

A risk-based approach to biopharmaceutical manufacturing

As the biotechnology industry has seen 2006 kick-off with big pharma pushing its way in, the industry urgently needs to transform its current drug discovery and development processes. This knowledge era is focusing on strong collaboration and both interdependency and individualization demanding new approaches and technologies.

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This column provides a practical perspective and recommendations for applying a risk-based approach within the guidance-regulated biotechnology industry, an approach that can affect time-to-market. Focusing on the implementation of a risk management strategy encompassing the regulatory framework is not at all new, at least not to pharma manufacturing. The operationalization of the strategy and subsequent deployment is difficult, however. In particular the biotechnology industry has first seat in the value chain, or what FDA has defined as the critical path for new drug development.

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new approaches and technologies to secure compliance with regulations and fast-track initiatives. This means validation and documentation resources need to be prioritized. The biotechnology industry's own challenges and the legal challenges of how to secure safe and efficient new drugs faster are intimately connected.

The science-based regulatory framework for development of new drugs is dynamic in that public health objectives may change in response to patient needs and society's interests. In this column no distinction is made between traditional chemically synthesized drugs and respective biological drugs derived from living sources (such as humans, animals and micro-organisms). Most biologics are complex mixtures that are not easily identified or characterized and many are manufactured using biotechnology. FDA has traditionally regulated biologics and traditional drugs in different centres, but this separation is being rapidly accentuated by organizational changes.

Given the dynamic character of these factors and also the fact that the process involves many different parties — pharmaceutical sponsors, the scientific and healthcare communities, the government and society at large — a potential synergy exists where these parties could collaborate to improve methods, approaches and technologies for development of new drugs. And it all begins with biotech (Figure 1).

Most of the contemporary debate on regulatory topics is in fact old news presented in more modern vocabulary. Controversies are inevitable. From an industry perspective, revision of the regulatory context under FDA is challenged more so today than at any time since the 1962 amendments to the Food, Drug and Cosmetic Act recreated FDA by mandating it to require proof of efficacy as well as safety when approving new drugs.¹

One main 'safety' criticism is that FDA favours the pharma industry by placing too little focus and weight on safety when approving new drugs and monitoring them afterwards, a chief criticism mainly grown upon Merck's withdrawals of Vioxx September, 2004 and Pfizer's withdrawal of Bextra in April, 2005. Alternatively,

To further enhance understanding, the column focuses entirely on regulation and biotechnology. This is a rather simplistic and academic approach, as other stake holders of course engage in this collaborative work. Furthermore, it has a sole focus on validation and documentation only, even though it is noted that in the very early stages of discovery and development, to a certain extent these compliance activities are optional and not enforced as in pharma. This transformation should result in earlier trial completion, earlier regulatory approval, earlier marketplace introduction and thus longer patent utilization — resulting in significant financial and competitive advantages.

From a biotechnology industry perspective, the definition and deployment of the traditional legal interpretation of risk-assessment is particularly timely. It is required for a variety of reasons, but primarily because this era's new business paradigm forces the integration of

academic medical communities (also great supporters) have criticized the agency for being too slow to approve new drugs or too quick to remove them.

FDA balances risks and benefits for the intended population and the drug’s intended use as it decides that a drug is sufficiently safe and effective for marketing, and obviously the stringency of FDA approval standards ultimately has an effect on the pace with which new molecular entities (NMEs) are developed (Figure 2, Table 1).

Rapid advances in basic and applied science pose a great challenge for FDA. Of course, the same logic applies to good manufacturing practice (cGMP) regulation as pharma manufacturing has become increasingly obsolete even as the advent of biotechnology cries out for radical changes. Despite technological progress and the adoption of new technologies in high-tech industries, such as petrochemical, software, hardware, communication etc. this industry routinely accedes to requirements that have become obsolete because of the costs for obtaining regulatory approval for changes.

In March 2004, FDA published the report “Innovation or Stagnation? — Challenge and Opportunity on the Critical Path to New Medical Products”, which examines the critical path needed to bring therapeutic products to fruition. It highlights how FDA can collaborate in the process from laboratory to end-use, to make medical breakthroughs available to those in need as quickly as possible.² This report analyses the “pipeline problem”, that is, the slowdown in innovative medical therapies reaching patients as a result of the current new drug development path becoming increasingly challenging, inefficient and costly, and this has manifested itself in a lower number of new drug approvals and biologic applications (Table 1).

Only scientific and technical dimensions are included in the table, and all three dimensions are interdependent and none guarantee success. In January 2006, FDA published the Exploratory IND3 Studies.³ The guidance is to build in line

with the critical path initiative and will facilitate very early exploratory scientific studies in people before the standard safety studies (Phase 1) begin, though limited to drug and certain well-characterized therapeutic biological products. One of the biggest barriers research and academic institutions face is the ability to get discoveries made in the lab into clinical testing. Because only small amounts of drugs are used in these early studies, they represent fewer potential risks for people in these trials. FDA makes recommendations about safety testing, manufacturing and clinical approaches that can be used in these very early studies.

The guidance explains how medical researchers can take full advantage of the flexibility built into existing regulations in the amount of data needed when asking FDA’s permission to proceed with such a study, enabling more rapid delivery of innovative products to patients.

