US Industrial Perspective of Remaining Challenges in Biologics Development and Control

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Brief Review of Biopharmaceutical History

- 1982 – First product approved (rDNA-derived human insulin)
- Next 25 years saw approximately 100 molecules approved or licensed as biological products derived from recombinant DNA or monoclonal antibody technologies

Brief Review of Biopharmaceutical History

- Many millions of people have received rh-insulin
- Hundreds of millions have received rHBsAg vaccines
- Millions have received rDNA derived thrombolytics, erythropoeitins, and many other therapeutic proteins
- One million patients with autoimmune diseases have received Remicade (monoclonal antibody against TNFalpha)
- Hundreds of thousands of patients with oncology or immunological diseases have received benefits from other monoclonal antibody products

Brief Review of Biopharmaceutical History

- This present generation of biotechnology products possesses an unprecedented level of freedom from process-related safety risks
  - No product recipient has ever been reported to have become infected by a viral agent contamination the product
  - Compared with the record of the previous generations of biologicals products (conventional viral vaccines & plasma derivatives), this safety record is truly remarkable
  - This safety record is not an accident

Brief Review of Biopharmaceutical History

- The safety of modern biotechnology products reflects
  - Improved power of modern technology to separate the beneficial product from the undesirable risk factors
  - Concern on the part of industry, regulatory, & academic scientists to attempt to learn from history of virus vaccines and plasma derivatives
  - Willingness of industry, regulatory, & academic scientists to work together to discuss issues and answers
- This spirit of cooperation was infused into the early efforts of International Conference on Harmonization (ICH) to reduce needless duplication of technical requirements for product approval in different geographical regions

Given this very positive history of ICH & cooperation between the regulatory community and industry, what are some of the things that may be in our future?

Old Model of Biological Product Development

- Large biotech (7) and Big Pharma (10) companies with biotech units developed most of the early rDNA and MAb products (1982- 2000)
  - 60 of first 67 products with known history fit the model
- Define product acceptabilty by test results & compliance within a fixed process
  - Critical Quality Attributes (CQAs) judged *via* specifications & QC release testing
  - Fixed process parameters under GMP
  - No process or product changes permitted without regulatory approval

New Model for Biotechnology Product Development

- New model has simultaneous changes in the responsibility for product development as well as the definition of product quality
- Drivers of new model
  - Changing regulatory + industry vision of Quality (led by ICH Q8, Q9, Q10)
  - Changing pattern of responsibility for development
  - Economics of developing and marketing products

Drivers: Changing Quality Vision

ICH Q8, Q9, Q10

- These new ICH Guidances collectively drive a vision of Quality determined by knowledge-driven Design Space, PAT, QRM, and other tools (=QbD)
  - Definition of product acceptability by specifications + fixed process moves to specification and Design Space with other appropriate controls
- Key Question:What will be the “regulatory relief” provided under such approaches & how will it be administered?

Drivers: Changing Responsibility for Product Development

Biopharmaceutical Industry 2006
- Products in Development (PhRMA Surveys)

- 418 biopharmaceuticals in nonclinical or clinical development (22 in late development, -9 from 2004)
- Of these, 216 (+95 more than 2004) are novel therapeutic biological products in the clinic
  - 23 cellular therapies (1 in late development)
  - 30 are microbially-expressed rDNA (5 late, -6 from 2004)
  - 33 are mammalian-expressed rDNA (7 late, +1 from 2004)
  - 130 (+69 more) are MAbs (9 late, -2 from 2004)
- Two – thirds of the therapeutic biological molecules presently in the clinic are monoclonal antibodies, and 85% are cell culture products

Who Was Developing Therapeutic Biopharmaceutical Products in 2006 ?

- Large biotech firms are developing 35 entities (4 microbial, 5 cell culture, 26 Mab)
- Small biotech firms are developing 123 entities (19 microbial, 23 cell culture, 81 Mab)
  - if promising, many are likely to be inlicensed by large biotech or large pharma for PhIII
- Large pharma are developing 28 entities (3 microbial, 4 cell culture, 21 Mab)
- US National Cancer Institute is developing 8 entities (mostly Mabs)

Developing Therapeutic Biopharmaceutical Products in 2006 vs 2004

- 95 more biotech products are in development in 2006 compared to 2004 (216 vs 121)
- Biggest increases are in Mabs (130 vs 61)
  - Most of the increase in activity is in small biotech companies (81 vs 26)
  - Some increase in big pharma (21 vs 5)
  - Little change in big biotech firms (26 vs 23)
- Most of the increase is in early stage development which is within the financial capability of small firms
- Late stage products decreased from 31 to 22 (same number?)

