EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Generics in the Centralised Procedure

Progress and Current Issues

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An agency of the European Union

Overview

Performance Statistics 2010 - 2011

- CP generics currently are a limited pool, centralised reference products only

Pro-CP Factors

- Dedicated process-facilitating 'Team' at EMA
- 11 Fixed submission dates per year / start of procedure dates
- One authorisation valid throughout the whole EU.

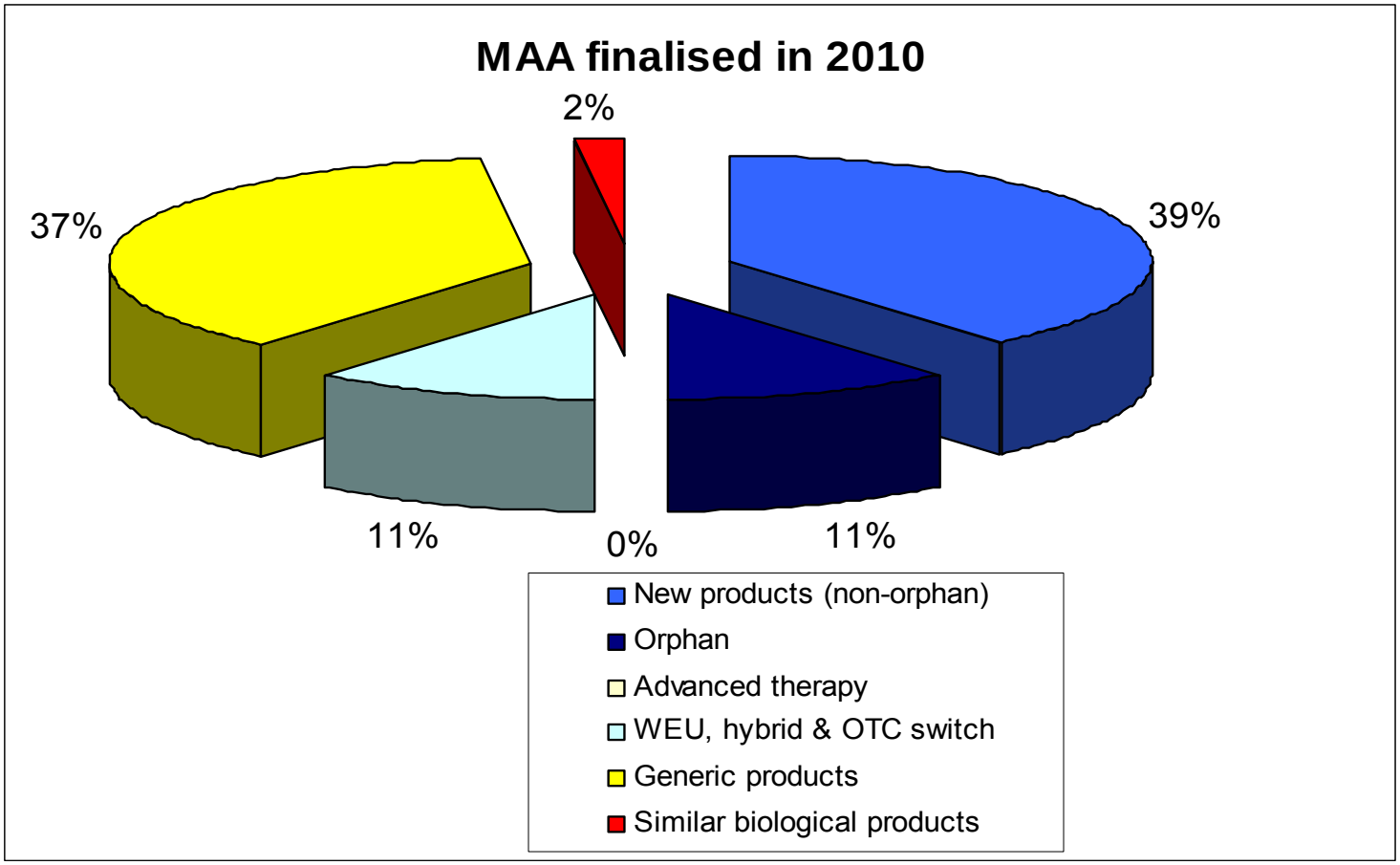
Regulatory Issues : Contra-CP Factors?

