crowell moring

Biosimilars: Regulatory pathways and debated issues

Kristof Roox
Crowell & Moring (Brussels)
kroox@crowell.com

crowell moring

Introduction

Terminology

- Europe : Similar biological medicinal products (biosimilars)
- US : follow-on protein products or follow-on biologics
- Similar versions of originator reference products containing recombinant DNA-derived proteins

Scientific discussion

- Can biological products be replicated in a manner that ensures quality, safety and efficacy given their complex nature?

crowell moring

Introduction

Omnitrope® and Valtropin®

- First approved biosimilars in Europe:

  - Omnitrope®(Sandoz): Submission (01/07/04) ; EMEA (26/01/06) ; EC (12/04/06) + FDA approval (after litigation against the FDA)

  - Valtropin®(Biopartners) : EMEA (23/02/06) ; EC (24/04/06)

- First refused biosimilar in Europe:

  - Alpheon®(Biopartners) : EMEA (negative opinion: 03/07/06)

  - Characterisation, manufacturing and quality control concerns

crowell moring

Introduction

The Omnitrope®story (1)

- 2001 : First attempt to obtain EU approval

  - application to have the product considered for **generic** authorisation based on a detailed scientific bibliography

  - accompanied by studies aimed at showing comparability with the reference product

- 06/2003 : CHMP issued a positive opinion
- European Commission (EC) decided not to follow the opinion
- 03/20004 : After legal action by Sandoz, EC publication:

  CHMP had improperly accepted Sandoz' application as a bibliographical application based on the well-established use of the medicine, while at the same time it had accepted/required comparability studies to be performed

crowell moring

Introduction

The Omnitrope®story (2)

- Sandoz appealed the EC decision with the ECJ:

  Sandoz contests that the performance of comparability studies implied that the legal conditions for the application of the bibliographical application procedure were not met.

- Second attempt after new regulatory framework

  - 01/07/04 : new submission

  - 26/01/06 : CHMP positive opinion

  - 12/04/06 : EC approval

- Clear example of a need for a regulatory pathway

crowell moring

Regulatory pathway (EU)

Long time to come up with a regulatory pathway:

- 2000/2001 EMEA Guidelines :

  - adoption of the International Conference on Harmonization guidance on comparability;

  - primarily dealing with variations to the manufacturing process by originators' own products, but also containing observations on applications of follow-on products by third party applicants not connected to the originator (only covering situations where the biosimilar is a linear descendant of the reference product e.g. when a production process is acquired by a third party??);

- 06/2003 (Directive 2003/63) Provisions on biosimilars into an Annex (Section 4, Part II) to the Community Code on medicinal products (Directive 2001/83/EC)

- End/2003 : General EMEA guidelines on comparability

crowell moring

Regulatory pathway (EU)

- 2004 : Pharmaceutical review (Directive 2004/27)

  - "definition" of biosimilar in article 10(4): merely stating that a biosimilar is not a generic and emphasizing what data are required (broad concept)

