New Frontiers in the Quality of Medicines

Workshop Conclusions
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Updating monographs & methods
Modernizing monographs & methods

• EP work programme takes account of revision requests and modern monograph submissions

• Updated general methods e.g. NMR, ICP GC-MS methods are in place and were demonstrated to be powerful tools. This allows further evolution of monographs
**Updating monographs & methods (2)**

- **Areas of particular interest:**
  - Heavy metals test to be rediscussed when EMEA-GL on metal catalysts and reagents becomes effective
  - Instrumental method for colour determination needed to harmonise the ICH-Q6A related general methods within PDG. Should be added to 2.2.2 as an alternative approach to visual examination
  - Revision of chromatographic separation techniques (2.2.46) should be adopted and preferably considered for subsequent PDG harmonisation

**Excipients: FRC & ICH Q8 (1)**

- **FRC: a controllable physical characteristic of an excipient that is shown to impact on its functionality**
- **Non-mandatory FRC section added to excipient monographs to inform about FRCs that may be critical for the intended function of the excipient**
- **Information on an FRC:**
  - name
  - name and methodology
  - name, methodology, typical values
Excipients: FRC & ICH Q8 (2)

• FRC concept in line with “quality by design” cf. ICH Q8
• Critical characteristics to be identified during development work
• Depending on the application, an FRC may or may not be relevant, thus …
• FRC section contributes to the desired regulatory feasibility

Pharmacopoeial Discussion Group (PDG) & ICH Q4B(1)

• The essential aim of the ICH Q4B EWG is to develop a harmonised regulatory assessment of texts signed off by the PDG
• The group has developed a guideline defining procedure and will add a specific annex for each text that is assessed
• The guideline and the first annex should be finalised in 2007
• This harmonised view should ensure that regulatory submissions based on signed-off chapters will be acceptable in all 3 ICH regions
Pharmacopoeial Discussion Group (PDG) & ICH Q4B(2)

- EFPIA is supportive of the activities of the PDG and Q4B but finds the work much slower than expected
- PDG representatives outlined the achievements (sign off) over the last few years:
  - About 40 excipient monographs
  - 10 of 11 Q6A general chapters
  - 6 biotech general chapters
  - 7 powder characterisation general chapters
- Will Q4B assess these signed off texts

New challenges for Pharmacopoeias

- New quality vision by industry and regulators supported by the ICH Q8, Q9, and Q 10 guidelines
- Design space & PAT as important elements of the control strategy
- Discussion on Quality by design
- Ph. Eur. allows already alternative approaches and parametric release
- CEP links pharmacopoeial specifications and manufacturing process
New challenges for Pharmacopoeias

- QbD Products: testing would differ from traditional testing
- Specification setting would differ based on product performance
- Monographs will play an important role for shelf-life testing
- Move to real-time release
- Compliance with the specification - if tested - still required

Reference standards: how to characterise them, key elements and qualifications

• Biological
  - Three approaches in establishment depending on type of substances
  - Peptides/proteins of known chemical structure: primary standards as CRS by physico-chemical analyses. Replacement batches in the same way. Alternative suggestion first standards retained for calibration of secondary standards
  - First standard established expressed in mg of proteins with potency. Subsequent batches calibrated against previous batch.
  - Potency assays in vivo and in vitro differently not yet resolved in expression of potency moving from in vivo to in vitro methods
Reference standards: how to characterise them, key elements and qualifications (2)

- Chemical
  - Well established procedures for establishment of CRS
  - Uncertainty of measurements is not taken into account as included in the content limits

Quality standards for biologicals (1)
Biotech products: characterisation

- There remains a characterisation gap in Pharmacopoeia monographs for some biotech products
- The gap becomes more significant as second-generation products are developed
- The gap is being filled but creative thinking is needed for setting of specifications
Quality standards for biologicals (2)
Biotech products: characterisation

