

2ND REGULATORY WORKSHOP: NEW DEVELOPMENTS IN DRUG REGULATION

EU Regulation of Generic Drugs

Pretoria

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c/o EMA, London

and

European and International Affairs

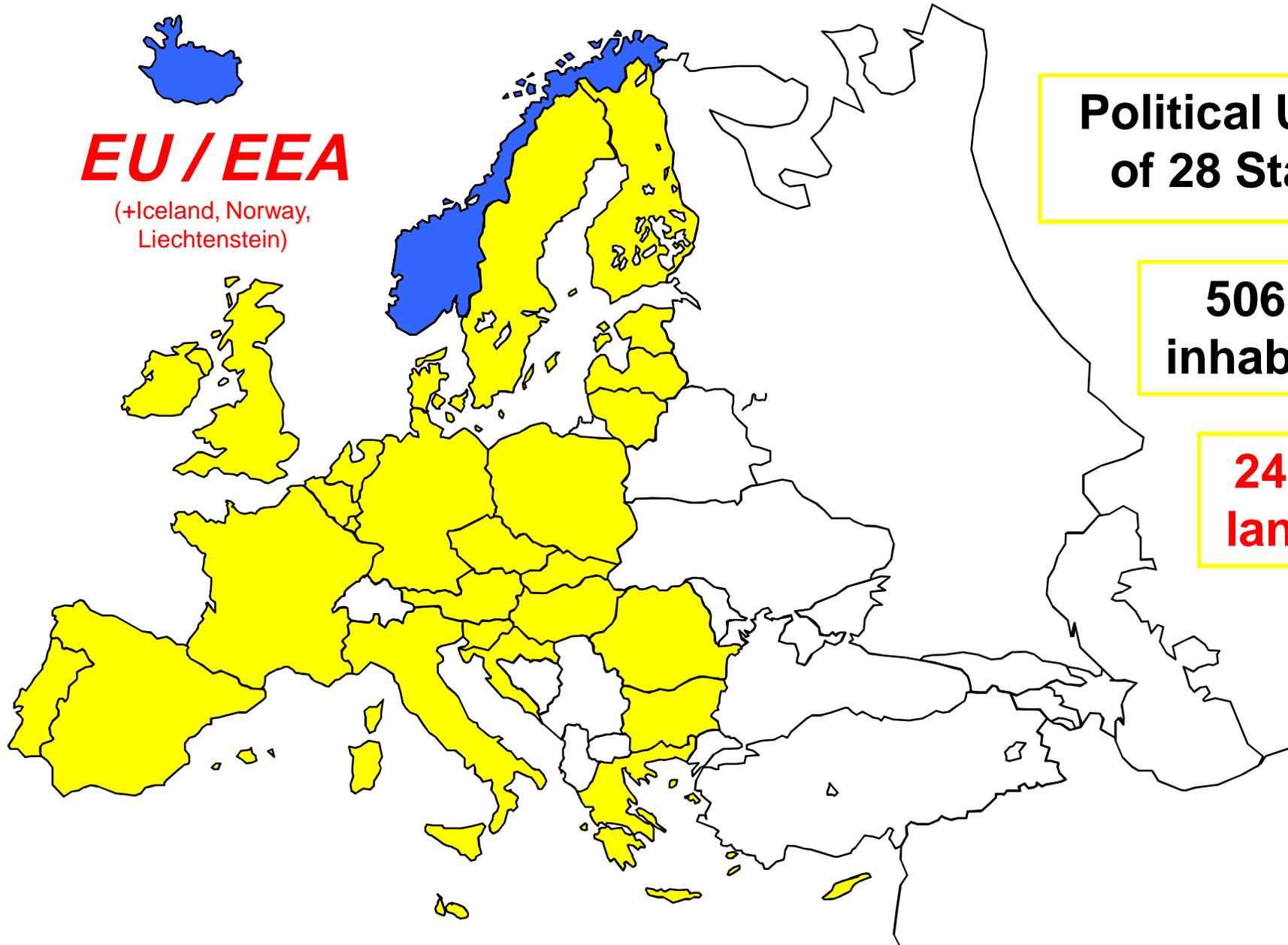
Federal Institute for Drugs and Medical Devices (BfArM)

“United in Diversity”



EU / EEA

(+Iceland, Norway,
Liechtenstein)



**Political Union
of 28 States**

**506 Mio
inhabitants**

**24 official
languages**

... European Pharmaceutical Legislation

- **Directive 2001/83/EC**, as amended (human)
 - Directive 2001/82/EC, as amended (veterinary)
- to be transposed into national legislation

therefore

- harmonised data requirements and assessment for a marketing authorisation are in force in the EU/EEA

but

- prescription status (Rx / OTC)
 - reimbursement by health insurance
- are within the competence of the National States

