Key Lessons from the First Successful Biosimilar Application in the EU: Omnitrope® - A legal perspective

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a Novartis company

Omnitrope®: First Biosimilar approved in Europe

Omnitrope® Pen L

Omnitrope 5.8 mg

Powder for Solution for Injection

Dilutent Cartridge

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Directive 2003/63/EC
Part II of Annex I to Directive 2001/83/EC

Well-Established Medicinal Use	Essentially Similar Medicinal Product	Mixed Marketing Authoris. Application	Similar Biological Medicinal Product
CTD Modules 1, 2, 3: Full data (similar to a full MA Dossier)			
Modules 4,5 ↓ Detailed Scientific Bibliography	Modules 4,5 ↓ 1. Cross-reference to the original MA (if agreed with the MAH) 2. Bio-availability and Bio-equivalence	Modules 4,5 ↓ Combination of Studies and Bibl. References Case-by-case basis	Modules 4,5 ↓ Additional non-clinical and clinical data Case-by-case basis

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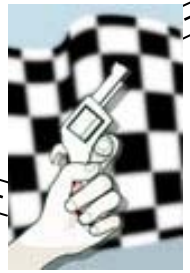
OMNITROPE®/rhGH - a long path to success

April 2006:
EC decision
MA granted

January 2006:
Positive opinion from EMEA

June 2004: New submission under the biosimilar pathway



May 2001:
Submission of file (based on well-established use)

June 2003:
Omnitrope receives positive opinion from CPMP

November 2003:
The EC refuses the MAA

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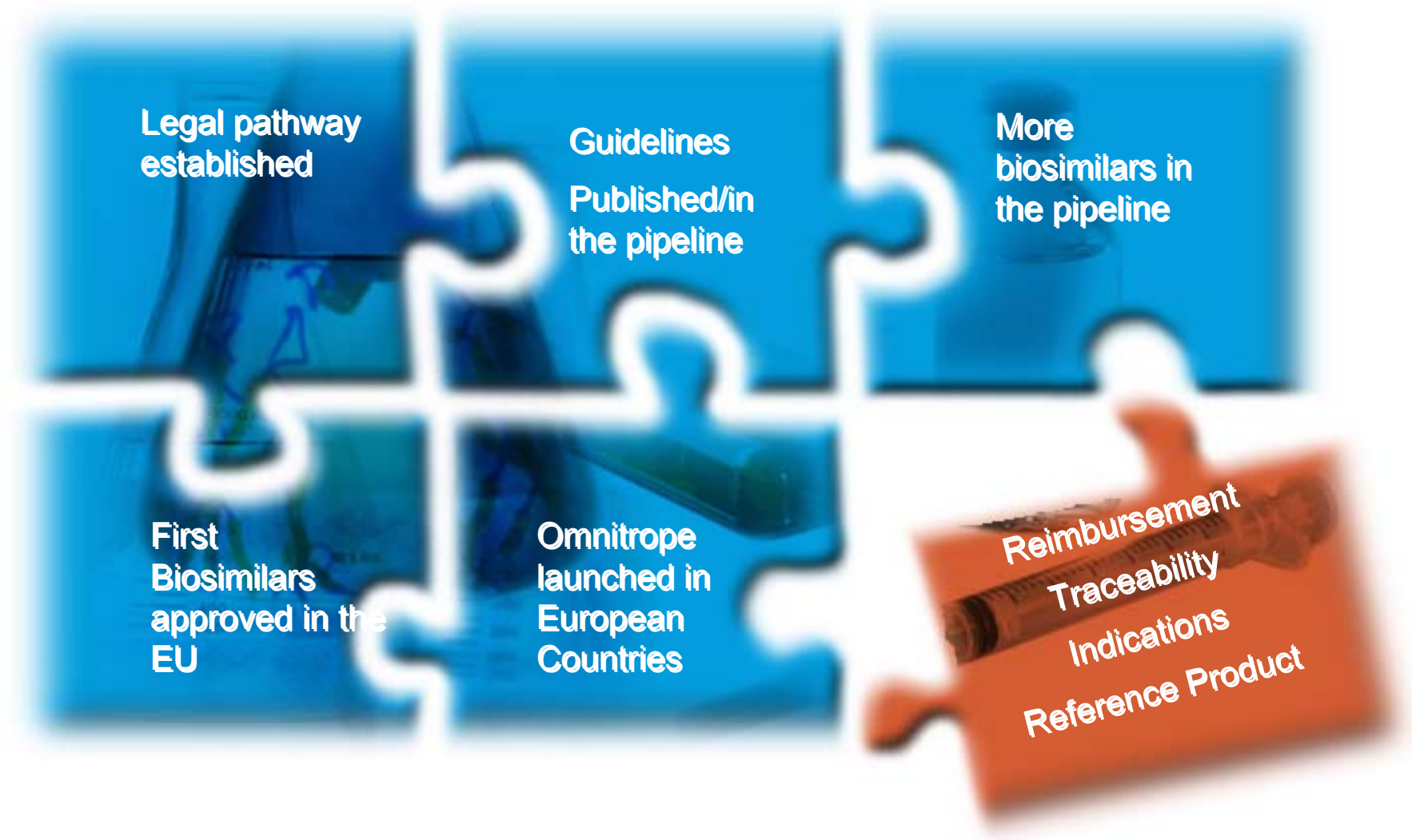
The major part of the EU- Biosimilar puzzle is completed



