



Biosimilars: how to manage risks

Introduction

As biopharmaceutical patents start to expire, biosimilar products are beginning to enter the European regulatory system and the wider marketplace. Several biosimilars have already been approved through the recently established EMEA regulatory pathway and an embryonic market is beginning to take shape.

The financial incentives are high, both from an investor's and a health economics perspective. Strong opportunities are predicted for successful biosimilars developers with the potential to increase significantly patients' access to life-saving medicines.

However, to what extent is biosimilar development commercially viable and achievable from a safety and clinical standpoint? Significantly, structural and manufacturing differences between the biosimilar and the parent product may change the whole scenario, with safety the paramount issue. Additional sources of complexity and uncertainty are creating new risks at various levels of product development and commercialisation. Based on the increasing importance of risk mitigation in drug development, research was initiated with the aim of providing a strategic decision-making framework for biosimilars to help choose successful development of products with an optimum safety profile.

Biosimilars have enormous market potential

Biologics coming off-patent between 2006-2010 are estimated to have a market value of \$10bn. However, as biosimilars are priced at a lower level than their expensive reference products, savings are unlikely to be as much as for conventional generics.

These generics have made a major contribution to accessible and affordable healthcare with an estimated 20 billion euro saving annually in the EU. However, the new generation of biologicals addresses a great unmet need and it is clear that an increasing percentage of overall drug

expenditure will be on these medicines. The use of biosimilars could reduce this spend significantly, with the estimated savings of currently approved biosimilars at 2.5 billion euros annually in the EU.

However, biosimilars pose a variety of significant risks. In choosing and producing the product there is a manufacturing and legal risk. In bringing the product to market there is a development and regulatory risk, especially when it comes to pre-clinical and clinical trials.

There is also a commercial risk in selling the product and a financial risk with regard to making a profit. Finally there is a post-marketing risk as far as continuing value is concerned.

Thus despite significant enthusiasm and expectations, the question still remains to what extent biosimilars are clinically and commercially viable, because of potential safety, manufacturing, regulatory and commercial risks. In order to address this question, these issues and others identified through a literature survey were used as the basis for stakeholder research with key opinion leaders and senior industry executives involved in biosimilar development and commercialisation.

Objectives and methodology

An extensive literature survey identified the most important issues and uncertainties surrounding this emerging market. Based on this information, we conducted 18 interviews with key opinion leaders and senior executives involved directly or indirectly in biosimilar development. The information was compiled and analysed qualitatively and quantitatively to confirm, adjust and formulate key findings about risk assessment and risk mitigation, as well as market projections.

Results

Our research led to the following:

- ▶ A detailed picture of the current situation and associated risks at the drug safety, manufacturing, legal, regulatory, commercial and financial levels.



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- ▶ Balanced suggestions for potential risk mitigation and prioritisation of each type of risk, based on expert recommendations and our analysis.
- ▶ An identification of the sources of risk ranked by product class.
- ▶ A risk model based on a fault-tree analysis, compiling and presenting in a logical and comprehensive way the different factors and pathways that may lead to major failures. For each category of risk, we identified and ranked the different sources, the determinants of these sources and the general constraints leading to these determinants, distinguishing product-specific, decisional and external factors.

The results of these interviews showed that the process of developing and marketing biosimilars is still uncertain and risky, and that complex hurdles make development difficult. Two main challenge areas were identified: regulatory/safety – a typical comment was *“Every product is a unique and individual case: just ticking the boxes can be a disaster”* and commercial/financial: *“The current players went through the approval jungle and now they face the market jungle”*.

Major risks

The major risk sources were seen to be commercial, financial and development/regulatory. *“The biggest challenge was seen to be how to get the product to market and make money out of it”*. Respondents felt there was a lack of credibility, with a perception of greater safety/efficacy associated with the established reference product. Also, there is no established agreement on rules for substitution/naming and automatic substitution is banned for biosimilars in some countries. In any case uptake may be more directly associated with hospital formularies than substitution at pharmacies. As one interviewee said *“For the sake of patient safety there must be no automatic substitution”*.