Legal Basis for MAs in the EU/EEA

Article 8 **full dossier**

Article 10 (1) Generic

**Article 10 (3) „Hybrid“
(Generic with additional own data)**

Article 10 (4) Biosimilar

Article 10a **well established use application**

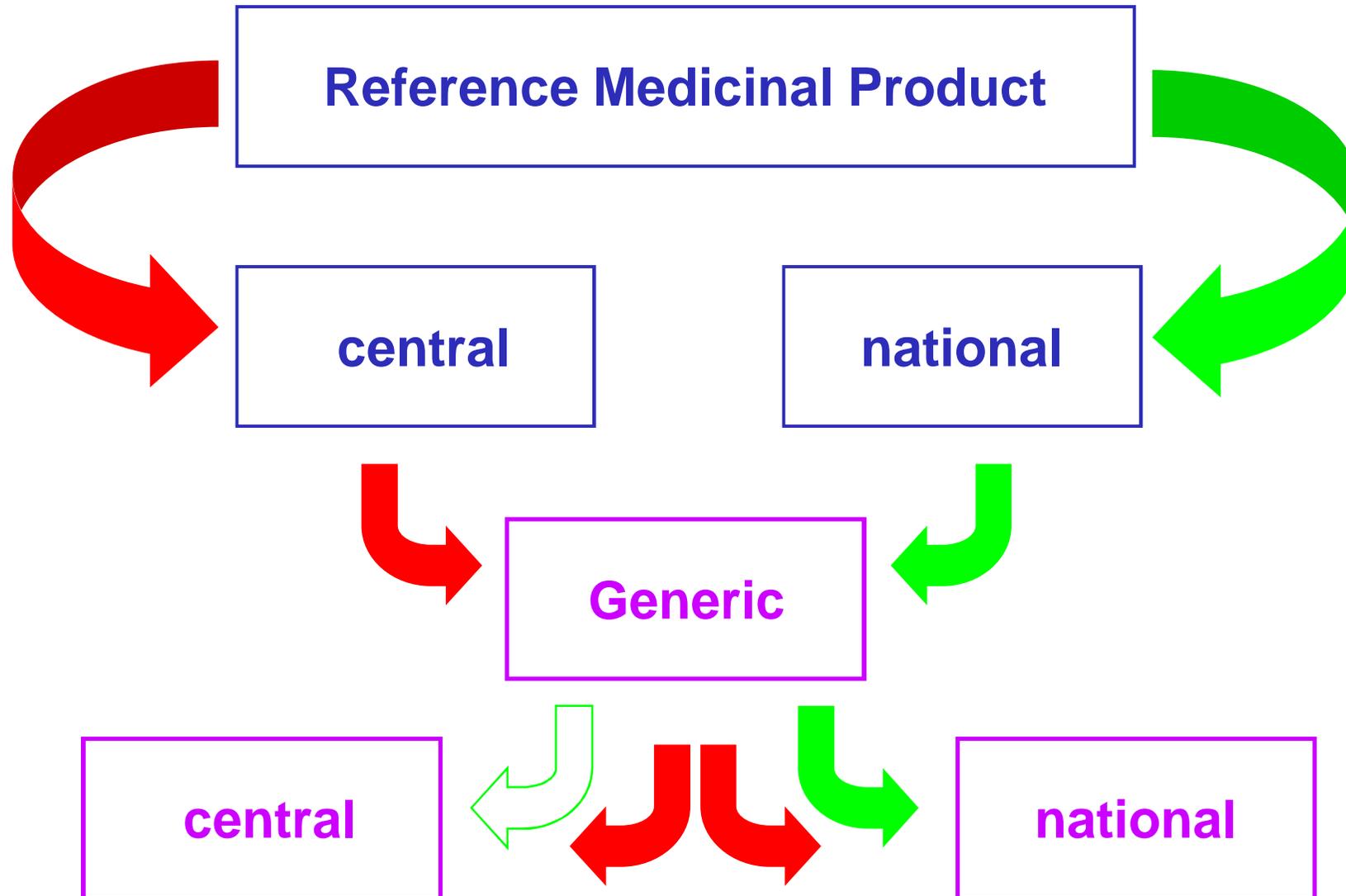
Article 10b **combination of known constituents**

Article 10c **informed consent**

Generic Medicinal Product

- an application according to Article 10 is a deviation from the normal route of approval (Article 8(3))
- therefore and from a legal point of view, an application for a generic marketing authorisation is not a right in its own
- it is an option if all requirements of the legislations as stated in Article 10(1), 10(3) or 10(4) are fulfilled, respectively
- each subarticle of Article 10 is selfstanding – no combinations are possible

Routes for a generic application



Which way to go ?