Two Biotechnology Industries

- Big Biotech (7) + Big Pharma doing Big Biotech (10) are developing 34% of products (63/185)
  - **Experienced at clinical & product development**
  - **Development infrastructure & supply chain largely in place (or resourced to use CMOs essentially at will)**
  - **When justified, can trade money for time**
  - **Goal is to develop & sell marketable products**
- Small firms developing 66% of products(122/185)
  - **Mostly virtual organizations with minimal experience or with a few experienced senior executives from Big Firms**
  - **Limited infrastructure and resources**
  - **Limited ability to trade money for time**
  - **Goal is to survive to next financial milestone or "cash in" point**

Meaning of "Product Development" to Big Firms

- Be proactive at addressing potential issues that might slow down development progress ("QbD")
  - **Use technology platforms which are friendly to supply chain & regulatory agency needs, & have at least partially commonality**
  - **Do as much as possible right the first time**
  - **Identify major risks early & mitigate them**
  - **Do enough nonclinical work to progress asset consistent with corporate tolerance for risk**
  - **Formulate a development strategy consistent with a comparability strategy & develop the tools to execute the strategy with minimal risk**
- Typically, manage multiple biotechnology assets as part of larger portfolio of NCEs,NMEs,Devices
  - **Rarely betting the future of the company on one product**
  - **Primarily, optimize getting to PoC ASAP**
  - **Secondarily, optimize getting PoC to market ASAP**

Meaning of "Product Development" to Small Firms

- Most lack resources, infrastructure, or experience to be proactive
  - **Struggle to get minimum package acceptable to regulators to get into early development or next milestone**
  - **Management often focused on searching for funding, not on formulating a realistic development strategy**
- May only have one or a few assets; will bet the future of the company if necessary
  - **Primarily, optimize getting to nonclinical and FIH ASAP to seek additional funding while minimizing the expense budget**
  - **Optimization is whatever achieves survival while saving capital**
  - **Rely extensively on generally available technology advances, competition among CMOs, & technology gotten from partners & CMOs (may or may not be "platform", may or may not match ultimate supply chain)**

“Product Development” Means Different Things to Big and Small Firms

- Clearly, Big Firms have much greater opportunity to invest in early development & “QbD” than Small Firms
- Clearly, Big Firms have the only opportunity to invest in late development & “QbD”
  - Small Firms who get a major payout upon partnering an asset for late development with a Big Firm are often conflicted over investing in late development of the partnered asset versus advancing its early portfolio
  - Big Firms who purchase post-PoC assets from Small Firms may have limited opportunity to incorporate “QbD” into late development, especially if remedial development work is needed to achieve commercialization

Typical Quality Approaches for Products Developed by Small Firms

- Development & Manufacturing by CMO
  - Few batches to set specifications based on data and experience
  - Less money invested in QC assay design, process validation, & stability study customization to address QbD considerations
  - Less flexibility to make changes later
  - Control of product by specifications + fixed process is only feasible route to approval

Typical Underdevelopment Issues for Products Developed by Small Firms

- Process
  - **Inadequate expression or purification scheme to achieve CoGs targets or capacity to satisfy market demand**
  - **Use of human or animal derived raw materials**
  - **Use of processing conditions or ingredients which lead to product quality degradation or compendial issues**
  - **Inadequate analytical characterization to define product quality properties, mechanism of action, or stability**
  - **IP considerations**
- Product
  - **Use of excipients or storage conditions which lead to product degradation or compendial issues**
  - **Lack of ex-US considerations, depth of quality systems, & adequate integration of drug product with desired target product profile, competitive reality, & supply chain**
  - **Risk of non-comparability from changes in late development or after approval**

What Does New Model of Biological Product Development Look Like?