- Single Tradename
- Submission of multiple applications in case of Usage patents
- The Commission's recent view on Duplicates/Multiples

Handling Technical/Scientific Issues

- Consistency in Scientific Evaluation of similar/identical dossiers
- CHMP Workprogramme for generics
- Complexity in generics – biosimilars or chemisimilars?

Generics in the overall CP context



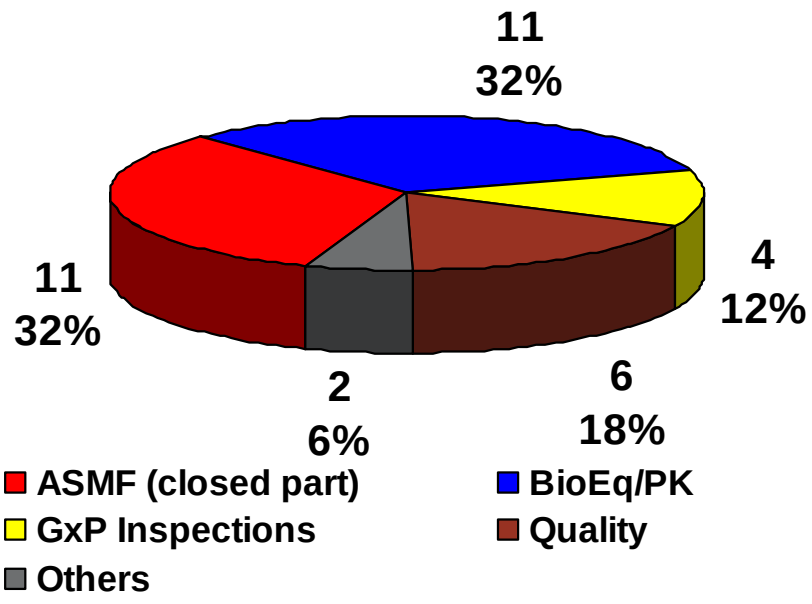
Timetable – Overall CHMP active time

(excluding multiple applications)

	2008	2009	2010
Mean (days)	182	194	200
Standard deviation (days)	9.5	16.6	11.8
Maximum (days)	196	210	210
Minimum (days)	177	148	181