- if there is a choice, its the strategic decision of the applicant
- some points for consideration
 - entire EU or only some MS (e.g. translations) ?
 - can I scope with one name of the medicinal product for all MS ?
 - do I have marketing partners ?
 - is one MA sufficient ?
 - different patent situation in the member states
 - ...

Harmonised Evaluation

Harmonised evaluation ?- (1)

Problem:

one submitted dossier should result in one final outcome of the evaluation

Within one procedure:

dialogue between RMS and CMS

but if

- different procedures
- procedures with several RMS
- different applicants
- different assessors

Harmonised evaluation ?- (2)

Solutions

- harmonised Guidelines
- working together in working parties
- workshop with european assessors
- exchange of information between EMA and CMDh with the aim to identify
 - identical dossiers
 - same bioequivalence study
 - same pharmaceutical dossier
 - same source of active substance (e.g. ASMF)

Application for a Generic MA

Generic Medicinal Product - (1)

Article 10 (1), first subparagraph

*“1. ...the applicant **shall not be required** to provide the results of **preclinical tests** or **clinical trials** ...*

therefore:

- the generic applicant has to provide its **own pharmaceutical dossier** to prove the quality of the (generic) medicinal product
- independent evaluation; **no assessment in comparison to the pharmaceutical quality of the reference medicinal product**
- no relaxation of any requirements by legislation (e.g. Ph. Eur.) and/or ‘soft law’ (Guidelines, ...)

Biological Medicinal Products

Monographs of the European Pharmacopoea for active substances likely to be defined as 'biological medicinal products'

- List compiled by the CMD(h) and sent for discussion to the BWP – 'open' list published by the CMD(h) (June 2007)
- clarification for two substances already achieved (CMD(h) Press Release June 2006)
 - ✓ low molecular mass heparins
 - ✓ Pancreatins
- Consequences:
 - ✓ legal basis either Article 8(3) or Article 10(4)
 - ✓ no ASMF acceptable for Module 3
 - ✓ no CEP can replace Module 3 (only supportive)

see: Guidance for applicants on biologicals (June 2007) – Q&A 1-3

Generic Medicinal Product - (1a)

Article 10 (1), first subparagraph

*“1. ...the applicant shall not be required to provide the results of preclinical tests or clinical trials **if he can demonstrate** that the medicinal product is a **generic of a reference medicinal product** ...*

Reference Medicinal Product: Definition

Article 10 (2) (a)

“... shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;”



- ❖ Article 8 full dossier
- ❖ Article 10a well established use application
- ❖ Article 10b combination of known constituents
- ❖ Article 10c informed consent

Generic Medicinal Product - (1b)

Article 10 (1), first subparagraph

*“1. ...the applicant shall not be required to provide the results of preclinical tests or clinical trials **if he can demonstrate** that the medicinal product is a generic of a reference medicinal product which **is or has been authorised** under Article 6 for not less than **eight years** in a Member State or in the Community.”*

 but this periods of protection **should not apply** to reference medicinal products for which an application for authorisation has been submitted before October 30th, 2005.

 new provision is applicable in 2014 ...

Data Exclusivity (before October 30th, 2005)

Period of data exclusivity for the **clinical** and **nonclinical documentation** of an application for marketing authorisation in EU

10 years: centrally / ex-concertation authorised products

for national approved new medicinal products

10 years: BE, DE, FR, IT, NL, SE, UK

6 years: all other MS

Data protection for the other parts of the application: **FOREVER**



but - no link to existing patent(s) !!!

Generic Medicinal Product - (2)

Article 10 (2) b: “generic medicinal product”

- same qualitative and quantitative composition in active substances

but

- the different salts, esters, ethers, isomeres, mixture of isomeres, complexes or derivatives are the same active substance, **unless they differ significantly in properties with regard to safety and/or efficacy.**
- in such cases additional information of the proof of safety and/or efficiency of the different salt, ... **must be supplied by the applicant.**

Generic Medicinal Product - (3)

cont.

- if the different salts, esters, ethers, isomeres, mixture of isomeres, complexes or derivatives are the same active substance **differ significantly in properties with regard to safety and/or efficacy.**

- ➔ application according to
 - Article 10(3) or
 - Article 8(3)

Generic Medicinal Product - (4)

Article 10 (2) b: “generic medicinal product”

- ✓ same qualitative and quantitative composition in active substances
- **same pharmaceutical form** as the reference medicinal product - but all immediate-release oral pharmaceutical forms are the same

... same pharmaceutical form - (1)

Standard Terms (pharmaceutical forms) of the European Pharmacopoeia are applicable by law

- therefore exemption by legislation – “... but all immediate-release oral pharmaceutical forms are the same”
- consequences for all non-immediate-release oral forms e.g. modified release, gastro-resistant tablets, gastro-resistant capsules: not the same !

