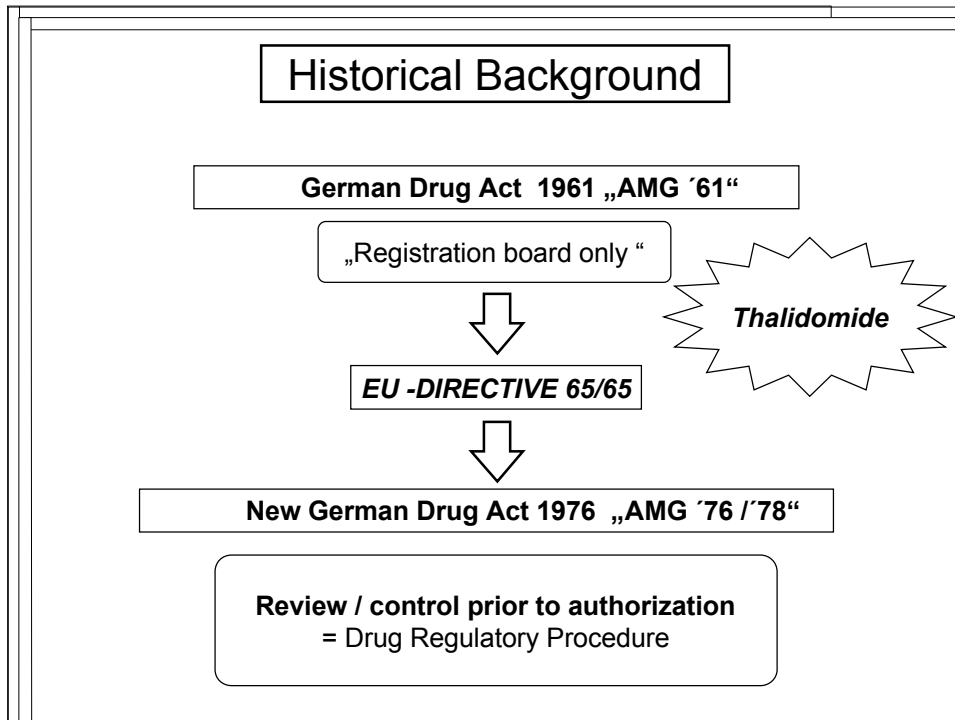
European Cooperation and Synergy in Quality
Standards Beyond the European
Pharmacopoeia
Strasbourg, June 15/16, 2007

The German System of Standard Licenses and Standard Registration

according to a presentation
given by a BfArM specialist in 2006

Layout

1. Historical Background
2. How to get a monograph
3. Surveillance of Standard Licensed drugs



How to get a monograph

Principals of the Drug Regulatory Procedures:

Initial control of an individual drug documentation by an authority review

= Procedures in accordance to the Directive 2001/83

Initial control of a drug formulation standard

(by the responsible authorities, by designated experts and with respect to public need)

= German Standard Licensing

How to get a monograph

proposal of a new medicinal product
applicable only for well established drug substances

by e.g.
physicians, veterinarians, pharmacists/chemists
pharmaceutical industry, army, health insurances,
corresponding societies



**German
Ministry of Health**

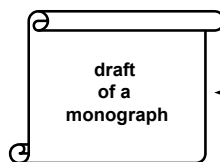


BfArM

„Research“ & Development

- formulation
- manufacturing procedure
- analytics
- templates of labelling, leaflets, and additional information
- microbiological tests