  - under same article as abbreviated applications

- 2004 : EMEA Guidelines

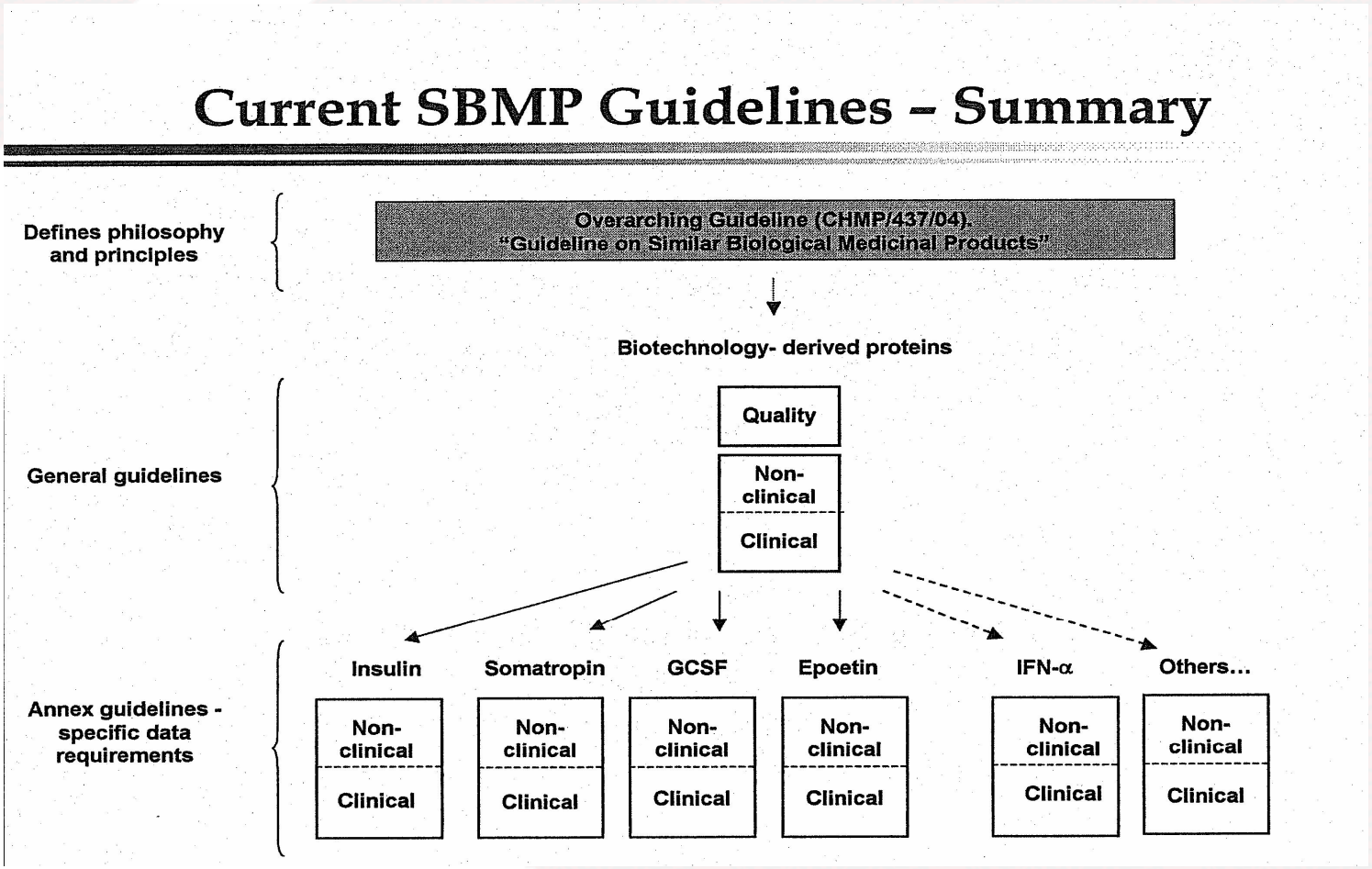
  - Latest step in In Europe's refinement of a regulatory pathway for biosimilars

  - Seven guidance documents issued to date describing general requirements for demonstration of the similar nature of two biological products in terms of quality, safety and efficacy with product-specific guidance

crowell moring

Regulatory pathway (EU)

EMEA guidelines: science based procedure



crowell moring

Regulatory pathway (EU)

- Overarching guideline (CHMP/437/04) defining philosophy and principles:

  "*The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived products. Due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for these products. The similar biological medicinal approach,* ***based on a comparability exercise****, will then have to be followed.*

crowell moring

Regulatory pathway (EU)

- Two general guidelines covering quality (CPMP/BWP/3207/00) and non-clinical/clinical issues (CPMP/3097/02) related to the assessment of marketing authorization application for biosimilars
- Four product-specific guidelines (Insulin, Somatropin, GCSF, Erythropoeietin)
- EMEA : These are open documents that can be discussed and amended ; learning process ; scientific advice is key

crowell moring

Regulatory pathway (US)

No regulatory pathway:

- 04/1999: Draft guidance on "Application covered by Section 505(b)(2) FDCA:

  - this section could be used to obtain approval for therapeutic protein products and sponsors could make change to the reference product if the change were supported by clinical data

  - goal : encouraging "different" generics;

- Innovator industry intimidated the FDA by continuously filing citizens petitions challenging the use of Section 505(b)(2) FDCA to approve biosimilars

- 2004/2005: increased attention

  - two public workshops (09/2004 and 02/2005) to address scientific and technical (but not legal) issues ;

crowell moring

Regulatory pathway (US)

- announcement of a White Paper “in the next months”, draft guidance documents and a third public forum

- nothing happened

- The US Omnitrope-story:

  - 07/2003: 505(b)(2) Omnitrope application

  - 2004: FDA declined that a decision could be made due to “unresolved scientific and legal issues”

  - 09/2005: Sandoz files a lawsuit against the FDA for failure to take action on its pending application

  - 04/2006: Court ordered the FDA to comply with its statutory obligation to act on the application

  - 06/2006: FDA approval

- Pressure from US Congress (Hatch and Waxman) to issue guidance documents:

crowell moring

Legal problems

Legal issues

- No specific new legal problems;
- Same rules as regards to generics will be applied : for example Bolar-provision (article 10(6) Directive 2001/83):
  - "*Conducting the* ***necessary studies and trials*** *with a view to the application of* ***paragraphs 1, 2, 3 and 4*** *and the* ***consequential practical requirements*** *shall not be regarded as contrary to patent rights as or supplementary protection certificates for medicinal producst*"
  - S*tudies and trials*? Type of studies and trials have been discussed but no list has been agreed upon at EU level

crowell moring

Legal problems

– *with a view to the application of* ***paragraphs 1, 2, 3 and 4***

- Generic abridged applications (10.1/10.2), hybrid applications (10.3) and biosimilar applications (10.4). Not for bibliographical applications or applications for new combinations.

- Limitation to applications in the European Union

- no exemption for all activities: e.g. use of trial information or production in Europe in support of applications outside the EU ; acts done for export (rejected by the European Commission*)* ; production for trials in support of applications outside the EU;

- Not applicable to experiments with the aim of proving product yield or a new variant of the patented product?

- What if the application for a MA fails?

– " *and the consequential practical requirements*" (application for a MA, filing, samples, P&R, production of commercial batches, stockpiling

crowell moring

Barriers

Preventing same INN for biosimilars

- INN = international, non-proprietary name
- Managed by WHO ; Nomenclature based on scientific rules
- Originators are proposing that biosimilars be given different generic names than brand-name biologics : this is not a science but a political issue
- INN issue is used to introduce hurdles for market entry of biosimilars. Unacceptable:
  - Extensive comparability testing has been completed
  - No innovator INN change when product/manufacturing process changes ; also not if variability in the glycosylation pattern between batches is seen (See also Interferon beta 1a : Avonex® and Rebif ®);
- EMEA: open discussion which will not influence MA registration process

crowell moring

Barriers

New traceability requirements

- An issue for all medicines ; needs to be considered holistically, not special case for biosimilars;
- Overarching guideline: "*in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified*"
- Hampered by standard pharmacy practice today ; Given current practice, is patient's safety ensured today?

  - Eprex® and Neorecormon® are not recorded on patients' notes

  - mostly EPO is recorded; sometimes Erythropoeitin;

  -hardly ever seen EPO alpha or EPO beta

crowell moring

Barriers

Interchangeability

- Hurdle of interchangeability might be higher than they already are for generics despite clear statements of equivalent effectiveness in biosimilars EPARs.
- If a biosimilar is not therapeutically equivalent, what else does 'biosimilar' mean;
- Investors : "Without substitution, there will be no generic market and hence no true competitive advantage for generic companies";

crowell moring

Barriers

Pricing and reimbursement

- Open question.
- National pricing and reimbursement authorities must not allow pricing to delay market access or maintain disincentives to use biosimilars
- Price setting must reflect added cost of development

crowell moring

Investor's view

Investor's view:

- Estimate total global sales of biologics in 2005 at $44bin
- This number is expected to grow substantially, due to new launches (mostly of antibodies) and growing sales of existing products
- Assumption : biosimilars will be priced at only a relatively small discount to original products resulting in a large potential market for biosimilars in the long term, with no impacted forecasts:

  - Explicit forecast sales of biosimilars for the major generic companied sofar = nil

  - Explicit forecast sales loss for originator products = minimal

crowell moring

Investor's view

- Biosimilars are expensive to develop (+/- €50min for relatively straightforward products)
- Characteristics of biosimilars : branded products, high R&D costs to bring to market, lower prices than the originator, but higher than classic generics, penetration low immediately after launch and grow relatively slow, sales force necessary to detail to specialists, marketing cost high, ongoing clinical trials necessary to support sales, head-on competition with originators
- These are the characteristics of originator products
- Biosimilars represent an important opportunity for the generic industry, but only for companies with an extensive R&D budget, an appropriate, marketing infrastructure and the necessary financial resources