... same pharmaceutical form - (2)

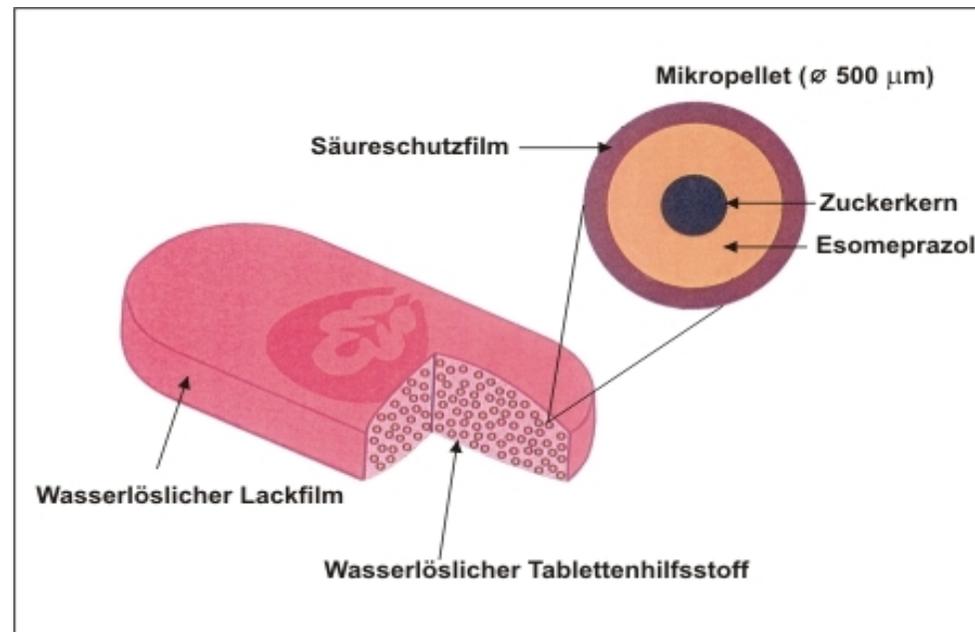
What to do if there is no correct standard term for the pharmaceutical form of the Reference Medicinal Product?

The case:

Losec MUPS gastroresistant tablets / capsules

- MUPS = Multiple-Unit Pellet System
- gastroresistant pellets used for the production of tablets and capsules

***... same
pharmaceutical
form - (3)***



- Is this a gastro-resistant tablet ???
 - MUPS vs monolithic gastro-resistant tablets
- the correct term should have been
 - ‘gastroresistant pellets in tablets / capsules’
 - however, nobody has applied for it ...

... same pharmaceutical form - (4)

Why is the question important? It decides ...

- the legal basis of the application (capsules vs tablets ...) – Article 10(1) vs Article 10(3)
- how to prove bioequivalence
- Pharmacovigilance requirements (PSUR)
- generic reimbursement in some MS

Discussion at CMDh

... and agreement on ‘gastroresistant pellets’

Bioequivalence and RMP

... be careful!

- tablets and capsules are immediate-release oral pharmaceutical forms, and therefore reference to both is legally possible
- but this may not exclude in very specific cases the necessity to show bioequivalence to both pharmaceutical forms individually !



CMDh-Referral for Sertralin 50 mg/100 mg
(UK/H/0863/001-002/MR)

Generic Medicinal Product - (5)

