

Workshop Conclusions



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Characterisation of biological molecules

Workshop 1



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Biosimilarity

- Some differences may be expected
- Comparability exercise relies on thorough characterisation
- Analytical comparability determines the extent to which non-clinical and clinical studies may be reduced



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Guidelines

- WHO guideline on similar biotherapeutic products
 - Scope
 - IN: well-established and well-characterised biotherapeutic products such as recombinant proteins
 - OUT: vaccines, plasma-derived products and their recombinant analogues
 - Challenges: diversity of national requirements worldwide, diversity in terminology
- EMA guideline on biosimilar mAbs
Draft expected end of 2010



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Conclusions

- Comparability is an issue for innovators too
- Need to apply QbD principles to comparability studies
- Understanding of product is critical for definition of CQAs
- Analytical techniques available, selection is key



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Pharmacopoeia

- Rely on compendial tests / assays
- Acknowledgment: impact of monographs +++ (standardization, unitage)
- However, monographs too general, slow revision process
- Solutions:
 - alternatives allowed if equivalence shown
 - Ph. Eur. Should be informed when new state-of-the-art methods available
- Issues for further consideration
 - Should standardisation of immunogenicity test methods be tackled?
 - Reagents for testing



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New technologies and their impact on the Pharmacopoeia

Workshop 2



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QbD /RTRT is already reality in industries – a case study was presented where an EMA approval was granted in 2009. Many companies are successfully using this approach and more applications are expected in the near future.

QbD can result in a win-win situation for both industries and regulators – e.g. reduction of variations, less rejections...

Approach can be applied for both API and finished product but is mainly being used for finished products – RTRT – limited impact on API monographs / standards.



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Importance to use correct terminology and to avoid “in-house” vocabulary was underlined to avoid misunderstandings.

Moreover, it is crucial to demonstrate a science and risk-based approach – discussion and demonstration of knowledge is essential in a submission for MA.

Acceptance of RTRT approach requires process understanding and control strategy. It is handled both by assessment and inspection (GMPinput).

As regards biological products the concept of RTRT is already applied in practice. No special requirements for concept, but adaptations are necessary.



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Regulatory Guidance (RTRT)

Parametric release guidance (CPMP/QWP/ 3051/99) (Sep. 01) primarily based on sterile products

Draft guideline on RTRT (CPMP/QWP /811210/2009 Rev.1 – consultation deadline 31/08/10).

EDQM / European Pharmacopoeia

Already allows flexibility (e.g. parametric release, use of alternative methods).

PAT WP

e.g. adaption of NIR general method to PAT needs, sample size and acceptance criteria for uniformity of dosage units (2.9.40)

Future focus: e.g. additional spectroscopic methods.



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Industries stressed the importance of a dialogue / close co-operation with regulatory bodies and would appreciate additional regulatory guidance, e.g building and maintenance of models and criteria for model acceptance.

Challenges

- Currently limited experience on both sides (industries and regulators) but expected to rapidly increase
- How to report RTRT on CoA
- Qualification of staff
- Translation of specifications into RTRT acceptance criteria
- How to treat data outside the Design Space
- Handling of « Control Space » (which is focus for inspectors) by quality assessor; close liaison is required
- Validation/verification strategy of a DS.



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Control of Impurities – A challenge for all stakeholders

Workshop 3



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Use of Fast-LC (1)

- Fast LC is more and more used
- Introduction in monographs depends on provision of validated methods by industry
- Industry viewpoint: development only viable for new substances/products
- Does migration to fast LC require validation? Yes! To what extent?



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Use of Fast-LC (2)

- Availability of stationary phases to be improved
- Revision proposal chapter 2.2.46 will appear soon
- Feedback highly appreciated



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Control of purity and impurities by NMR

- NMR seems now to offer a variety of options
- Identification, residual solvents,
- Control of impurities???
- Quantification/assay ???
- NMR was challenged in terms of
 - Cost, Availability
 - Validation requirement
 - Justification if used in monographs



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LC-MS techniques

- LC-MS instrumentation evolves rapidly
- Method description has to allow for flexibility
- Not yet an universal detection method
- Rather optimized for individual impurities or specific topics (such as counterfeits)
- Acceptance criteria for method performance to be discussed (RSD, response etc., choice of internal std)



Combating Counterfeiting

- “counterfeit” what is it meant by that?
 - Counterfeits: lookalikes
 - Counterfeits: placebos...
 - Clones
 - Similar products
 - Spiked / adulterated API or products
 - Illegal products
 - Clarification in terminology is needed
 - Illustrative examples were presented and discussed



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Quality of Medicines in a Globalised World Dreams and Reality

International conference of the
European Directorate for the Quality of Medicines & HealthCare
(EDQM, Council of Europe)
14-15 October 2010, Prague

Workshop 4 sessions report

Application of 3R principles in a globalised world: dreams or reality ?



