European Union and U.S. Perspectives on Biosimilarity

CAPRA, Toronto
November 21, 2006

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- Counsels clients in the food, pharmaceuticals, medical devices, animal health and cosmetics industries on regulatory requirements of the European Union, the U.S. Food and Drug Administration (FDA) and the requirements of the agency's counterparts elsewhere.
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What is a Biosimilar?

A Biosimilar is not a Biogeneric

What are Biosimilars?

"Biosimilars" are products that cannot meet the criteria for "generics", generally because they are large-molecule proteins and one cannot be sure they are sufficiently close to the originator's product.

Each Manufacturer's Cell Line is Unique

As a consequence of this…….

Although the same cell line will have to be used, this does not guarantee an identical product

Immunogenicity is a Unique Safety Issue for Biological Medicines

- Therapeutic proteins have the potential to induce immunogenic responses
- A significant difference in antibody responses between the biosimilar and the reference product should be taken as evidence that the products have significant differences

How are Biosimilars Regulated?

- In both EU and in the U.S, it is generally accepted that it is not possible to regulate biological medicines under the same kind of abbreviated application approach that can be used with small-molecule chemical drugs

- The EU pathway for biosimilars is very recent in origin
- To date two biosimilar medicines have been authorized at the EU level

EU Legislation

- Community Code on Medicinal Products, Directive 2001/83, as amended
- 2003/63: Annex 1 to Directive 2001/83

Approval of Generic Products

- An exception to the usual requirement of a complete application for marketing authorization
- Without prejudice to the law relating to the protection of industrial and commercial property
- Not required to provide the results of pre-clinical tests and of clinical trials
- ….if it can be demonstrated that

Approval of Generic Products

- ….if it can be demonstrated that
- the medicinal product is a generic of a reference medicinal product
- that has been authorized…for not less than eight years by an EU Member State or by the Community. …"
- A generic medicinal product authorized pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorization of the reference product.

What is a Reference Product?

A medicinal product authorized in accordance with the provisions of the Community Code or the EMEA Regulation

10+2+1

- 10 years market exclusivity period
- Extended to a maximum of 11 years if, during the first eight years, authorization is granted for one or more **new therapeutic indications** which bring a significant clinical benefit in comparison with existing therapies.

- 8 years data exclusivity

Definition of a Generic Product

A medicinal product

- with the same qualitative and quantitative composition in active substances and
- the same pharmaceutical form as the reference medicinal product, and
- whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. …

What does a Generic Authorization cover?

- Initial reference product authorization
- Any additional strengths, pharmaceutical forms, administration rates, presentations
- Any variations and extensions

Effect on Exclusivity

- Between the “generic” definition and the “global marketing authorization” concept, innovators will not be able to get extensions of exclusivity based upon product improvements other than significant new indications or conversion to OTC switches

Hybrids with bridging studies

- "In cases where the medicinal product does **not** fall within the definition of a **generic** medicinal product…
- or where the **bioequivalence cannot be demonstrated** through bioavailability studies or in the case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product….
- the results of the **appropriate pre-clinical tests or clinical trials** shall be provided."

Hybrids

- "In the case of medicinal products containing active substances used in the composition of authorized medicinal products….
- but **not hitherto** used in **combination for therapeutic purposes**,
- ….the results of **new pre-clinical tests or new clinical trials relating to that combination** shall be provided [in accordance with usual requirements for applications]….
- but it shall not be necessary to provide scientific references relating to each individual active substance."

Reminder
Biosimilars in EU Law

"Biosimilars" are products that cannot meet the criteria for "generics," generally because they are large-molecule proteins and one cannot be sure they are sufficiently close to the originator's product

Biosimilars under the Community Code

- Similar to a reference biological product….
- not generic medicinal products,
- owing to, in particular, **differences** relating to **raw materials** or **differences in manufacturing processes** of the biological medicinal product and the reference biological medicinal product,
- the results of **appropriate pre-clinical tests or clinical trials** relating to these conditions must be provided. …

Data

- How much data will be required for the follow-on applicants?
- Or, to put it another way, what data requirements are biosimilar applicants be allowed to skip?
- European regulators are very aware of potential for immunogenecity and other safety problems with biologics, so immunology data are always to be required

What additional data?