CTD
internal
assessment
according to
the current
regulatory
standards



**draft
of a
monograph**



**publication
If required:
revision of the draft**

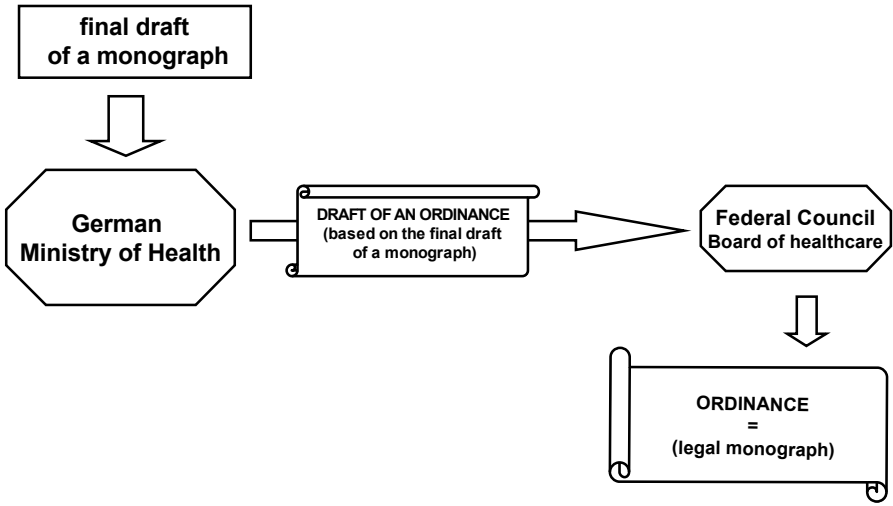


**GROUP of EXPERTS
Examination
of the draft**

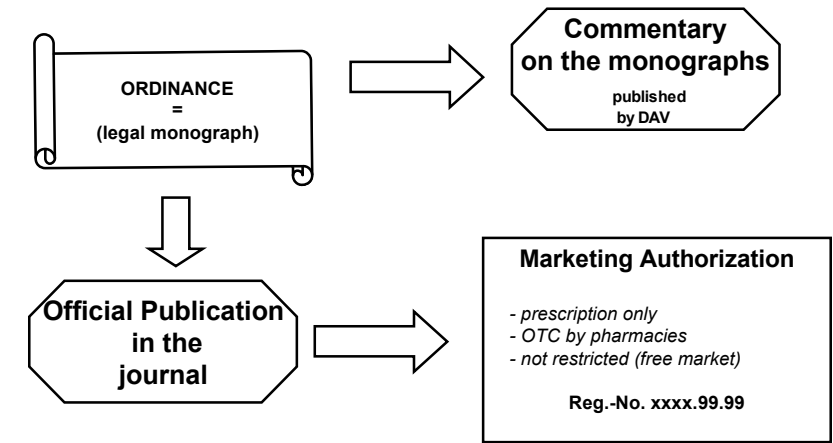


**final draft
of a monograph**

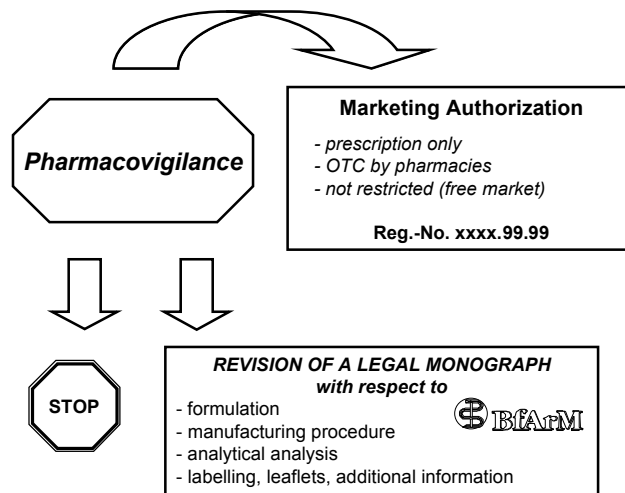
How to get a monograph



How to get a monograph



Surveillance of Standard Licensed drugs



Surveillance of Standard Licensed drugs

RIGHTS AND DUTIES OF THE APPLICANTS

Marketing Authorization
according to
the Standard Licensing
(Reg.-No. xxxx.99.99)

=

Marketing Authorization
according to
a regular procedure
(Reg.-No. xxxx.00.00)

Surveillance of Standard Licensed drugs

DUTIES OF THE APPLICANTS:

- *PSURs (on request of the authorities)*
- *Case Reports*
- *Manufacturing respecting GMP conditions*
- *Batch documentation*
- *Variation control by the competent authorities*

SUMMARY

- *Standard licensing is only applicable on well established drugs (traditional drugs, generics)*
- *efficacy and safety are well known; normal surveillance applies*
- *high transparency in development and requirements for the standard licensed drugs*
- *low costs in drug development and marketing authorisation procedure*
- *control of product variability by the authorities*

In short:

The German standard licensing procedure is not an exception of a regular authorization procedure.