- Glycan mapping is being developed as a key technique for bridging the characterisation gap
- The range of possible techniques is bewilderingly large, even under the heading ‘glycan mapping’
- Different methods are often not equivalent
- Reference standards to judge method performance will have an important role

Quality standards for biologicals (3)
Monograph development

- Two examples: chondroitin sulphate (animal origin), filgrastim (recombinant DNA product)
- Chondroitin sulphate: co-operation with all manufacturers led to a single, well founded monograph for a substance from a wide variety of sources (avian and mammalian terrestrial, marine)
- Filgrastim: innovator initially reluctant to participate but progress is being made towards a satisfactory monograph
Quality standards for biologicals (4)

Monograph development (2)

• For biotech products will innovators co-operate? Despite reluctance, they have nothing to lose
• What does a monograph mean: scientifically based quality specification for routine production: no waiver for upstream development work, which is described in guidelines from licensing authorities
• See also the general monograph ‘Products of recombinant DNA technology’

International Harmonisation: Microbiological Techniques (1)

• Implementation of the internationally harmonised chapters: EMEA to publish detailed Q&A on their website
• The new chapters have raised a number of questions from users, which illustrate:
  – The need to educate the users
  – The need to make small changes to the chapters
• Future activities related to the chapters
  – EDQM will publish a detailed Q&A on the technical aspects of the chapter
  – The PDG will study possibility to revise the chapters
European Biological Standardisation Programme (BSP) (1)

• Standardisation is a pre-requisite for licensing and quality assurance of biologicals
  – Ensure sustainability of activities in providing written, physical standards and standardised methodology
  – Ensure sufficient funding of resources and development in standardisation
  – Involve Industry

European Biological Standardisation Programme (BSP) (2)

• Be pro-active and anticipate development of next 10 years eg
  – Standardisation of measurement of immune responses
    • Antibody formation (coagulation factors, EPO, IFN): unwanted responses
    • Response to vaccines: wanted response
    • Endogenous substances modified on purpose (eg pegylated molecules)
  – Foster standardisation of methods used in different countries/regions

– Continue and increase communication/collaboration/worksharing between different partners
  • Eg with regulatory authorities, WHO, partner organisation in other continents (USA FDA, TGA, Health Canada, JP & China)
  • Eg by involvement of OMCLs in pre-licensing activities/testing.
Herbals: implementation of the new legislative framework (1)

- Regulatory tools for registration and marketing authorisation are already in place (Dir. 2001/83 as amended by 2004/24 & 2004/27)
- More regulatory experience needs to be gained with traditional and well-established herbal medicinal products
- Companies can profit from the Certificate of Suitability
- Good quality of the herbal drug preparation in accordance with Ph.Eur monographs will ensure a safer and more efficacious herbal medicinal product

Herbals: implementation of the new legislative framework (2)

- In contrast to dietary supplements, traditional herbal medicinal products will guarantee quality, efficacy and safety
- The registration procedure provides the opportunity to go from a dietary supplement with medicinal indication to a medicinal product with a therapeutic claim
- Listing products as traditional herbal drugs/preparations and combinations according to article 16f together with the Ph. Eur. monograph facilitate access to the market
- Community herbal monographs according to article 16h allow more flexibility than is currently assumed.
Herbals: Traditional Chinese Medicines (1)

- Traditional ethnic medicinal products are becoming more and more important in Europe like TCM, Ayurvedic, South American or African herbal drugs.
- For safe use by the patient/consumer, quality control is essential.
- For the development of Ph. Eur. monographs, authentic reference materials and reference compounds are essential.
- Collaboration with Chinese counterparts is important and should be increased.