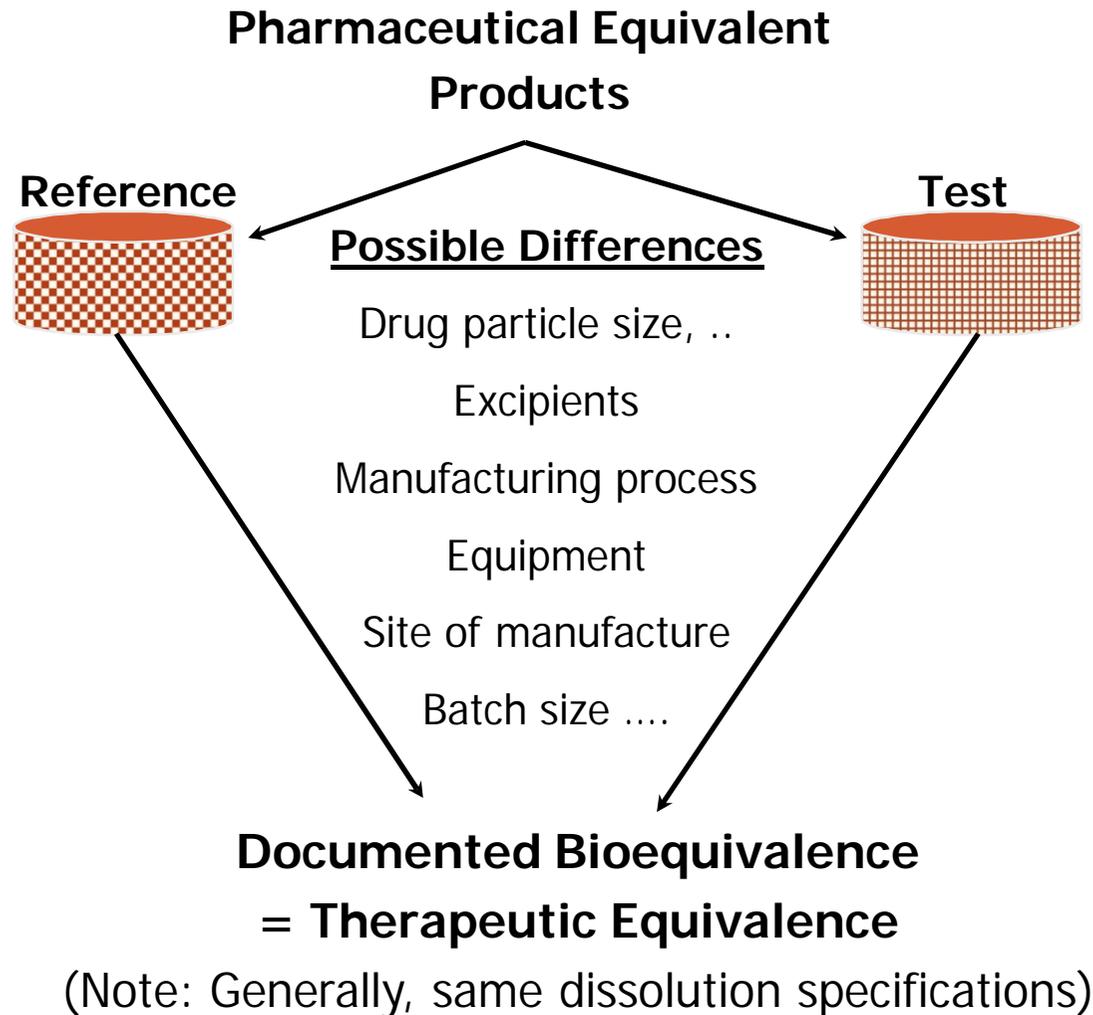
Article 10 (2) b: “generic medicinal product”

- ✓ same qualitative and quantitative composition in active substances
- ✓ same pharmaceutical form as the reference medicinal product - but all immediate-release oral pharmaceutical forms are the same
- **bioequivalence** with the reference medicinal product **or** **waiver of bioequivalence** according to guidelines

Bioequivalence - (1)

- bioequivalence is the surrogate for efficacy and safety - as such
 - the **BE-study is the pivotal study** on which the granting of a generic marketing authorisation is based
 - need to stick to the relevant Guideline
- the preferred way to show therapeutic equivalence between the generic and the reference medicinal product/originator

Bioequivalence - (2)



Bioequivalence - (3)

Bioequivalence studies:

in vivo comparison of products
by means of volunteers serving
as “in-vivo dissolution model”

‘biological quality control’

comparison of product
characteristics to ensure
therapeutic equivalence

How specific is the ‘system’ working?

- ‘normal’ medicinal products: 80 – 125 %
- narrow therapeutic drugs: 90 – 111 % (def.??)

of the active substance in the RMP

Bioequivalence - (4)

- no need to show bioequivalence if the active substance **and** the finished product is identical (= same source)
- can be used to show therapeutic equivalence of new formulations
- EU: major shift from clinical to pharmaceutical relevance (biopharmaceutical quality, 'biological quality control')

Bioequivalence - (5)

Scope of the EU-Guideline

- focuses on recommendations for bioequivalence studies for immediate release formulations with systemic action
- sets the relevant criteria under which bioavailability studies need not be required
 - for a specific type of formulation
 - waiver for additional strength
 - BCS (Biopharmaceutics Classification System) based Biowaiver

Bioequivalence - (5)

cont. Scope of the Guideline

the limits

- guidance on BE-studies for modified release products, transdermal products and orally inhaled products are given in other guidelines
- scope is limited to chemical entities
- the general principles outlined in this guideline are not applicable to herbal medicinal products

General principles for BE

- the strength with the greatest sensitivity to bioequivalence assessment should be administered
- single dose studies are preferred to multiple-dose studies as single-dose studies are considered to provide more sensitive measurements of the release of API
- drug intake (fed and/or fasted state)
- generally, evaluation of pharmacokinetic bioequivalence is based upon the parent drug
- participation of healthy volunteers (“in vivo model”)
- phenotyping for metabolizing activity e.g. slow metabolizers

Special case - I

Waiver ...