- New model has two tiers of products
  - First tier looks like Old Model with Quality determined by specifications + fixed process
  - Second tier looks like “QbD” with Quality determined by specifications + Design Space
- For most of biopharmaceutical products coming to market 2007 to 2015, first tier will predominate, with second tier substantially increased by 2015 (tend toward 34%) as Big Firms use QbD more often
  - Beyond 2015, use of QbD will depend on economic value of “regulatory relief”

Drivers:Economics of developing and marketing products

Cost of Biotech Product Development

- Most recent academic study of biotech development costs done by DiMasi & Grabowski published in Management & Decision Economics 28:469-479 (2007) states that developing one approved or licensed biotech product in 1990 – 2003 cost
  - $ 559 million out of pocket, or
  - $ 1.2 billion capitalized
- Average time from FIH to approval was 8.2 yrs
- Probability of success from FIH to approval was 30%

Cost of Biotech Product Development

- During 1990 – 2003, a total of 79 biotech products (rDNA therapeutics & Mabs) were approved or licensed in the USA
- This translates to a total estimate investment of $ 44 billion in out of pocket development funds on 79 biotech products between 1990 – 2003, or $ 95 billion in capitalized development funds on 79 biotech products between 1990 – 2003

Cost of Biotech Product Development

- This is a lot of money
- Once the product is approved or licensed, this development investment begins to be transformed into revenue cash flow, which funds the next generation of product development for both new products and improvements to existing products
- Just as on product safety matters, industry, regulatory community, and academic community have a collective responsibility to invest development money wisely to achieve benefits for patients and citizens with medical needs

Some New Model Predictions

- In the 8 years (typical FIH to approval metric for biotech) going forward from 2006, applying the DiMasi-Grabowski study results to the PhRMA survey output would predict 30% success rate for 193 protein products in clinical development
  - This translates to 58 new approvals 2007 – 2015 at a capitalized cost of $ 70 billion (plus inflation)

Suggestions to Reduce Development Costs

- Continue to expand the ICH model to provide expert guidances which
  - Eliminate duplicative studies
  - Eliminate unnecessary studies by utilizing modern approaches (e.g., quality risk management) to invest in studies which create value and add quality, and avoid those which do not add value or quality
  - Provide common technical platforms which are broadly accepted for how to conduct expensive efforts (e.g., process validation, analytical method specification setting)

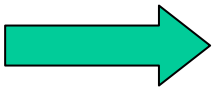
MANAGING WORLDWIDE SPECIFICATIONS :

IMPLICATIONS ON PRODUCTION DISTRIBUTION

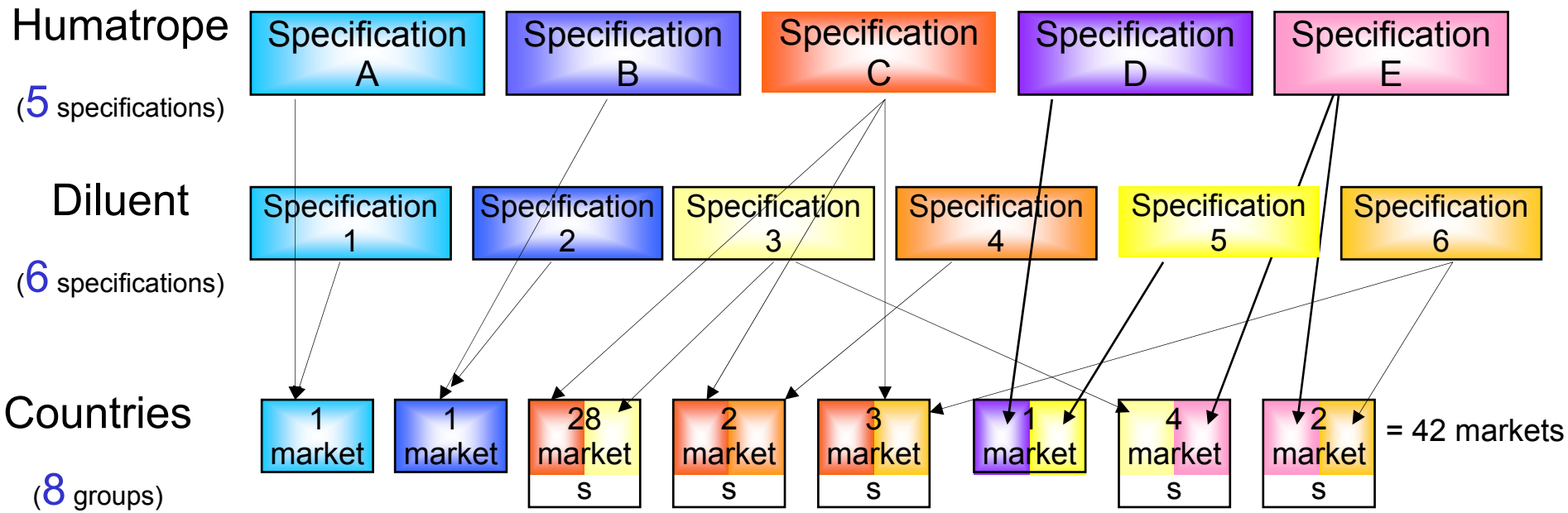
Nadia BEAUDOUX – Fegersheim Regulatory Affairs Manager, Eli Lilly & Company