Herbals: Traditional Chinese Medicines (2)

- Harmonisation of quality standards should be further encouraged between China and Europe.
- In case of any processed herbal drug, it has to be decided whether the definition corresponds to a herbal drug or herbal drug preparation.
- A new working party on TCMs has been decided by the Commission and will start work in 2008.
Homoeopathy (1)

- Monographs in Ph. Eur. 6th edition
- Regulatory exchange and co-operation
- MRP/DCP open for simplified procedure
- Expectations for HMM and HOM Pharmacopoeia WG
- Manufacturers reach a higher quality level for products with natural variability

Homoeopathy (2)

- Different interpretations of quality requirements between MSs
- Predominant different national (Pharmacopoeia) homoeopathic traditions
- Building up regulatory experience is trial and error
- European Pharmacopoeia cannot solve everything!

- Way for the future: certification of suitability for homoeopathic mother tinctures…?
Certification: how to use a certificate (CEP) (1) - Points for improvement

- Delay for 1st assessment of new applications and quinquennial renewals.
- Recognition of CEPs by National Authorities: avoidance of requests for data already assessed.
- Reduction of the burden linked to revision of CEPs:
  - In line with revision of regulation on variations.
  - End of incrementation of revision number for unchanged content.
  - Attempt at harmonisation of the approach between Authorities for treatment of revisions.
- Non sterile substances: Policy for microbiological purity to be defined.

Certification: how to use a certificate (CEP) (2) - Possible further development

- Need for systematic assessment of stability studies: re-test period no longer optional but mandatory.
- Development and acceleration of the process of elaboration of new monographs.
- Extend the scope of certification to non-Ph. Eur monographs.
Certification: Inspection (1)

- Inspection is “product specific”, but in case of GMP non-compliance, action on other products can be considered (on a case-by-case basis).

- Need for developing a system for rapid and harmonised actions and sanctions for the non-compliant sites (with EMEA and concerned authorities).

- Need to control all the supply chain from the manufacturing site to the product distribution (traders, etc…).

Certification: Inspection (2)

- Networking is essential with collaboration of all stakeholders (inspectors, manufacturers, regulators, …) at national/international levels:
  - to optimise resources,
  - for more transparency,
  - for sharing information (developments of Eudra GMP, etc…),

- Consideration of third party audit reports during inspections
Partnership developed within the Official Medicines Control Laboratories (OMCLs)

• Continue QA activities and PTS activities as much as possible to foster work sharing

• Feed back OMCL results and expertise to assessors and inspectors

Partnership developed within the Official Medicines Control Laboratories (OMCLs)

Control activities

1. Pre-autorisation testing for biologicals & non biologicals by OMCLs
   non bio + bio
   Evaluation of methods
   Bio
   Contribution to evaluation of biosimilar products by independent testing

2. Creation of centers of expertise/excellents
   → e.g. combating counterfeits

3. OCABR substantially contributes to Quality/Safety efficacy of biological products (both Human+Veterinary)

4. Risk-based approach for sampling + testing will be taken more and more into account

5. Continue regular exchange between
   EDOM/EMEA/Industry/HMA’s etc recommended
Building a partnership for the investigation of counterfeit (1)

- Facts:
  - Counterfeits are a major public health concern
  - Worldwide increased number of counterfeit medicines via legal or illegal distribution chains
  - European Network of official medicines control laboratories owning appropriate skills/experience and equipments
  - Industry associations and International Organization/Health Authorities established Task Forces devoted to develop concept/solutions to circumvent the issue
  - Absence of harmonized legislation regarding the role of the different stakeholders (Health Authorities, police, customs, industries)

Building a partnership for the investigation of counterfeit (2)

How to improve:

- Knowledge sharing:
  - Access to essential information (analytical methods, fingerprints, reference standards, authentic samples, packaging security systems, …)

- Work sharing:
  - Centers of expertise
  - Testing/Inspections (risk-based)
  - Improved communication system through secured databases
  - Ensure the integrity of each step of the supply chain

- Educational measures:
  - Public policymakers/patients awareness (internet sales, safety)
  - Brokers/traders/wholesalers: parallel importation requires special attention

- Harmonization of legislation and strengthening of laws and enforcement