- *based on dose-proportionality of formulations*
- BCS-based - Biowaiver.....
.....is defined as
 - in vitro instead of in vivo (bio-)equivalence testing
 - comparison of test and reference
- for specific pharmaceutical forms – e.g. i.v

Special case - II

No possibility to show bioequivalence due to

- the mode of action (e.g. local applied local acting)
- route of administration (e.g. inhaled products)
- the specific pharmaceutical formulation
- an active substance which is (bio)similar
- new strength and/or new therapeutic indication

→ the results of the appropriate pre-clinical tests or clinical trials shall be provided

... if BE can not be shown: 'Hybrid'

Article 10(3) of Directive 2001/83/EC

“In cases where the medicinal product does **not fall within the definition of a generic medicinal product** as provided in paragraph 2(b) **or where the bioequivalence cannot be demonstrated** through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, **the results of the appropriate pre-clinical tests or clinical trials shall be provided.**”

Biosimilar Medicinal Products

Article 10 (4): “biosimilar medicinal product”

“Where a biological medicinal product which is **similar** to a reference biological product does not meet the conditions in the definition of generic medicinal products, **owing to, in particular, differences** relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the **results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided**. The type and quantity of supplementary data to be provided **must comply** with the relevant **criteria** stated in the **Annex** and the related detailed **guidelines**. ...”

‘Chemsimilar’ Medicinal Products ?

Bioequivalence

- could be proven – Article 10(1) Generic
- could no be proven, due to
 - form of administration
 - mode of action

therefore

- additional studies (clinical, local tolerance, ...) – Article 10(3)
- but no general questions concerning toxicology

... but, data requirements for

- complex chemical mixtures
- complex optic isomeres with several chiral centres
- encapsuled, highly toxic active substances
- Nanoparticles ??????????

Example 1: Glatiramer

Glatiramer (Glatiramoids) are complex polypeptide mixtures that share the same structural formula –



m – length of a sequence

n = 15-24 units per 100 amino acids containing sequence

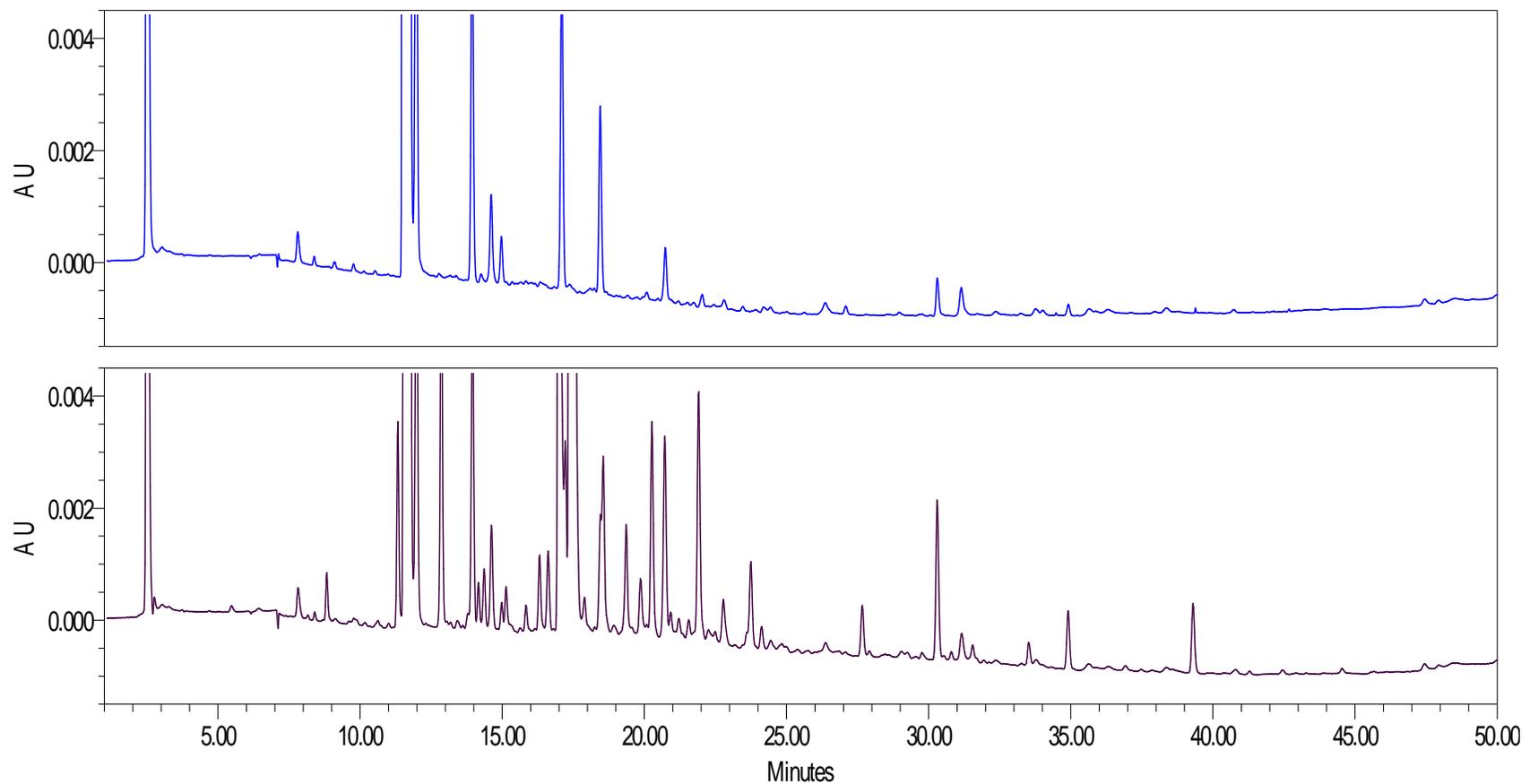
- Glatiramoids can be different in
 - sequence of amino acids
 - distribution of molecular weights of the polypeptide mixture
 - physico-chemical properties
 - biological characteristics (safety and potency)