Profitability

According to one participant *“there is no guarantee of profitability”*. There are costly requirements for clinical comparability, with a high cost of goods and high costs of manufacturing scale-up and facilities. There is uncertainty around competition, price imposition and product quality. It is also difficult to shape a

financial strategy in a newly emerging and uncertain market: *“It is an extremely good investment but a risky one”*.

Regulatory challenges: How similar is similar?

Despite significant and helpful advances by the EMEA, fulfilling regulatory requirements is still seen as a very significant hurdle. The approach is seen as stringent with a high risk of failure. Products and regulatory pathways are still relatively untested. It was felt that the EMEA pathway sets a significant but surmountable entry barrier with the complex scientific issues and some uncertainty due to unclear or evolving requirements. There are also product-specific challenges with a risk associated with being unable to fully characterise biologicals: *“If you can't demonstrate sufficient comparability your product won't be authorised as a biosimilar”*.

Characterisation

Deciding the extent of characterisation required is complex. Weighing the cost of an extensive clinical trial approach against the risk of a more contained comparability exercise is not an easy decision, although advanced analytical techniques and a good risk minimisation plan may reduce the need for extensive clinical comparability. Some respondents felt that they should: *“Conduct only limited research, otherwise what is the point of going into the biosimilar business?”* whereas others felt: *“It is going to be an issue currently if you only present the minimum”*.

Manufacturing risk

Participants ranked this lower because although costly and complex, it was seen as well established and with potential to be controlled. However, it could be technically and financially challenging: *“A single mistake in manufacturing may jeopardise the whole development.”*

Post-launch safety risk

Immunogenicity was seen as one of the most significant hurdles, with risks dividing into either product-related or patient-related issues.

Product-dependent immunogenicity risks:

- a) Post-translational modification/glycosylation
- b) Contaminants (process/packaging)



- c) Formulation
- d) Storage/handling (aggregation)

Patient-dependent immunogenicity risks:

- a) Disease-related
- b) Individual patient-related
- c) Dose/route

“The biggest challenge is having a physician understand what ‘biosimilar’ means and the associated risk-benefit issues”

However, safety risks can be mitigated by:

- a) Sufficiently thorough pre-launch trials
- b) Risk minimisation planning
- c) Post-launch studies and monitoring

“Drug safety is about risk management, not risk elimination”.

Legal risk

Identification and analysis of patents is time-consuming and complex, yet the potential

impact of litigation is high. Nevertheless, this was seen as the lowest risk category: *“As some biological molecules are covered by 300 patients it may be easy to overlook one of them”.*

Recommendations

Regulatory/development/manufacturing

- ▶ Choose the right product and process
- ▶ Get external scientific and regulatory advice
- ▶ Address concerns over similarity and differentiation
- ▶ Decide on the most efficient strategy to prove similarity: clinical/analytic balance
- ▶ Address product-specific concerns, including immunogenicity

“You have to establish similarity rather than efficacy and safety per se”

Figure 1. on Regulatory/Clinical Risk shows the different types of failure source and factors that impact them. Similar figures can be made for financial and commercial risks.

