
Dr. René Thürmer
BfArM - Federal Institute for Drugs and Medical Devices
AGAH Workshop on Liposomal Formulations
Bonn / 21. September 2012

EMA Activities

• 1st International Workshop on Nanomedicines, September 2010, London
• Need of pooling regulatory expertise
  – to provide sound Scientific Advice
  – to establish regulations for safe approval of 'generic' nanomedicine products
• Expertise for upcoming new nanomedicines is required
CHMP Drafting Group on Nanomedicines

- Established in November 2011
- Multidisciplinary Group
  - 3 Quality Experts
  - 3 Non-clinical Safety Experts
  - 3 Pharmacokinetic Experts
  - 3 Experts from Academia
- 2 F2F Meetings in 2012
- Virtual Meetings (TC, E-Mails)

CHMP Drafting Group on Nanomedicines

- Reflection paper on data requirements for intravenous liposomal products developed with reference to an innovator product (public consultation finalised)
- Reflection paper on non-clinical studies for iron oxide nanoparticles - proposal for an extension of the document to incorporate Q and PK elements
- Joint EMA/MHLW reflection paper on block copolymer micelles
- Reflection paper on nanoparticles coating
QWP Activities

- QWP (Quality Working Party) Sub Group
  - Liposomal Drafting Group (5 quality experts)
  - Discussion of quality sections for EMA Scientific Advices on liposomal formulations
  - Discussion of quality comments received after public consultation of the reflection paper

BfArM – Nanomedicine Working Group

- Identification of scientific issues based on the review of current experience
- Expertise from
  - Clinical trial unit
  - Licensing departments
  - Pharmacovigilance
  - Medical devices department
- Exchange with European and International experts
- Internal education and training
- External contact point
- Contact: nanomedizin@bfarm.de
The critical quality attributes of liposomal formulations may have a major impact on the in vivo PK and PD properties:

- Release rates from the liposomes can affect PK and PD and therefore the safety and efficacy profile of the medicinal product.
- PK of the encapsulated substance may be controlled by the PK of the liposomal formulation which is influenced by:
  - physicochemical properties of the liposomes
  - physico-chemical state of the encapsulated drug substance
  - interactions between the components of the liposome and the biological environment

- Pharmaceutical comparability between the applicant’s product and the innovator product should be established before progressing to non-clinical and clinical investigations.
- Establishing pharmaceutical comparability to the reference product alone cannot replace the need for non-clinical and/or clinical data but may justify reduction in the amount of such studies.
- The extent and complexity of clinical and non-clinical studies should be driven by the results of the comparability work at each stage.
Quality Characterisation

- Critical discussion of the lipidic components (description, source and characterisation, manufacture, assay, impurity profile, isomers and stability characteristics)
- Quality, purity and stability characteristics of other critical excipients
- Identification and control of key intermediates in the manufacturing process
- Active substance/lipidic moiety ratio at relevant manufacturing steps to be within acceptable range to ensure consistent formulation performance
- Liposome morphology, mean size and size distribution, aggregates

- Fraction of encapsulated active substance (amount of free/entrapped)
- Stability of the active substance, lipids and functional excipients in the finished product, including quantification of critical degradation products
- Reliable and discriminating validated in-vitro release methods should be developed to:
  - monitor the simulated release of the active substance from the liposomes in physiologically/clinically relevant media
  - if justified an in-vitro leakage test in relevant media under multiple conditions (e.g. range of temperatures and pH values) could be appropriate
Quality Characterisation

- Batch to batch consistency
- Stability on storage
- Stability studies under proposed in-use conditions
- Robustness of process for reconstitution and/or pharmacy preparation

Quality Characterisation

- Quality and purity of the lipid starting materials is essential
- Appropriate characterization and specification of the lipid starting material is considered as vital
- Functionality-related characteristics as described in the Ph. Eur. monograph 5.15 ‘Functionality-related characteristics of excipients’ should be adequately addressed
- The level of information to be provided with the relevant submission depends on complexity of the excipients
- Use of multiple sources (e.g. animal, plant, synthetic sources) or suppliers for the lipid components would require additional characterisation and comparability studies
Quality Characterisation

Depending on the specific function of the liposomal formulation the additional parameters should be also considered:

- Maintenance of liposomal formulation integrity in plasma
- Characterisation of lipid bilayer phase transition behaviour (e.g. temperature and enthalpy of transitions)
- Determination of liposomal ‘surface’ charge
- pH of internal compartment for pH-gradient loaded liposomes
- Characterisation of physical state of the active substance inside the liposome (e.g. precipitation in the case of doxorubicin) - if relevant

Quality Characterisation

- Distribution of drug substance within liposome (e.g. surface, bilayer, interior, etc.)
- For conjugated (e.g. pegylated) liposomal formulations:
  - details of linkage chemistry
  - molecular weight of conjugated lipid and size distribution
  - disposition of e.g. PEG at surface
  - stability of conjugation
Establishing Pharmaceutical Comparability

- The qualitative and quantitative composition of the developed product should be identical or closely match the reference product.
- Extensive investigations using state of the art characterisation methods should be applied to both products in parallel in order to demonstrate that the characteristics are comparable.
- Such studies should include all the relevant tests mentioned in the reflection paper.

Establishing Pharmaceutical Comparability

- The relevance of the selected tests for equivalent performance of the drug product in vivo should be discussed. Any differences between the products identified in the comparability investigations should be addressed and thoroughly evaluated and justified with regard to implications on safety/efficacy.
- Comparative stress test studies of both products, should be conducted in order to compare physical and chemical degradation.
Pharmaceutical Development of the Applicant’s Product

- Well-defined manufacturing process for liposomes with satisfactory process controls is required
- Small changes to liposomal products can significantly influence their performance
- Approaches to determining the impact of any process change will vary with respect to
  - the specific manufacturing process
  - the product
  - the extent of the manufacturer’s knowledge and experience with the process and development data provided
- Comparative investigations should be undertaken when a change is introduced into the manufacturing process during development but also after marketing authorisation (e.g. for scale up)

Pharmaceutical Development of the Applicant’s Product

- In vivo studies may be necessary to demonstrate that any changes do not affect the safety and efficacy profile of the product when results from physicochemical testing indicate a change in the properties of the product
- It is recommended that the applicant should consider the basic principles as outlined in section 1.4 of ICH Q5E (Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process)
ICH Guideline Q5E – Comparability of Biotechnological / Biological Products

- **Scope**: Demonstration of comparability after changes in the manufacturing process
- Changes in process / scale / equipment / facility could result in major changes in product
- Analysis before and after manufacturing changes including non-routine characterisation methods
- Comparison of in-process controls
- Process validation data
- Purity testing
- Stability testing

External Quality Comments after Public Consultation

- Quality comments received from 8 stakeholders
  - Regulatory agencies
  - Big Pharma
  - SME
  - Manufacturers of generics
- Very specific comments have been received
- Inconsistencies and potential misunderstanding could be overcome Many comments addressed in-vitro dissolution
- All comments will be published on EMA website
External Quality Comments after Public Consultation

• Comment from European regulatory agency:
  – To include additional general parameters and attributes in comparability exercise and text of the reflection paper
  – To include specific analytical techniques in the reflection paper

It was decided to include only attributes relevant for liposomes
No inclusion of specific analytical methods

Assessment of Submissions – Open Issues

• Which extent of characterisation / comparability will be required / is acceptable?
• What is similar?
• Which differences in numerical values for certain attributes are acceptable?
• Source of reference product

• More experience is required – will likely be available after assessment of future applications
• Experience from biosimilar applications over the last few years showed that experience of assessors is increasing
What was the recommendation of the CHMP at that time?

Based on the review of the data and the company’s responses to the CHMP lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Doxorubicin SUN could not have been approved. Based on the data submitted, the CHMP was of the opinion that the studies did not provide enough evidence to show that Doxorubicin SUN was similar to the reference medicine. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the company had not provided enough data to support the application for Doxorubicin SUN.

Scientific Advice

- Scientific Advice is highly recommended in the conclusion of the reflection paper
- Numerous EMA Scientific Advices have been given for liposomal doxorubicin and amphotericin
- Content of Scientific Advice is in agreement with the content of the reflection paper
- Scientific Advice is available from EMA or National Competent Authorities
... thank you

The views expressed in this presentation are those of the speaker and do not necessarily represent those of the BfArM and other European Regulatory Agencies.