1. EXAMPLE OF HUMATROPE : FEW NUMBERS (1/3)

- 3 dosage forms : Humatrope 6 mg, 12 mg, 24 mg
- 5 different specifications registered at release for each dosage form of Humatrope
- Used in combination with a diluent (2 dosage forms)
- 6 different specifications registered at release for each dosage form of diluent
- Currently registered in 42 markets
- 8 different groups of countries :



1. EXAMPLE OF HUMATROPE : FEW NUMBERS (2/3)



1. EXAMPLE of HUMATROPE : FEW NUMBERS (3/3)

•The DIFFERENCES between specifications are linked to :

• differences in Pharmacopoeia (USP, EP, JP) :

- difference in the content : if not harmonized, this means at least 3 different specifications
- difference in publication dates

• also specific requirements from local Authorities

• time of approval : the commitments change

• timing for a registration : if a variation is in progress, some countries have already approved, some others have not yet approved

3. SPECIFICATION CHANGES AND IMPAC ON DISTRIBUTION (1/3)

A. Reasons of changes :

- Monograph update
- Specific requirements from Authorities
- Internal decision to harmonize methods between products
- Internal decision to update analytical method following new technology
- …

Most of the time, each of these changes require about 6 months delay before approval : in Europe for biotech products, about 90% of changes are type II, even for a drug product to comply with European Pharmacopeia whereas the same change might be annual reportable in the US….it may also be the opposite.

3. SPECIFICATION CHANGES AND IMPACT ON DISTRIBUTION (3/3)

C. IMPACT :

- All these changes mean that Regulatory Affairs manages 10 or 20 groups of countries rather than 8

- We manage about 2 manufacturing changes by quarter, that means huge amount of hours to track the registered commitments month by month

4. CONCLUSION

- Managing worldwide specifications is a daily activity in industry
- Huge amount of hours and ressources used to track commitments

➡ To reduce the workload :

1. already in place internally :
   - laboratory experts write internal methods which complies both with EP/USP requirements (harmonized methods) or with 2 internal Lilly methods

2. would be strongly appreciated from Agencies :
   - to lighten the process for changes to comply with Pharmacopoeia
   - to recognize other Agencies rules in order to reduce the registration timings
   - to accelerate Pharmacopoeia Harmonization.

ICH Q4B Pharmacopeial Harmonization

- Now an official Step 4 document, regional regulators (through ICH Q4B EWG) can now declare when compendial monographs are considered interchangeable
  - Not same as mutual recognition
  - Not same as harmonized compendial monographs or analytical methods (although this is still a goal of Q4B EWG)
  - Does encourage reasonable interpretations of compendial quality considerations based on scientific principles to take precedence over other considerations
  - Will hopefully minimize the number of manufacturing changes needed to be made to biotech products which only add to cost, and not provide real improvements in quality

Suggestions to Reduce Manufacturing Costs

- Provide incentives via ICH Guidances and regulatory process harmonizations to facilitate adoption of process improvements and QbD approaches for biological products
  - Regulatory community must make regulatory relief a reality which translates to economic value
- Minimize the number of regulatory changes to approved/licensed products required for global compendial compliance
  - Harmonized global specifications
  - ICH Q4B harmonization of compendial requirements

Vision of the Future – Development

- If the regulatory relief and other benefits under QbD approaches are significant and create economic value, they will encourage investment in application of QbD approaches
  - In early development for new products
  - In late development products and even post-approval processes for some products developed in the old paradigm where value is greatest

Vision of the Future – Manufacturing

- In the major pharmaceutical marketplaces, the incidence of drug quality problems is very low, and there are very few patient problems resulting from product quality issues
- In most of the major pharmaceutical marketplaces, the regional government is also a major payor or purchaser of pharmaceutical products, as well as the source of funding for the pharmacopeia
- It makes good scientific sense, and from many other perspectives, to approve products with harmonized global specifications, and to limit changes in compendia to those which truly affect product quality in a positive manner, and to abstain from compendial changes which only add cost
- Industry welcomes ICH Q4B and encourages the regional regulatory community to use it wisely to reduce the burden for themselves, for the industry, and for the payors