It is a different procedure but not a reduced *regulatory procedure* (not a „*light*“ version).

Quality standards beyond the
European Pharmacopoeia
**Standard licenses and
Formulae magistralis -
The European perspective**

D. Schnädelbach
Strasbourg 15-16 June 2007

Basis for safe medicines

- Development and clinical trials according to the state of the art
- Licensing of medicines
- Production according to GMP
- Inspection
- Starting materials of appropriate quality

- Does this solve all problems?

Medicines less regulated

- Unlicensed medicines
 - extemporaneous production by pharmacists
 - production by hospital pharmacies
 - other small-scale production
 - production for exportation
- Traditional medicines such as TCM
 - herbs and mixtures thereof
 - other preparations

Regulations for less regulated medicines

- European Pharmacopoeia
 - Quality of starting materials
 - Quality of dosage forms
- Formulae magistralis of Member States
 - Composition of medicines
- Maybe local regulation of GMP for small-scale production

The Gap

- There is a substantial production of medicines above the extemporaneous production by pharmacists but below the level of licensed medicines produced by the industry.
- These may be produced by pharmaceutical manufacturers, wholesalers, hospital pharmacies, etc.

Means for closing the gap

- Affordable licenses for “smaller products”
- Formulae magistralis
- Disadvantages of the existing system:
 - Local regulations
 - Not known throughout Europe
 - European harmonisation of the quality and safety is missing.

Basic requirements

- Any new system should aim at medicines which are produced according to the same quality standards as licensed medicines – as far as this is achievable.
- The new system should help fill the gap.
- Any new system should be a harmonised European one.

Fields for European solutions

- Standard licenses
- Formulae magistralis
- Traditional Chinese Medicines
- We may need to consider specific GMP requirements for small-scale production.
- This could include GMP for pharmacies.

European standard license

- Aims
 - Affordable licenses
 - High quality standard
 - Pharmacovigilance
- Principles
 - European co-operation
 - Co-operation of national agencies
 - Share workload

Possible organisation

- Within the EDQM & HealthCare
 - Separate Convention
 - Separate Commission
 - Separate Groups of Experts
 - Separate publication
- Decisions by Commission
- Implementation by national authorities

Formulae magistralis

- There may be cases in which a standard license is not the best solution.
- Therefore additional solutions could be envisaged.
- European formulae magistralis could solve some problems.

Elaboration of Formulae magistralis

- The same organisation could be applied as in the case of European standard licenses.
- FM could be part of the Convention on standard licensing.
- FM could be elaborated and published in the same system.

TCM in the new system - 1

- Many European countries see a need to regulate TCM.
- The Ph. Eur. regulates the quality of herbs used in TCM.
- It would make sense to regulate the quality of preparations produced from these herbs on the European level.
- The products would be used according to TCM but unacceptable indications could be omitted.

TCM in the new system - 2

- According to the importance of the product we could regulate it as a
 - European standard license
 - European Formula magistralis
- We would providing for all Europeans the same level of quality and safety of TCM.
- We would share the workload, thus avoiding duplication of work.

Other fields for standard licenses

- Medicines for human or veterinary use in which the industry is not interested.
 - Specific preparations for infants, elderly patients or other specific groups
 - Preparations for rare diseases
- Medicines for situations such as production by hospital pharmacies or the military.

Further application of the system

- Regulation of European traditional medicines which are not yet licensed.
- European standard registration of homoeopathic medicines.
 - The number of preparations that are not yet registered may be very high.
 - A European solution could save resources.