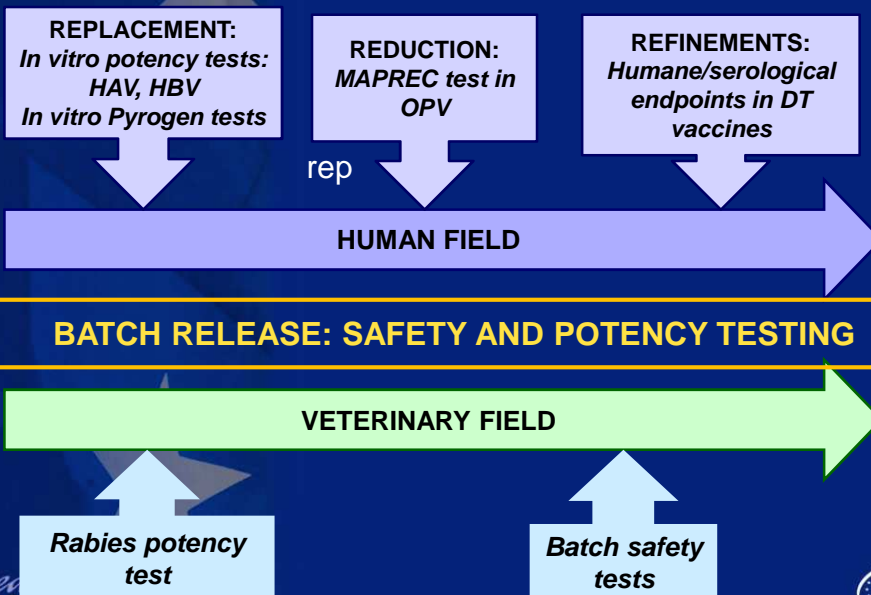
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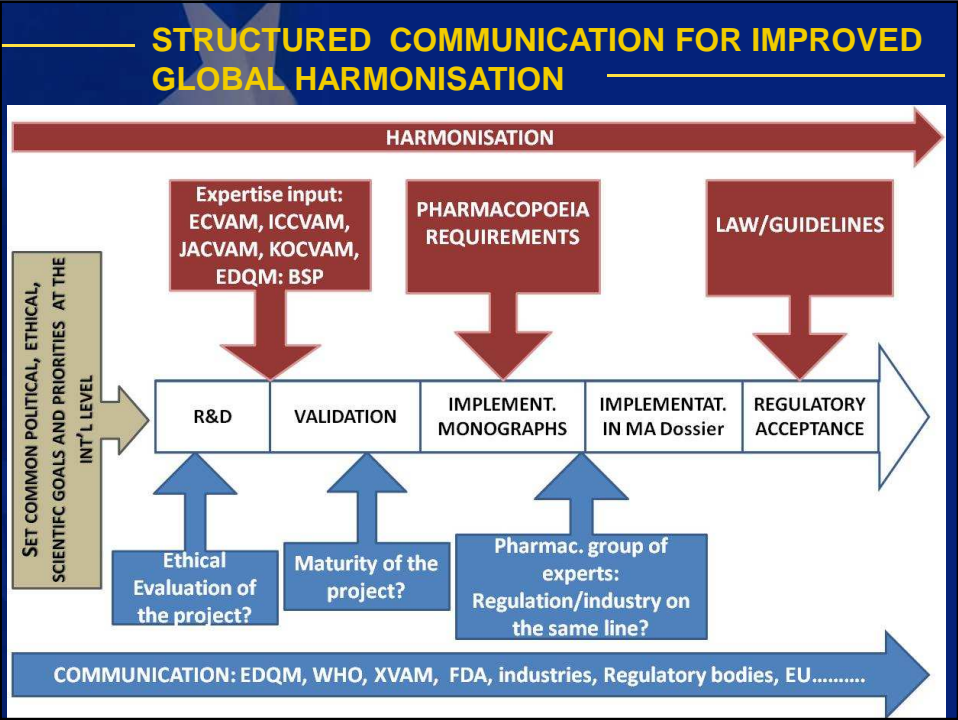
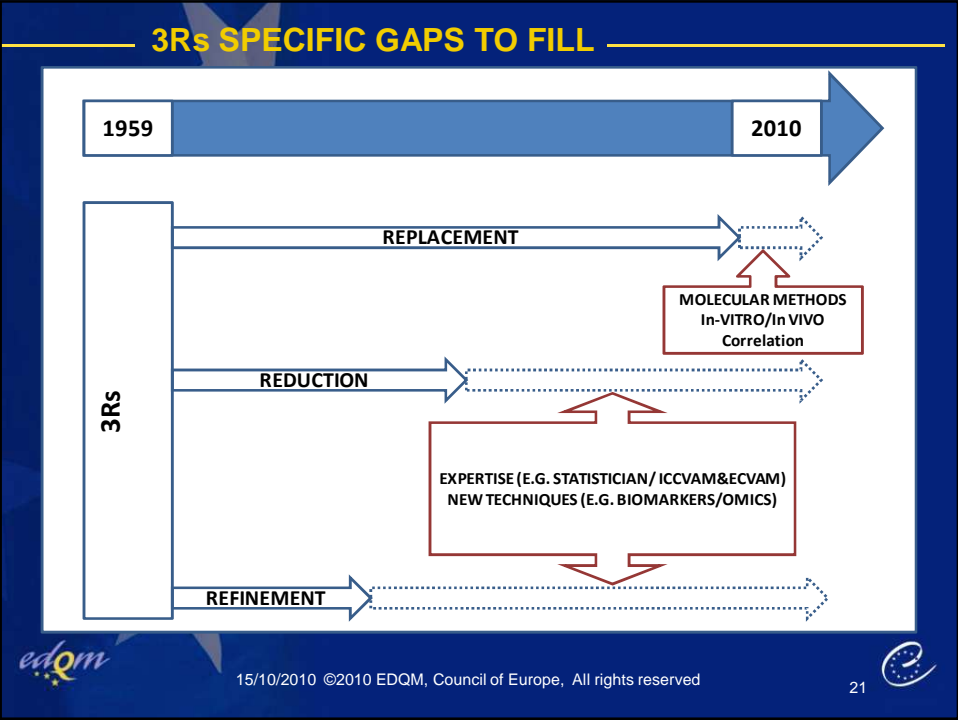