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Current Challenge: Reimbursement

Issue:
Products are approved centrally, but all preparatory launch activities such as pricing and reimbursement are local.

Legal Environment:
No system of direct recommendations or guidance from the EMEA and/or the EC, which are the authorities knowing the product and its interchangeability.

⇒ Biosimilars are a new product class - national authorities as well as the distributors need to build experience.

Current Challenge: Traceability

Issue:
Lobbying by originators for introduction of increased tracing obligations for patients under Biosimilar therapy compared to patients medicated with originator product.

Legal Environment:
The entire Pharmaceutical industry is obliged to trace any product with respect to manufacturer and batch number.

Current Challenge: Traceability -2-

- **Pharmacovigilance systems need to be in place anyway (risk management plan for newly approved products including Biosimilars, post marketing surveillance)**

- **Biosimilar and originator products (and their risks) are duly evaluated and approved by the same authorities**

- **Biosimilar approval includes comparability with respect to safety**

⇒ No general additional tracing obligations for Biosimilars needed

Current Challenge: Harmonisation of indication scopes -1-

Issue:
Can the scope of indications of the Biosimilar be smaller than the scope of the reference product (e.g. in case of patent protected indication)?

Legal Environment:

Art. 6 Regulation (EC) 726/2004
Art. 8(3) Dir. 2001/83/EC
Art. 10 Dir. 2001/83/EC (as amended by Dir. 2004/27/EC)

Art. 11 Dir. 2004/27/EC, Art. 3 (B) and Art. 6 Regulation 726/2004/EC:
"For authorisations under Article 10, those parts of the summary of product characteristics of the reference product referring to indications or dosage forms which were still covered by patent law at the time a generic medicine was marketed need not be included" (Art. 11 sentence 2 Dir. 2001/83/EC)

Current Challenge: Harmonisation of indication scopes -2-

- **No legal requirement of identical SmPC to the reference product**

⇒ Approved indication scope of the Biosimilar can be smaller than the scope of the reference product

Current Challenge: Choice of reference product -1-

Issue:

Improvements of the reference product during data protection phase, biosimilar application referring to first form (e.g. vials/pre-filled syringes)

Legal environment:

Art. 6 Dir. 2001/83/EC (as amended):

… any additional strengths, pharmaceutical forms, administration routes, presentation, as well as any variations and extensions ... Shall be granted … or included in the initial M.A. All these M.A's shall be considered as belonging to the same global M.A., in particular for their purpose of the application of Article 10 (1).

Current Challenge: Choice of reference product -2-

⇒ **Reference to the earliest approved product is legally possible**

⇒ **Data protection phase starts with first „family members“ approval**

Future Aspect:
Global Approach on Reference Products -1-

Issue:

Regional/National Approval pathways for Biosimilars tend to restrict the choice of the reference product to regionally/nationally approved products.

⇒ Global developments need to be compared to different reference products,

⇒ Ethically not justifiable: Studies need to be repeated

⇒ Increase of development costs

Future Aspect:
Global Approach on Reference Products -2-

Ideas for solution from the recent WHO meeting:

- **Introduction of smaller bridging studies?**
- **WHO definition of Global reference product?**

Any Questions?

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