Must comply with the relevant criteria stated in Annex I to the Community Code and the related detailed guidelines.

The results of other tests and trials from the reference medicinal product's dossier shall not be provided

Guidelines

- 1. Guideline on Biosimilar Medicinal Products
- 2. Recombinant Human Erythropoietin
- 3. Recombinant Human Growth Hormone
- 4. Recombinant Human Insulin
- 5. Recombinant Human Granulocyte-Colony Stimulating Factor

EMEA guidelines concerning biosimilars

- These include:
  - A general guideline document;
  - Guidelines concerning clinical and non-clinical issues relating to the comparability of biotechnology-derived proteins as active substance; and,
  - Guidelines concerning quality issues relating to the comparability of biotechnology-derived proteins as active substance.
  - Due to the complexity of biological/biotechnology-derived products, the generic approach is considered scientifically inappropriate for these products.
  - Rather the “similar biological medicinal products” approach, based on a comparability exercise, would have to be followed.

Clinical Safety and Pharmacovigilance

- **For clinical safety and pharmacovigilance requirements, a distinction is made between:**
  - pre-approval phase: safety data from pre-authorization studies **from,**
  - the post-approval phase: close monitoring of the product.

- **The applicant should include in the application:**
  - a "risk specification" (describing possible safety issues due to the manufacturing process being different from that of the innovator).
  - a pharmacovigilance plan in accord with EU legislation/guidelines.

Issues

- The same reference medicinal product should be used for all parts of dossier (quality, safety and efficacy).

- If the reference product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

- In some cases a biosimilar applicant may be able to justify an extrapolation of “therapeutic similarity” shown in one indication to other indications of the reference product. Consultation with EMEA advised.

1st Biosimilar Approval - Omnitrope

- Sandoz GmbH Somatropin, a recombinant-DNA growth hormone
- Reference product – Pfizer's Genotropin
- CHMP Opinion – January 2006
- Commission Decision – March 2006

2nd Biosimilar Approval

- Biopartners‘ Valtropin recombinant human growth hormone
- Reference product was Lilly's Humatrope
- CHMP Opinion - February 2006
- Commission Decision – 24 April 2006

Not approved as a biosimilar

- Biopartners' Alpheon (recombinant human Interferon-alfa-2a)
- CHMP Opinion – June 2006
- CHMP found major quality concerns and differences (such as impurities) between Alpheon and the reference product Roferon-A in the quality and clinical comparability exercise
- Not enough data on the stability of the active substance and of the medicine
- The process used for making the finished medicine was not adequately validated

Is there a U.S. Biosimilars legal pathway?

- Currently, most biotechnology products are licensed as biological products under the PHSA
- However, for historical reasons, FDA has approved certain products, such as insulin and human growth hormone, as new drugs under the Federal Food, Drug and Cosmetic Act (FDCA)
- FDA agrees that the PHSA does not contemplate a regulatory pathway for follow-on biologics and that the scientific barriers likewise are insurmountable at this time.

Is there a 505(b)(2) pathway for some products?

- A few large-molecule protein products were approved as new drugs under section 505 of the Federal Food, Drug and Cosmetic Act, rather than as licensed as biologics under the Public Health Service Act
- FDA has permitted certain follow-on versions to be approved under the 505(b)(2) mechanism
- In a 505(b)(2) application, one or more investigations necessary to approval were not conducted by the applicant and as to these the applicant has not obtained a right of reference

What does 505(b)(2) provide?

- Products approved under the 505 (b)(2) pathway are not the “same” as the pioneer product, so cannot enter market via Abbreviated New Drug Applications (ANDAs)

- 505(b)(2): is it just a “paper NDA” provision or is it a way to rely on FDA’s finding of safety and effectiveness and thus on an innovator’s data?

Regulatory Status of Follow-on Proteins in the US

- In April 1999 the FDA published a draft guidance on *Applications Covered by Section 505(b)(2).*
- This stated that § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA):
  - could be used to gain approval of therapeutic protein products; and,
  - sponsors could make changes to a reference listed drug if the change were supported by clinical data.
- This encouraged "different" generics that rely on safety and efficacy data of the innovator.