GMP for small-scale production

- The Ph. Eur. has no mandate to deal with GMP issues.
- If we create regulations for small-scale production (“the gap”) we could consider elaborating specific GMP requirements.
- Though GMP should not be regulated by the Ph. Eur. it could well fit into regulations for small-scale production.

How could we start the new system?

- Compile the documents of this conference.
- Prepare an explanatory note on the new system.
- Inquire whether there is a substantial number of interested parties.
- If there is sufficient interest: look for legal advice.

Handling of legal aspects

- Involve the legal department of the council of Europe right from the beginning.
- Involve the EU right from the beginning.
- Prepare a feasibility study exploring possible ways of the organisation.
- Prepare draft documents for further discussion.

Conclusion

- There are sound reasons to extend our European co-operation to new fields.
- We should seriously examine possible activities and benefits.
- We should find out whether there is a sufficient number of interested parties.
- We should define a work programme acceptable to all interested parties.

Licensing of Standard Preparations

European Cooperation and Synergy in Quality
Standards Beyond the European
Pharmacopoeia

Strasbourg, June 15/16, 2007

Dr. Susanne Keitel

Structure

1. Introduction
2. Possible General Principles
3. Summary

Introduction

“The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.”

Recital 2, Directive 2001/83/EC, as amended

Introduction

“Standard Preparations” can be an alternative to individually authorised products

- For badly needed medicinal products with a small market share, e.g.
 - certain antidots
 - veterinary medicinal products
 -
- For medicinal products to be manufactured on a larger scale in hospital pharmacies
- For medicinal products to be manufactured on a small scale in pharmacies
-

Introduction

BUT:

- In selecting the medicinal products which may qualify to be exempted from the obligation to apply for an individual marketing authorisation, account must be taken of the legitimate interests of the consumer of the medicinal product, the health professions and the pharmaceutical industry.

Introduction

THEREFORE, any kind of standard licensing system must ensure that

- medicinal products are only exempted from the obligation to obtain an individual marketing authorisation in so far as no direct or indirect danger to human or animal health is to be feared, since it is evident that the requirements with regard to the necessary quality, efficacy and safety have been met.

Introduction

Points to be considered

- Standard preparations should be based on
 - a defined composition
 - a particular manufacturing procedure
 - adequate specifications (acceptance criteria and test methods)
 - defined labelling, package leaflet, expert information
- May need to be limited to certain methods, fields or ranges of application

Structure

1. Introduction
2. Possible General Principles
3. Summary

Possible General Principles

- From a regulatory point of view, the following issues should be defined
- The solutions offered in this presentation should serve as “food for thought”, they do not necessarily provide the optimal answer

AND

- The list of issues addressed in this presentation merely provides examples, it does not attempt to be exhaustive!

Pharmacopoeial Requirements

- All ingredients of the medicinal product have to meet pharmacopoeial standards, where applicable
- The user of the standard license is responsible for the demonstration of the suitability of pharmacopoeial monographs to adequately control the quality of all ingredients

Pharmacopoeial Requirements

- Substances of animal origin have to fulfill the requirements of the general monograph “Products with a risk of TSE” as well as the current guidelines of the EU and the competent authorities
- Excipients which are not covered by the Ph.Eur. have to meet the requirements of the pharmacopoeia of an EU Member State. In the absence of a monograph in one of these pharmacopoeias, the use of this excipient has to be commonly known in pharmaceutical sciences and practice. In this case, its quality has to be specified in accordance with the monographs of the pharmacopoeia

Composition

- For tablets, it may be advisable to allow the amount of excipients listed in the monograph to be modified quantitatively up to a maximum of 10 % of tablet weight while keeping both total amount of excipients and tablet weight unchanged as long as the user demonstrates that the final product meets all specifications listed in the respective monograph

Manufacture

- For the manufacture of the product, other means than the ones described can be used, provided they yield the same product quality
- In-process controls listed in a monograph can be substituted by other controls, provided their equivalence has been demonstrated
- Substances that are known to possibly contain pyrogens have to be tested accordingly before being used in the production of sterile solutions