Types of Questions raised at day 120

Generic Centralised Procedure Assessment



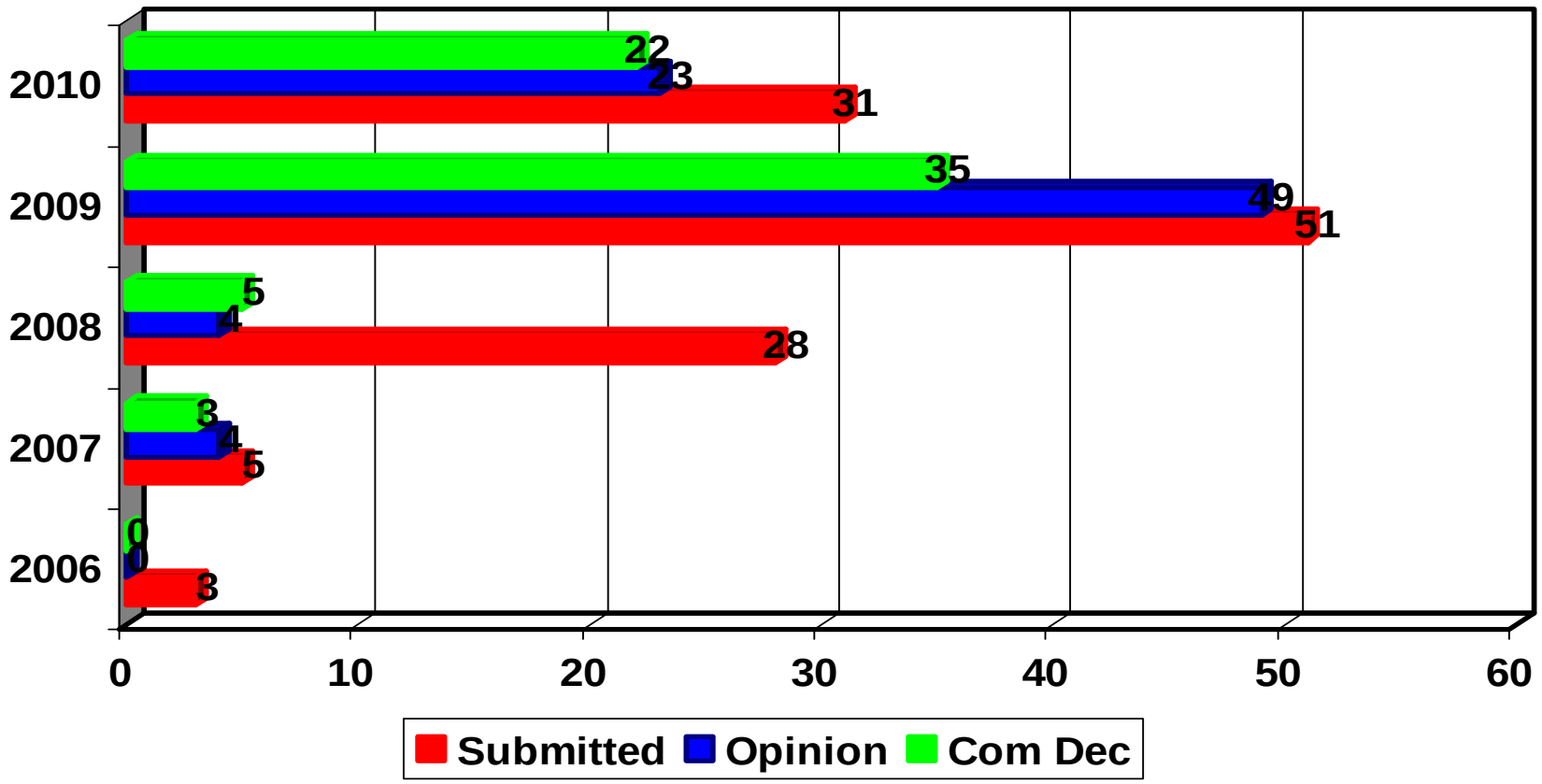
No Negative Opinions !

Generics	2008	2009	2010
Negative opinions	0	0	0
Withdrawals prior opinion	0	1	2
Withdrawals post authorisation	0	1	0

EMA website: Withdrawn applications

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/wapp_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d128

Status of Generic Applications in CP



Pro-CP Issues

Fixed timetables

Guarantee of start of clock (if valid)

Dedicated EMA Team

Reduced fees applied for Generics

Reduced Timetable for assessment

External Communication: Press release / CHMP monthly report, Summary of Opinion (SmoP) EPAR, SPC / PIL / Labelling and General Q&A document on generics

Regulatory Issues : Usage Patents

The SPC for a generic of a Centrally Authorised Product (reference) is in all relevant respects consistent with the CAP reference ….

***except for those parts of SPC referring to indications or dosage forms which are still covered by patent law..*" [Art 3.3. of REG]**

Current CHMP Policy regarding deletion of information:

- Delete information on patented indications from Sections 4.1, 4.2 and 5.1

- Maintain for public health reasons any safety related info in sections 4.3-4.8

Regulatory Issues : Multiples/Duplicates The Commission's interpretation

-Under patent grounds

In this context it is noted that Article 11 of Directive 2001/83 specifically allows for the submission of **different SmPCs on grounds related to patent law**. While this article refers to generic applications the same considerations (i.e. the need to ensure availability of the product in the Member States where there is patent protection) are applicable in the case of duplicate applications.

-Under co-marketing reasons

Multiple / Duplicate applications shall not be accepted under co-marketing grounds **when the two marketing entities belong to the same company group**. Likewise an application for a duplicate cannot be accepted if the co-marketing partners are already co-marketing (together) the product in the EU (i.e. product A is co-marketed by company X and Y and company Y applies for a duplicate marketing authorisation of product A on grounds of co-marketing withcompany X).

Handling Consistency in scientific evaluation of generics

1. Internal : between similar/identical dossiers in CP
2. External : between similar/identical dossiers in CP / DCP

In both cases there is a need for constant vigilance and networking in order to reduce the risk of divergent conclusions, and the EMA has started a number of initiatives.