(1) Debate over the use of § 505(b)(2)

- The innovator industry filed several citizen petitions challenging the use of § 505(b)(2) to approve FOPs.
- The Biotechnology Industry Organization (BIO) filed a citizen petition in April 2003 objecting to the use of this section to approve a biologic without a "full complement" of non-clinical and clinical data.
- The agency responded in October 2003 that its legal interpretation on 505(b)(2) applications was long-standing and it would resolve related scientific issues in the future.

(2) Debate over the use of § 505(b)(2)

- In April 2004, Genentech filed a citizen petition objecting to FDA's use of innovator data in the review of the generic manufacturer's product, on the theory that an agency reviewer must know details about the innovator's proprietary manufacturing process to determine whether the proposed follow-on is sufficiently "the same as" or "similar to" the innovator to support approval.
- In May 2004, Pfizer filed a citizen petition objecting to approval of the Sandoz Omnitrope 505(b)(2) application which in the U.S. (as in the EU) involves reference to Pfizer's Genotropin.

Both Genentech and Pfizer argued that FDA must necessarily rely on trade secret or otherwise confidential innovator data when it authorizes a follow-on version of that product.

Developments with regard to follow-on proteins in 2004 & 2005

- The Generic Pharmaceutical Association (GPhA) identified "biogenerics" legislation as a priority for 2005.
- Key leaders on Capitol Hill declared an interest in legislation or supported FDA's issuance of guidance on the topic.
- FDA held two public workshops in September 2004 and February 2005 to address scientific and technical issues (but not legal issues) related to follow-on proteins.
  - At the final workshop, Acting Deputy Commissioner of Operations Janet Woodcock said the agency would issue a background White Paper on its past regulatory and scientific treatment of protein products in the "next several months."
  - It would then issue a set of draft guidance documents on different scientific issues for follow-on proteins and hold a third public forum shortly thereafter.
  - Then, public statements and action stopped…

FDA's approval of Omnitrope

- While EU regulators were considering the Sandoz Omnitrope application, since July 2003 a similar application has also been under review at FDA:
  - Sandoz had filed a 505(b)(2) application for Omnitrope
  - August 31, 2004 FDA notified the company that its Review Division had determined it could not make an approval decision due to "unresolved scientific and legal issues."
  - September 13, 2005, Sandoz sought summary judgment against FDA for failure to take action within 180 days of submission of the application
  - On May 30, 2006, FDA approved the 505(b)(2) application for Omnitrope

FDA's approval of Omnitrope

- FDA said this was not ground-breaking: FDA pointed to its prior approval of other follow-on protein products under section 505 (b)(2) such as GlucaGen, Hylenex, Hydase and Amphadase
- FDA said Omnitrope is well-characterized: human growth hormone (hGH) has several characteristics that enable one rhGH product to be adequately compared to another for purposes of approval under section 505(b)(2)
- FDA said this is not a precedent: "the approval of Omnitrope does not create a new pathway for follow-on versions of all protein products"
- FDA said Omnitrope is not substitutable for other HGH products

What of the "name"?

- **INN** International Nonproprietary Name (for marketing in EU and Japan)
- **USAN** United States Adopted Name (for marketing in the US)

Role - Identifies the compound within a family of compounds based on chemistry

Impact on: prescription,
substitution of drugs, and
adverse event reporting process

Naming and interchangeability

- Similar and not identical → entails problems that are not prevalent as to small-molecule generic medicines
- Pharmacovigilance may not always be a suitable method to distinguish between events associated with innovator products and biosimilars
- Should there be special restricted substitution rules for biosimilars?
- Does the EMEA possess the authority do impose such rules?
- New system of nomenclature?

Naming and interchangeability

- As to complex proteins, the FDA has not determined how interchangeability can be established
- FDA: “the only way to establish pharmacologic interchangeability is through scientific data – nomenclature should not be used as a way to imply such when there are not credible supporting data”
- FDA: no need for changes of the INN policy for naming biosimilars since there are many alternative mechanisms to prevent inappropriate substitution
- FDA opposes assigning the same INN to two products if this resulted in the products being interchangeable without no scientific data to establish this

What do Biosimilars represent?

- More costly to develop than generic products
- More difficult to discount as compare to original products
- What is the realistic possibility of substitution?

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