Manufacture

- For parenteral products, the conditions for sterilisation listed in the monograph can be changed, provided that the efficacy of the modified method to attain sterility has been demonstrated.
- Acids or bases can be used to yield the pH-value described in the monograph in case of unbuffered liquid dosage forms

Analytical Tests

- Analytical tests and methods can be substituted by others, provided their equivalence has been demonstrated
- Test methods for any additional stability testing performed by the user have to be stability indicating. Validation of the method has to be documented
- Reference standards: in case no official compendial standard is used, the suitability of a substance for the respective use has to be demonstrated

Container/Closure System

- Container/closure systems described in a monograph can be substituted by ones of a different geometry or composition. However, in this case the user of the monograph is responsible for the conduct of relevant stability studies and the assignment of a shelf-life which should be adequate for the requirements of distribution, e.g. should not be shorter than one year.
- Pack size: has to satisfy therapeutic needs

Labelling

Should be binding as described in the relevant monograph

- exception: additional contra-indications, side-effects and interactions
- exception: free choice of brand name (in line with normal rules applied by the authorities) without simultaneous indication of the name of the monograph

Labelling

- The user of the monograph can renounce claiming indications listed in the monograph and thus the use of related applications and dosing regimen. This does not, however, impact the requirement to list contraindications, side effects or interactions unless they are specifically related to the renounced mode of application in an unequivocal way.

Efficacy/Bioequivalence

- Normally, elaboration of a standard license monograph should be limited to APIs/medicinal products that do not need bioavailability/bioequivalence or local tolerance studies
- For solid oral dosage forms, in a number of cases there is no need to perform bio studies based on BCS-classification

Documentation

- If a regulatory authority elaborates standard licensing monographs, the same standards/requirements should apply as for individual marketing authorisation applications
- The results of all development activities should not only be documented in the laboratories, but a state-of-the-art dossier should be compiled and assessed, applying EU standards (e.g. pharmacopoeial monographs, guidelines etc.)

Possible Guiding Principles

To summarise:

The general principles for the use of standard licenses MUST reflect current pharmacopoeial and regulatory requirements!

Structure

1. Introduction
2. Possible General Principles
3. Summary

Summary


- Pharmacopoeial and regulatory standards applied to the manufacture of products covered by standard license have to be state of the art
- Authorities elaborating standard licences should compile CTD-format quality dossiers for the monographs
- These dossiers should be assessed by appropriately qualified assessors who have not been involved in the development

Summary

- Where necessary, bioequivalence or local tolerance studies should be performed
- Notification of the use of a monograph to the competent regulatory authority should be a “must”
- Monograph- and GMP-compliant manufacture is within the responsibility of the user
- Inspections play a vital role in quality assurance!



Standard Marketing Authorisations based on § 36 German Drug Law



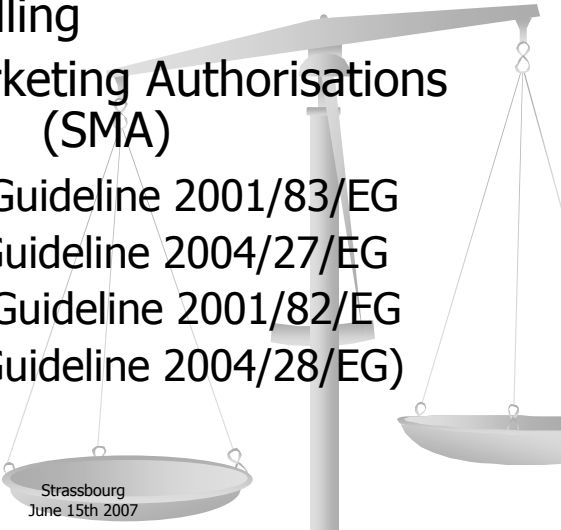
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Strasbourg
June 15th 2007

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Part 1

Obligatory Labelling of Standard Marketing Authorisations (SMA)