The CHMP Workprogramme for generics

High Priority – Generics **– Q2 / Q3 2011**

- Revised paper with concrete proposals for handling generics both at CHMP and CMDh level (Q1 2011)

- Setup **supportive subgroup** with Chair PKWP, Chair QWP, CHMP representative, CMDh representative and EMA colleagues

- Revise appointment of Rapporteurs for generics medicinal products. Proposal to appoint a generic peer reviewer in addition to the Rapporteur. Identification of a **cluster** of 3-4 Rapporteurs for each active substance

The New EU BioEquivalence Guideline

Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** 20 January 2010

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

Appendix II, Parenteral Solutions.

Bioequivalence studies may be required *"..if any excipients interact with the drug substance (e.g. complex formation)..",* ***(EVEN FOR INTRAVENOUS USE)***

"Complex" is defined by the Quality aspects of the product, in particular "Complex Formulations" or even "Complex Active Substances"

- Liposomal forms
- Emulsions
- *(Lipids for parenteral nutrition)*
- Micelle-forming solutions

} not exhaustive, there may be more !

Complex Formulations - 1

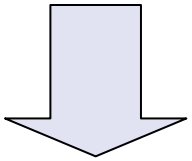
Micellar Solutions

Solubilisation of insoluble lipophilic drugs in surfactant solutions

Taxanes : e.g. paclitaxel, docetaxel

(Taxotere, Paxene)

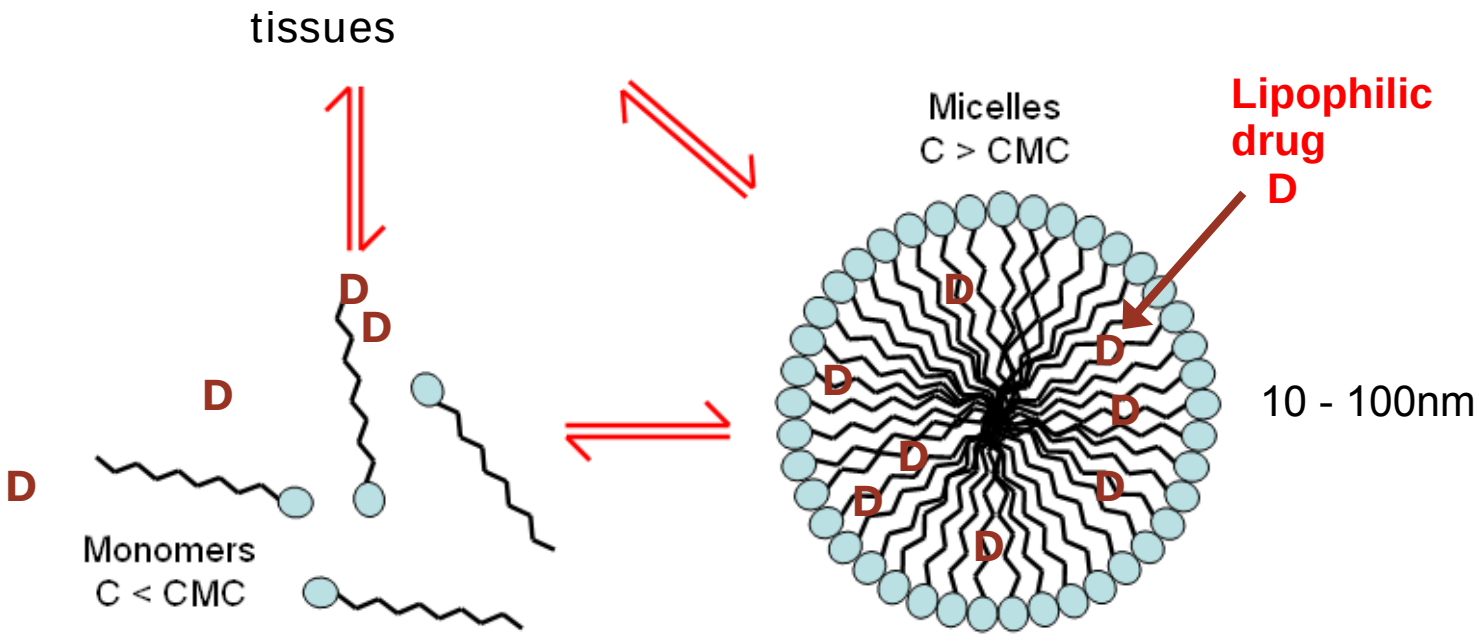
e.g. Polysorbate 80



A metastable situation, dependent on temperature, dilution, infusion fluids, etc. Problems of physical stability, tolerability,