- Challenges for the application of the 3R principles globally
Prof. D. Morton
- European Pharmacopoeia achievements and perspectives
Dr L. Bruckner
- Food and Drug Administration (FDA) perspective
Dr K. Chumakov
- Achieving the 3Rs in a globalised world: feedback from VICH
Dr K. Grein
- Korean perspective
Dr J. Jopung
- European Vaccine Manufacturers' perspectives
Dr C. Ponsar



EXAMPLE OF ACHIEVEMENTS





Better communication for improved harmonisation

- **Between control laboratories, manufacturers, academics**
 - for optimised use of resources
 - for development of common alternative methods
- **Between regulators (national, regional, global)**
 - for harmonised global requirements
- **Between all parties**
 - for better acceptance (education for attitude change)
- **Call for balance between 3R and risk management**
 - scientific bases of the alternative methods
 - clinical relevance vs consistency testing of products, also depending on:
 - (long) history of product manufacturing (“good old products”)
 - GMP compliance of production & post-marketing surveillance

The PhEur – Is it prepared for the future?

Workshop 5

- All stakeholders agreed that PhEur is prepared for the future.
- PhEur is recognized as necessary and accepted standardisation tool in European regulatory system.
- Mechanisms for adaptation to the changes of scientific, technical and regulatory environment are available.
- Flexibility is given by general notices and general monographs.
- Adaptation to the globalisation is given by CEP procedure and transparency list.
- Adaptation to new quality paradigm (e.g. PAT) has started
- Some processes for compendial harmonisation are available



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Further improvements proposed:

- More user- friendliness of the Pharmacopoeia
- Need and use of finished product monographs, including concept of flexible monographs (pros and cons)
- Integration of new technologies (e.g. UPLC, Raman)
- New approaches for harmonisation
- Possibility of mutual regulatory acceptance of non harmonised compendial tests
- Faster and regular update of the monographs
- Adaptation to new quality paradigm needs further improvement or measures



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A DREAM FOR THE FUTURE

- Based on the example of the Ph Eur in 1964, create a new global pharmacopoeia.
- Political decision must be taken and legal framework must be established beforehand.
- Collaboration between Regulators, Industries and Pharmacopoeias.
- Need of agreed working procedures including all parties



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Conclusion

- **The European Pharmacopoeia: is it prepared for the Future?** → Yes with continuous adaptation to regulatory, technical and scientific challenges.



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