(Art.54 Guideline 2001/83/EG
Art.1Nr.40 Guideline 2004/27/EG
Art. 58 Guideline 2001/82/EG
Art.1Nr.32 Guideline 2004/28/EG)

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Obligatory Labelling

➤ **Monographies of SMA**

- Special Requirements – strictly to follow the wording
- Minimal Requirements – wording detailed by:

➤ **Requirements of the Drug Law**

- § 10 Labelling of medicinal finished products (primary & secondary package)
- § 11 Package Leaflet
- § 11a Expert Information

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Labelling

(primary & secondary package)

- **Data shall be written in:**
 - easily legible and indelible
 - easily understandable German
 - accordance with the details

11a

in Section

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Labelling

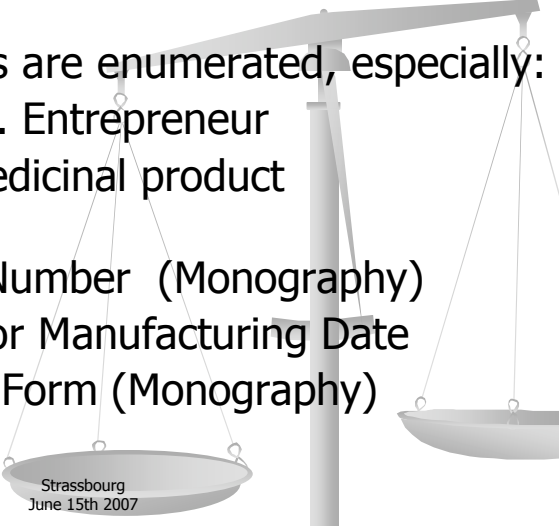
● Sub-section (1)

all necessary items are enumerated, especially:

1. Name of Pharm. Entrepreneur
2. Name of the medicinal product (Monography)
3. Authorisation- Number (Monography)
4. Batch Number or Manufacturing Date
5. Pharmaceutical Form (Monography)

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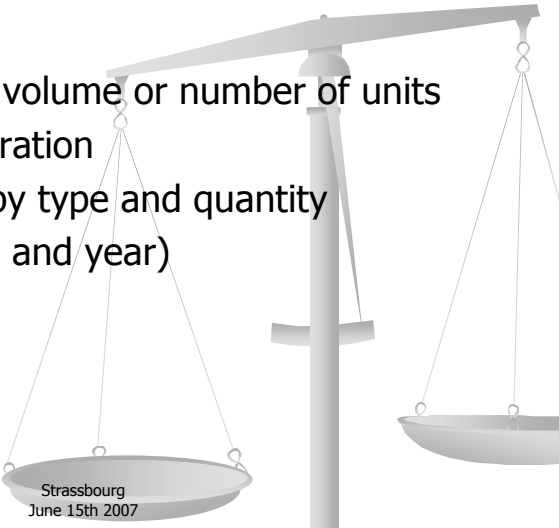
Labelling

... Sub-section (1)

6. Content by weight, volume or number of units
7. Method of Administration
8. Active Substances by type and quantity
9. Expiry Date (month and year)

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Labelling

- Other special references and recommendations (Monographies)
- **Special information for Animal Medicinal Products as e.g.**
 - animal species, withdrawal periods, pre-mixes etc.

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SMA and § 11 GDL - Leaflet -

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Leaflet

- Prescribed Title
- written in easily understandable German
- in conformity with Section 11a
- Special Requirements in the Monographies
- general requirements in § 11

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Leaflet

- **requirements for**
 - Identification
 - Application
- **Special Information as e.g.**
 - contra-indications, interactions, warnings
- **Special Instructions as e.g.**
 - dosage, administration, frequency

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Leaflet

- complete qualitative & quantitative composition
- all approved names of this product in EU
- Date of last Revision of the Leaflet
- Statement: „not applicable“, if it is the case
- **Special information for**

Animal Medicinal Products

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SMA and § 11- Leaflet

For all Medicinal Product Leaflets:

- ☞ Additional information is permitted but
 - clearly set out and
 - well separated

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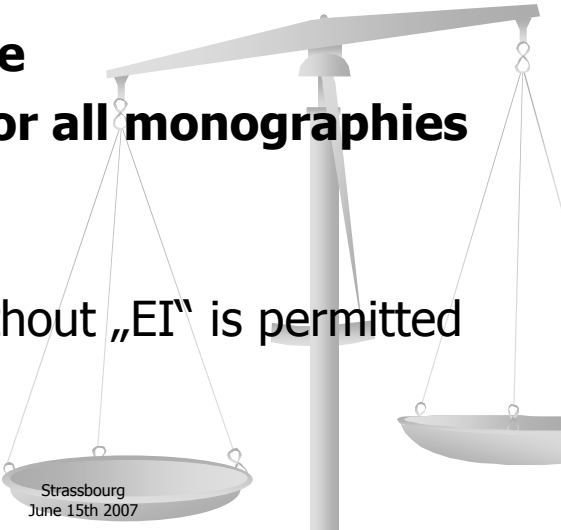
SMA and § 11a - Expert Information-



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- Expert Information - „EI“

- **Prescribed Title**
 - **Not yet „EI“ for all monographies available**
 - **Therefore:**
 - Marketing without „EI“ is permitted
- 

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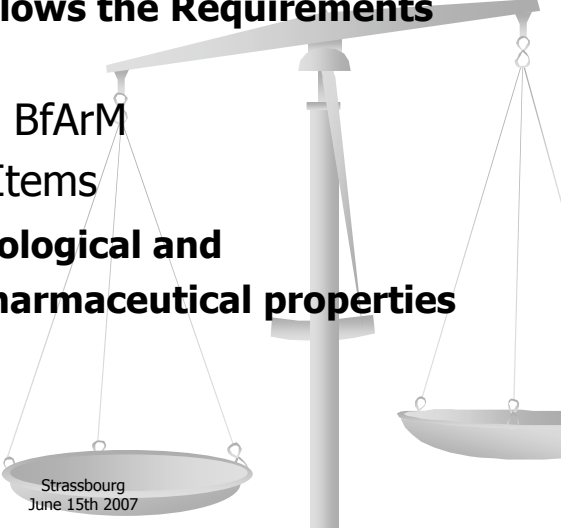
- Expert Information - „EI“

■ **If available „EI“ follows the Requirements of § 11a:**

- Text provided by BfArM
- Special order of Items
- clinical, **pharmacological and pharmaceutical properties**

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- Expert Information - „EI“

■ **Animal Medicinal Products**

- **Additional remarks**
 - - **especially to clinical details**

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SMA and § 11a - Expert Information-

- **Relevant modification for therapy**
 - made known by pharm. entrepreneur
- **Authority (BfArM) may prescribe**
 - form
 - size and extent of the information

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Standard Marketing Authorisation

Viewpoint of an Inspector

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Viewpoint of an Inspector

- Manufacturing Products of Standard Marketing Authorisations:
 - Regulations of the AMWHV
(Regulations for manufacturing Medicinal products and active substances)
 - EU GMP Guideline and the annexes
 - Monographies of SMA
 - Pharm Eur / other Pharmacopoeas

Viewpoint of an Inspector

- Very often ignorance of the Requirements using the SMAs
 - 1. Detailed monographies**
 - - e.g. problematic substances
problematic dosages etc.
-  **follow strictly step by step the monography**

Viewpoint of an Inspector

2. non detailed monographies

- - quality requirements of pharmacopoeas
- - own quality standards

 **Follow pharmacopoea or other specifications**

Viewpoint of an Inspector

- **Examination of**
 - transfer of requirements to specifications
 - - manufacturing and testing
 - - release for marketing
 - documentation of testing of incoming goods
 - - active substances and constituents
 - - auxiliary materials
 - - release for use

Viewpoint of an Inspector

- Examination of
 - manufacturing and testing protocols
 - - in-process-controls
 - - end-controls
 - - labelling
 - - deviations etc.
 - protocol of release for marketing

Viewpoint of an Inspector

- All requirements of GMP, e.g.
 - quality assurance system
 - rooms and equipment
 - personnel
 - hygiene etc.