Also, there have been questions about Bioequivalence – even in IV injections

Self-Assembly of surfactants can solubilise water-insoluble drugs in micelles - but if present *in vivo* they can act as an additional phase in competition with the drug target



Complex Formulations - 1

Micellar Formulations:

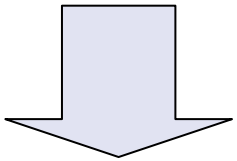
polysorbate 80 forms micelles in the product, but after infusion *in vivo*:

- is diluted below the capacity to form micelles
- is metabolised quickly; a micellar phase does not re-form during infusion

i.e. concerning its impact on bioavailability / equivalence,

the micellar phase is not a big problem if it does not exist *in vivo.*

- Full Physico-chemical characterisation of the reference product and generic 'in the bag'
- Bio-relevant modelling of the administration process to show minimal contribution of a micellar phase in both the reference product and the generic.



Biowaiver : Reduced need for bioequivalence studies : QWP Reflection Paper

Complex Formulations - 2

Liposomal injections

e.g. Doxorubicin hydrochloride (Caelyx)

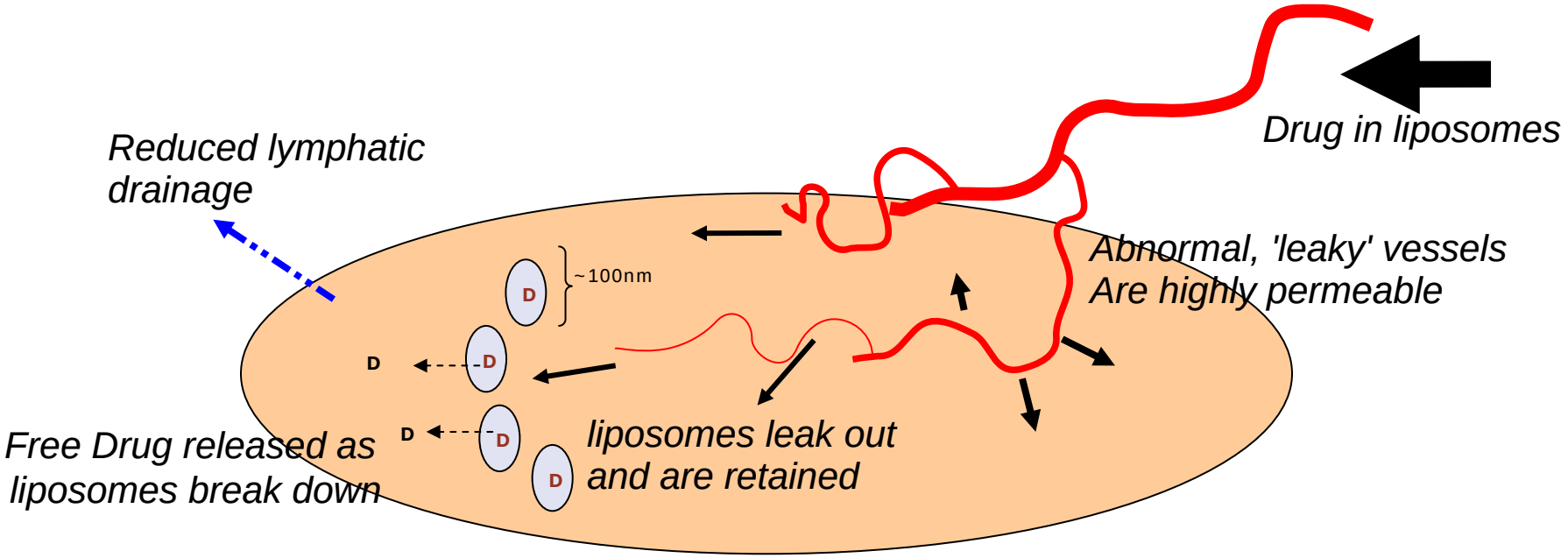
- Not necessarily Solubilisation of insoluble lipophilic drugs
- Better drug targetting and control of disposition
- increased halflife, especially with PEGylation of the liposomal surface

Amphotericin B – national – fatalities reported with different lipid/liposomal forms

Morphine sulphate – national

Nanostructures concentrate in solid tumours

The EPR effect (Extended Permeability and Retention)



Localised effect inside and around tumour, depending on size and surface characteristics

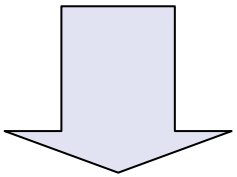
Opportunities for increased local efficacy and reduced systemic toxicity

comparisons between reference and 'generic' liposomes : (draft reflection paper)

Can we develop *in vitro* Quality tests to model the EPR context in oncology ?