Glatiramer - (1)

- is defined as a chemical active substance
- the active substance can not be sufficiently characterised with the currently available analytic tools
- the manufacturing process is determining the range of the single components and therefore the composition of the active substance
- the manufacturing process has an influence on the efficacy and/or safety of the medicinal product (consequence for manufacturing variations !)
- the ‚generic‘ active substance can only be similar – need for nonclinical studies?

Glatiramer - (2)

Peptide Mapping profiles of two glatiramoid-synthesis
(proteolysis followed by RP – LC separation)



SAME ?

Glatiramer – (3)

Conclusion

- a generic approach is only possible
 - if the sameness of the active substance could be proven
 - or shown that the active substance is not significantly different with regard to safety and/or efficacy
- the scientific approach looks comparable with the biosimilar idea
 - manufacturing process
 - toxicology (comparable to immunogenicity for biosimilar)
- Glatiramer could be the first member of a new family:

,chemsimilar medicinal products‘

Example 2: Iron Sucrose

- aqueous intravenous solution containing the same active substance as the currently approved product

 no BE-study necessary (Annex II)

However:

the excipient (carbohydrates) has an influence on the release of the active substance

 BE-study necessary (Annex II)

BE was successfully shown, but ...

- safety questions due to the high toxicity of iron
- the iron-carbohydrate complex is a nanoparticle (!)

Special case - III

Submission of a generic application by a Company using its own product as RMP?

YES – if the conditions for the legal basis are fulfilled (legal basis as procedural route)

- definition of RMP (full application)
- same qualitative and quantitative composition in terms of active substances
- same pharmaceutical form, but ...
- bioequivalence
- **data exclusivity has expired**

The Dossier

CTD	RMP Article 8(3)	Generic Article 10(1)
Modul 1	😊	😊
Modul 2	😊	😊
Modul 3	😊	😊
Modul 4	😊	-
Modul 5	😊	(BE)



*Federal Institute for Drugs
and Medical Devices (BfArM)*

*... many thanks
for your kind attention*

List of Abbreviations

BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - human
CHMP	Committee for Medicinal Products for Human Use
EC	European Community
EEA	European Economic Area
EU	European Union
MS	Member States
OTC	over the counter
Rx	prescription only
PL	Patient Leaflet
SmPC	Summary of Product Characteristics

Annex

Global Marketing Authorisation

Global MA for data exclusivity - (1)

Definition of Marketing Authorisation

Article 6 (1) of Directive 2001/83, as amended
second subparagraph:

*“When a medicinal product has been granted an **initial marketing authorisation** ... any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation ... or be included in the initial MA. All these MA shall be considered as belonging to the **same global marketing authorisation** , in particular for the purpose of the application of Article 10(1).”*

Global MA for data exclusivity - (2)

Pharmaceutical Committee (58th meeting 1st June 2005)

3. Recent Case-Law C-36/03, APS, judgement of 9 December 2004

„The ECJ was not called on to rule in those cases whether the same conclusion would apply (i.e. an additional period of data protection for the development product would to be available) even if the development product is authorised on the basis of a stand-alone application. The Commission’s representatives’ interpretation is that nothing prevents extending the findings contained in Generics, Novartis and APS so that, even in such cases, the development would not be afforded a new full period of protection.