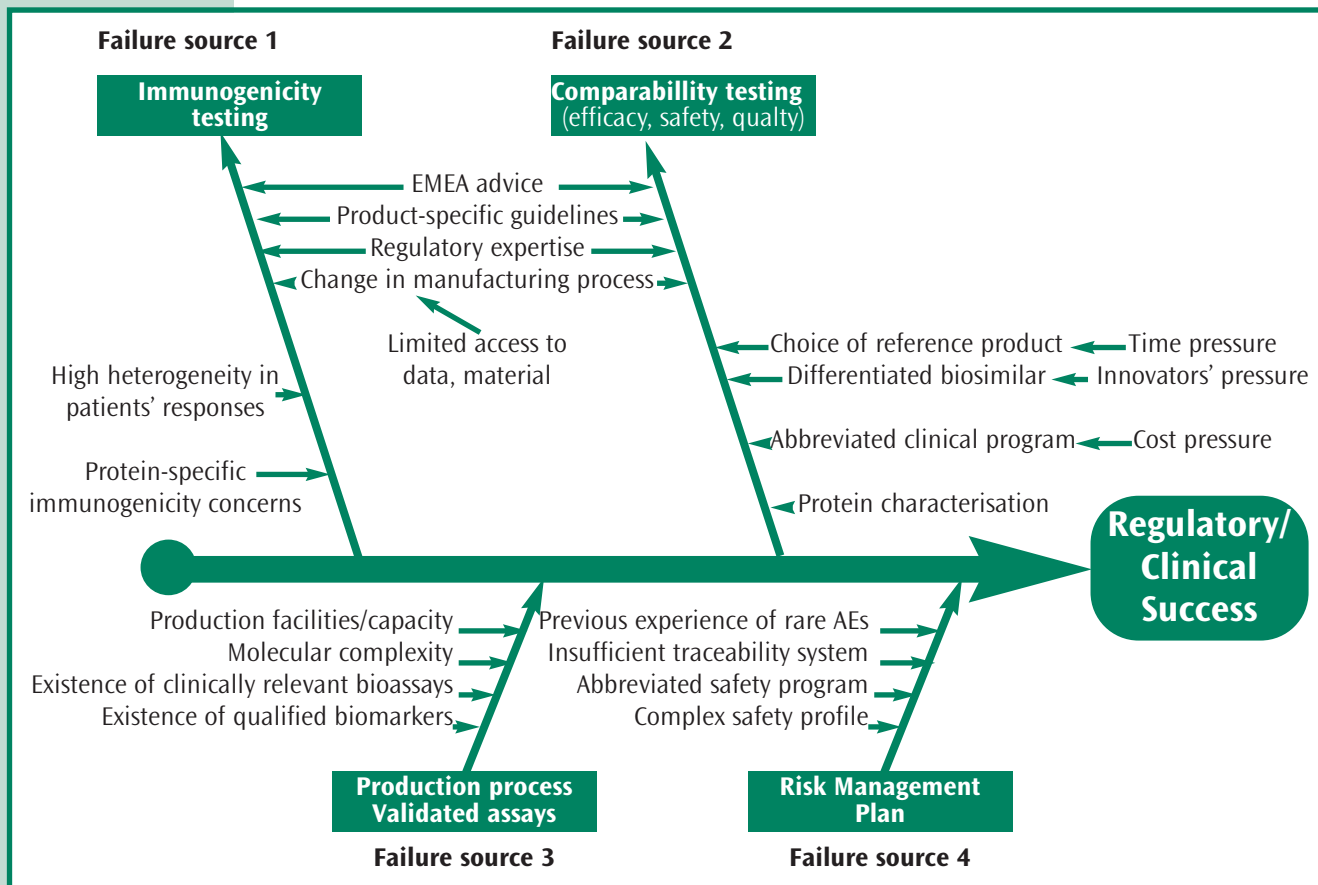


Figure 1. Regulatory clinical risk



Safety/Legal

- ▶ Follow EMEA guidelines on post-marketing surveillance
- ▶ Careful risk management and risk minimisation planning may to some extent counterbalance abbreviated clinical experience
- ▶ Address immunogenicity concerns where appropriate
- ▶ Anticipate clinicians' potential concerns and provide answers
- ▶ Check patent landscape with legal experts

Commercial/financial

- ▶ Understand your target market – existing/new customers, differentiators (price only?), marketing support
- ▶ Understand your customers – define target group

Educate stakeholders

“Biosimilar companies should focus on patients who cannot afford the drug, or markets which have not been given access to the originator product.”

- ▶ Commercial strategy: position your product – price shadowing branded price?
- ▶ Minimise costs and/or ensure adequate financial capability.

“Convince people that your cheaper product is just as good”.

Conclusions

Biosimilars are neither scientifically nor legally true generics and thus far, development has been slower and more expensive than expected. The biosimilar market is different, still evolving, complex and uncertain.

In the light of risks that still surround the business, the successful development and commercialisation of biosimilars is unlikely to be straightforward. Developers of biosimilars will have to methodically understand their own risk exposure in order to rigorously and proactively develop a risk management plan that makes optimal trade-off between costs and risks.

Overall, despite considerable risk and costs, the first winners in the market are likely to be highly rewarded.

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