A comparison of quality characteristics is fine *in vitro* but what do they mean *in vivo* ? What determines *in vivo* disposition ?

- Mean size and size distribution
- Liposome composition
- Surface charge, but you can't really see it if its PEGylated or has a corona of associated plasma proteins.
- Prolonged liposomal 'entrapment' in plasma vs rapid release of drug *in situ*
- Many other quality uncertainties



Unlike micellar products, it is very difficult to model these intracellular processes

Probably no *in vitro* biowaivers here !

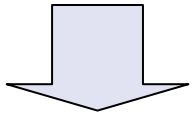
Furthermore, is a classic plasma-based bioequivalence study enough? What would you measure ?
Probably need animal disposition studies. - - - -> hybrid rather than generic ?

Complex Formulations - 3

Carbohydrate complexity and relative tissue disposition of nanosize structures

Iron Sucrose generics : a differential safety problem ?

These are not precisely-defined, there is physicochemical variability and a report of increased toxicity with generics, compared to the innovator….



CHMP/SWP : Reflection Paper on NonClinical Studies for generic nanoparticle iron products (March 2011)

Physicochemical characterisation is not enough.
Bioequivalence is not enough.
Animal disposition studies needed

Complex Active Substances

difficult to synthesise

Dydrogesterone (national)

Active not absorbed : **Orlistat** – need to compare clinical end-points, e.g. faecal fat levels

Substances of Variable Composition

Teicoplanin, Vancomycin, Glatiramer (Copaxone)

- Is it really “the same active substance” as the reference?
- Biological assay ?
- Extra non-clinical studies needed? (and maybe clinical?)
- A lot of work - Not a simple chemical generic?

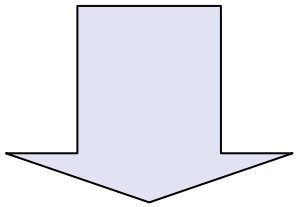
Complex Formulations and Complex Substances

Not all formulations are simple –not all chemical substances are well-defined.

This makes things difficult for a classic Art 10.1 generic dossier.

For complex formulations, we adopt a **"Biosimilar Approach"**

For complex substances, a new type of product: **"Chemisimilars"** ? *(P Bachmann CMDh Member from BfArM)*



- assessors need to think mechanistically.
- apply bio-relevant control tests and specifications.
- cooperation between Quality and PK experts.
- **We try to foresee these cases and to be prepared**

A recent Pharmacokinetic example

Mycophenolat mofetil – Parent Drug or Metabolite?

Normally the Parent compound is recommended → better sensitivity to detect formulation differences in the product

However, to be considered for the evaluation:

- Bioanalytical feasibility
- Pharmacokinetic properties of both parent and metabolite

For Mycophenolate Mofetil [MPM]

•Rapidly biotransformed into mycophenolic acid [MPA] (pharmacologically active)

•short half life of the MPM → difficulty to establish Cp(t) profile

⇒**Acceptable to use metabolite (MPA) data only to establish bio-equivalence**

⇒**(published position, see Q&A document on EMA website, Jan 2011)**

For the future

Eligibility – broader vision?

Timetable adaptation?

Best Practice Guide on exchange for information between EMA and CMD/MS

Active Substance Master File assessment exchange?

CHMP Work programme on generics:

http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2011/01/WC500101505.pdf

EMA Procedural advice for generic/hybrid applications in the Centralised procedure

Updated in January 2011

What is new?

Set of questions and answers on Usage Patents

Question & Answer re: user consultation

What has been updated?

FAQs e.g. identification of reference medicinal product, consultation of Name Review Group, data protection, etc

- Reference to the new Variations Regulation