Thank you for your attention!

Merci beaucoup pour votre attention!

Vielen Dank für Ihre Aufmerksamkeit!

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June 15th 2007





Securing the quality of extemporaneous and small scale preparations in community and hospital pharmacies

„The German View“

A. Kiefer, Federal Chamber of Pharmacists
Bundesapothekerkammer (BAK)



1

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Demand based on medical prescriptions



- 20-25 millions of extemporaneous preparations in community pharmacies annually
- 22000 pharmacies = Ø 4-5/day
- Unknown number in hospital pharmacies

Details see poster „ADKA“!

- Dispensing by pharmacies means:
 - ➔ EVERY PHARMACY CAN DO!



2

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Guaranteed Quality?



Structural Qualities (Council regulations)

- Most important regulation:
- „ApBetrO“
 - ➔ Rooms
 - ◆ Manufacturing Laboratory
 - ◆ Analytics Laboratory
 - ➔ Employees
 - ◆ Pharmacists
 - ◆ Pharm.-Lab.-Assistent
 - ➔ Requirements concerning machines
 - ➔ Work hygiene

Details see poster „AGP“!

Product Qualities (German features)

- German Pharmacopoeia
- Deutscher Arzneimittelkodex (DAC)
- „extra Pharmacopoeia“
- Neues Rezeptur Formularium (N.R.F.)
- Formularium Hospitale (hospital formulary)

Details see poster „NRF“ and session 3!

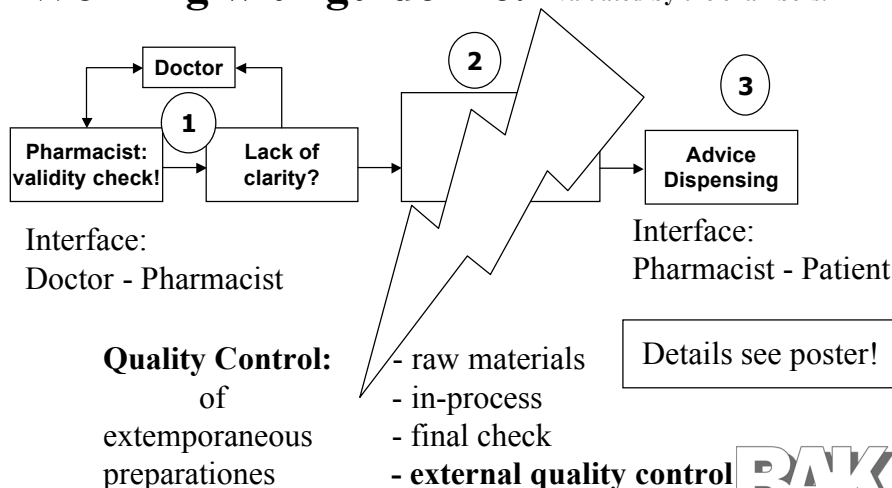
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Dispensing-Process-Quality!



Working with guideline! Evaluated by the chambers.



4

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External Quality Control = substantial analysis !



➤ Government supervision

- ➔ Federal Organisation: for example Rhineland-Palatinate
- ➔ Regular revision every two years
- ➔ With sampling of contemporaneous preparations
- ➔ Analysis in government laboratory

➤ Round Robin Test by the Central Laboratory of German Pharmacists (ZL)

- ➔ Every pharmacy that works with chamber-certified QMS
- ➔ Obligatory in one federal state
- ➔ Voluntary for the rest with increasing numbers of participants

Details see poster „ZL“!

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Summary



Manufacturing of extemporaneous preparations is described in a guideline that implies the complete dispensing process

THANK YOU FOR LISTENING!

Formularies for community and hospital pharmacies

Substantial quality Control by government and Central Laboratory of German Pharmacists (ZL)

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BAK