Clinical Trials for Biotechnology Medicines

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• A personal viewpoint

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Relevant Properties of Biotechnology Medicines

• **They are Biological Medicines**
  – The active ingredient and/or key excipients have been derived from living organisms or tissues, or manufactured using a biological process.

• **Expectations for Biological Medicines Registration**
  – Controlled Consistent Manufacturing process
  – Release specifications relate to biological activity
  – Clinical trials show Safety & Efficacy of formulation
Expectations for a Biological Medicine

• **Non-clinical & Toxicology**
  – May be limited requirements e.g. vaccines

• **Clinical Trials**
  – PK & PD needed for many BioTech medicines
  – Phase I, II, & III Studies
    • The same API and formulation throughout
    • Conflation of phases for vaccines
  – Phase III studies in target population
  – If prophylactic - Phase IV in use.
  – Post marketing Risk Management
Why should Bio-Tech Medicines be different?

- **The BT API may be much better defined**
  - Physico-chemical characters
  - Levels of impurities Limited range of iso-forms

- **What about Follow on B-T Medicines**
  - Can be registered as a new Biological Medicine
    - Different Name
    - Can only claim indications, as proven in Clinical Trials

- **Abbreviated Registration as “BioSimilar” ? BUT**
  - Different Manufacturing process
  - Different molecular structure - perhaps
  - Reduced clinical studies
  - Use data from “originator” product to support application
  - Intention is “INTERCHANGEABLE” use?
Approach of EMEA

• **Guidelines CHMP/437/2004**
  – Comparability of Biotechnology proteins in medicines
  – Specific guidelines published for rhEPO, rhGH, etc.

• **Define Comparator**
  – Registered product &
  – Form, strength & route - the same.

• **Not suitable for**
  – vaccines,
  – allergens
  – blood products
WHO Initiative - April 2007

• WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products.

• Issues & Problems reviewed
  – Many disparate views and approaches:
  – Different policies in use world-wide -EU-USA-India-Iran/etc.

• OUTCOMES
  – Proposed to Draft Guidelines (compatible with existing)
  – Use “Biosimilar” as interim terminology.
  – Limit to r-protein products (Exclude MAbs & Vaccines)
  – Establish a Working Group to report to ECBS in October
What will SA do NOW

• **MCC Draft Interim policy on Biosimilar Medicines**
  - A Biological medicine is where the active ingredient and/or key excipients have been derived from living organisms or tissues, or manufactured using a biological process.

• **Extracts are :-**
  - The Biosimilars Task Team will develop local policy and guidelines regarding registration of biosimilars and biological medicines.
  - In the interim, the MCC will follow the EMEA guidelines on biosimilars, unless there are local issues that are overriding.
  - Biological medicine applications will be considered by the BMC
  - Biosimilar medicines will be reviewed on a case-by-case basis.
MCC Draft Policy for Biosimilars

- **Information Required for Registration**
  - Full information on quality and consistency of manufacture
  - **Non-clinical and toxicology information**
  - Comparison to registered “originator” (not another BioSim)
  - Physico-chemical characterization & comparisons
  - **Clinical Studies**
  - Comparative PK & PD studies in animal & humans
  - Comparative Safety studies and PM risk management
  - Comparative efficacy studies - bridging Ph-III
  - Immunogenicity studies (may be comparative)
Clinical Trials of Biotechnology Medicines

- Defined formulation
- Full information on quality and consistency of manufacture
- Reports of non-clinical and toxicological studies
- Reports of prior clinical trials with defined formulation
- Protocol is Scientific and Ethical
- Requirement for comparator if bio-similar
- Inclusion of immunogenicity studies
Current problem areas

- **Vaccines: Combinations of antigens**
  - Extrapolation of information on components

- **Evaluation of manufacturing process changes for registered biological products**
  - Removal of preservatives

- **Flu vaccine - annual strain change**

- **Pharmacovigilance - differentiate products**
  - Record ADRs by Proprietary Name
What may happen in the Future

• Improved analytical characterization
  – Able to show physico-chemical identity
  – Development of clear surrogate of efficacy
  – PD could be accepted as evidence of efficacy

• Development of product-class guidelines

• Acceptance of WHO Guidelines
Conclusion

• Biotechnology medicines are Biological Medicines

• Biological medicines are reviewed differently

• Biosimilar medicines are a reality

• Abbreviated information for some may be accepted

• Current MCC policies are similar to EU

• WHO Guidelines will clarify situation