In the understanding of the Commission representatives’, this conclusion would also apply in the case where the original product is authorised nationally and, subsequently, the development is authorised through the centralised procedure.“

Global MA for data exclusivity - (3)

Conclusion:

The global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised **through separate procedures and under a different name**, granted to the **marketing authorisation holder of the initial authorisation**.

The initial approval of a MA will trigger the period of data exclusivity.

... as example: ropinirole - (1)

 two independent MA of the originator

Requip - FR/H/0111/001-005

- 0.25 mg, 0.5 mg, 1 mg, 2 mg, 5 mg film coated tablets
- Indication: Parkinson disease

Adartral - FR/H0258/001-004

- 0.25 mg, 0.5 mg, 1 mg, 2 mg film coated tablets
- Indication: Restless-Leg-Syndrom

... as example: ropinirole - (2)

Global MA for data exclusivity?

Yes, because

- same qualitative and quantitative active substance (ropinirole hydrochloride)
- same pharmaceutical form (film coated tablets)
- same company

... as example: ropinirole - (3)

therefore:

a Generic with both indications is possible

but

How to address the Reference Medicinal Product (RMP) in the application form?

CMDh-agreement:

use the RMP which starts the data exclusivity

... next example: Ibandronic acid-(1)

MAH: Roche Registration Ltd.

applications according to Article 8(3)

active substance: ibandronic sodium monohydrate

Bondronat

- EU/1/96/012/001-013
- first MA: 25. 06. 1996
- concentrate for infusion (1 mg/ml)
- film coated tablets (50 mg)
- Hypercalcemia of malignancy

Bonviva

- EU/1/03/265/001-006
- first MA: 23. 02. 2004
- solution for injection (1 mg/ml)
- film coated tablets (2.5 mg, 150 mg)
- Treatment of osteoporosis in postmenopausal women

... basic principles

- no approval „light“ for known active substances, but the same basic principles are applicable as for a medicinal product with a new active substance.
- each application for a marketing authorisation is assessed in line with the principles of
 - ✓ efficacy
 - ✓ safety
 - ✓ qualityand approved if the benefit-risk-ratio is positive
- but the amount of data within the application for a marketing authorisation may differ

Active Substance: Quality Dossier

- **Complete Module 3.2. S**
 - AS manufacturer = finished product manufacturer = applicant
 - no protection of know-how necessary/requested
- **ASMF**
 - for new or known chemical substances,
 - not for biological medicinal products
- **Certificate of Suitability** of the European Directorate for the Quality of Medicines EDQM (**CEP**)
 - only for substances with a monograph in the European Pharmacopoeia & not for biological medicinal products

Substances with a monograph in the Ph.Eur. - ASMF vs. CEP

Identical requirements for the documentation to be supplied, i.e.

- Demonstration that pharmacopoeial monograph is able to detect and determine all impurities

Assessment: Licensing authority ⇒ **ASMF**
EDQM ⇒ **CEP**

... but in fact assessors from the NCAs are doing the assessment in both cases

CEP (= Certificate of Suitability)

- for an active substance with a Ph. Eur. Monograph
- show the suitability of the monograph
- can replace CTD-Module 3S
- no commercial confidential information is provided to the applicant of the finished medicinal product
- evaluation of the submitted dossier of the active substance
 - at the EDQM
 - by assessors of the NCA
- unic CEP numbering system allows traceability

ASMF - CTD

- The "open" part of the ASMF - included in section 3.2.S of CTD-Q
- It is the responsibility of the applicant for a MA for a medicinal product to ensure that the complete **ASMF**
 - applicant's ("open") part and
 - the active substance manufacturer's restricted ("closed") part

is supplied to the authorities directly by the ASM **in the CTD format**, synchronised to arrive at around the same time as the MA application.

- Letter of Access to the CA

Current ASMF assessment

- The same ASMF

- same AS
- same manufacturing site
- same route of synthesis

often used in different dossiers for multiple procedures assessed by different assessors.

- MRP/DCP
- CP
- Human/Veterinary

- Pilot on ASMF-Worksharing is running

- a common platform for information exchange on ASMFs is established and running

- Stand alone assessment

ASMF Working Group

- joint WG of CMDh, CHMP(QWP), EMA, EDQM
- is working on procedural aspects:
 - updated Letter of Access is published and in force
 - unic european numbering system for the identification of ASMF
 - to have the ASMF-AR as a separate document of the AR of the medicinal product (but still no standalone evaluation of the ASMF)
 - store the ASMF-AR and the other relevant information in an EU-data base with access from all MS, EMA and EDQM
 - possibility to re-use the ASMF-AR (= worksharing) in the further regulatory work (e.g. Variations, new applications, ...)
 - ...