FDA has previously articulated its commitment to ensuring the appropriate flexibility is applied when patients with a serious disease and no satisfactory alternative therapies are enrolled in a trial with therapeutic intent.⁴

It is expected that all preclinical safety studies supporting the safety of an exploratory investigation new drug (IND) application will be performed in a manner consistent with good laboratory practices (GLP) (21 CFR Part 58).⁵ The GLP provisions apply to a broad variety of studies, test articles, and test systems.

In related draft guidance, INDs — Approaches to Complying with cGMP During Phase 1, FDA outlines a suggested approach to complying with current good manufacturing practice (cGMP) requirements for drugs intended for use solely in Phase 1 studies.⁶

With this new guidance and an accompanying regulation, FDA formally recognizes specific standards for the manufacture of small amounts of drug product for Phase 1 studies and formulates an approach to cGMP compliance that is appropriate for the particular stage of drug development.

Table 1 Three dimensions of the critical path.

Dimension	Definition	Examples of activities
Assessing safety	Show that product is adequately safe for each stage of development	1. Preclinical: show that the product is safe enough for early human testing. Eliminate products with safety problems early 2. Clinical: show that product is safe enough for commercial distribution
Demonstrating medical utility	Show that product benefits people	1. Preclinical: select appropriate candidate with high probability of effectiveness 2. Clinical: show effectiveness in people
Industrialization	Go from lab concept or prototype to a manufacturable product	1. Design a quality product <ul style="list-style-type: none"> • Physical design • Characterization • Specifications 2. Develop mass production capacity <ul style="list-style-type: none"> • Manufacturing scale-up • Quality control

Recommendations

Taking FDA initiatives even further from a regulatory perspective, the deployment of a risk-based, process-oriented approach would allow biotechnology to analyse and monitor their processes and implement appropriate controls to mitigate GxP risks.

In that sense, following a four-step model that covers both the scope and selection of appropriate, supporting new technologies and controls, can be deployed:

- Define overall responsibility for project team, i.e., system, business, quality assurance (QA).
- Define and identify critical GLP, good clinical practice (GCP) and good manufacturing GMP.
- GLP/GCP/GMP processes that could potentially compromise product safety, efficacy and quality
- Categorize all validation activities (Priority Plan).
- Non-critical processes (GLP/GCP/GMP) should be carefully analysed, and non-valuable adding processes (ideally) eliminated.
- Implement controls commensurate with the risk identified. These controls should be documented and justified with reference to the identified risks.

This top-down and very pragmatic, public-acknowledged approach needs to be transformed to operational, intuitive measures easily deployable in the biotech environments.

In operational terms this means a strong focus on failure investigation (falsification, fabrication, compromise to subject protection) and the documentation, monitoring and

reporting to authorities. In other terms, this means traceability and classification of deviations:

- risk-level classification (1–5)
- frequency (low/medium/high)
- detectability (low/medium/high).

Overall, the risk-based approach should be implemented in processes as follows:

- clinical research methodologies, including protocols and regulatory compliance (documentation)
- data collection, analysis and synthesis
- assessment and evaluation of safety/toxicity and efficacy.

Conclusions

Development of the necessary information to document safety, efficacy and utility involves a highly complex set of scientific and QA activities not commonly used in biotech, at least when entering fast-track programmes and partnering with pharma companies. For the biotechnology regulatory executive selecting the right compliance levels and systems supported by new technology (electronic record-keeping) is in today's collaborative environment essential, not least in the effort of securing a shorter cycle time. In fact one could argue, that GMP actually also yields significant benefit for biotech. Early implementation and education in compliance issues scaled and supported by using a risk-based approach towards this vital issue is resulting in synergism for all actors in the value chain, ultimately the patient and society.

Furthermore, with the deployment of new technologies (knowledge-sharing based), for example, electronic documentation, biotech companies will comply with the requirements for electronic applications that will become mandatory in the EC in 2009, as is already the case in Belgium, The Netherlands and the UK

Figure 1 Cooperation, interdependency and individualisation demands new approaches and technologies

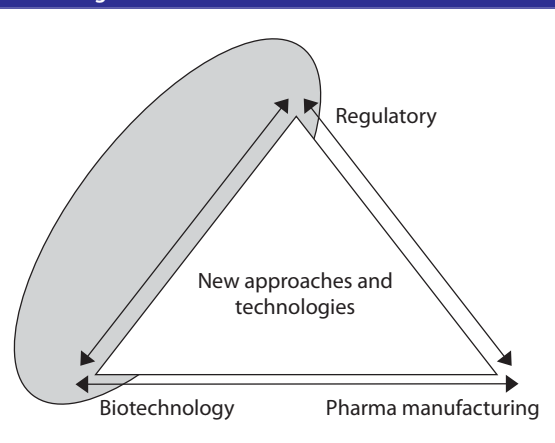
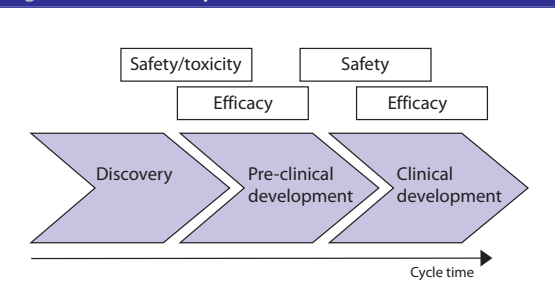


Figure 2 The critical path value chain.



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