Evolution in FDA’s Approach to Pharmaceutical Quality

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Agenda

• The historical trajectory of FDA quality regulation
• Current status
• Proposal for Office of Pharmaceutical Quality and further evolution
• Implications for generics industry
Quality Regulation is the Basis of Drug Regulation

- Initial impetus came from bad quality products being foisted on the American public
- Harvey Wiley and the “poison squad”
- The earliest drug regulators were chemists
- Focused on impurities and toxic substances
- Quality remains the foundation of assurance of drug performance
20th Century Saw Development of Standards for both Manufacturing and Testing

• GMP regulations published in 1978
• Evolution of CMC filing and submission requirements
• Beginning in 1990s, ICH sought international standardization of requirements, including many CMC areas; common technical document
• Ongoing reliance on USP and other national pharmacopoeias for public standards
Early 2000s: FDA Embarks upon Pharmaceutical Quality for 21st Century Initiative

• Vision:

• “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
21st Century Initiative

• Succeeded at many levels:
  – Introduction of QbD
  – Facilitated use of modern technology
  – Updates to GMP regs
  – Multiple ICH documents: Pharmaceutical Development; Quality Risk Management; Quality Systems
  – Focus on manufacturing science
  – Formation of pharmaceutical inspectorate
However, Did not Achieve a Regulatory System that would Enable the Vision

- Therefore, we are making another attempt
- Proposed reorganization is only a part; also working on changing work processes and content
- GDUFA is one impetus: requires more efficient CMC review process focused on risk
  - Need to make changes while also clearing backlog and getting review on a real-time basis
- Breakthrough therapies on new drug side another impetus
  - Faster clinical development puts pressure on manufacturing side
Current Problems

• OGD backlog and large number of manufacturing supplements
  – Time required for regulatory go-ahead holds back or blocks facilities improvements, e.g., site changes, major upgrades
  – Manufacturers with robust quality systems should be able to manage such changes without regulatory oversight

• Need for ongoing innovation in manufacturing
  – Regulatory oversight one factor in lack of industry adoption of modern manufacturing technology

• Drug shortages, recalls: lack of indicators of quality cross-industry; can we predict these problems?
Organizing Principles of Change

• Establish clear standards for review and inspection
• Clear enforcement policies
• Same standards for all drugs; lifecycle approach
• Specialization and team review: integration of review and inspection for a quality assessment
• Clinically relevant standards
• Surveillance using quantitative metrics (Russ Wesdyk will discuss in following presentation)
• Overall QMS and evaluation system
Clinical Relevance

• Definition of adequate quality: delivers clinical performance described in drug label and is not contaminated

• Clinically relevant specifications: based on risk to clinical performance, not what can be achieved by process

• Clinically relevant manufacturing standards: deviation should have clear link to risk of substandard clinical performance

• Standards should include human factors analysis—end user is very important for medicines
Lifecycle Approach

- Propose to organize review post original NDA by dosage form; same team to review generics for single innovator sequentially to improve efficiency and knowledge
- Integrated team for review of facility and manufacturing process therein, also assesses need for inspection
- Surveillance activity for all facilities manufacturing marketed drugs or API
Policy and Standards

• Much greater emphasis on transparent standards (and how they are enforced)
• Propose forming an Office of Policy in proposed OPQ
• It would both develop standards and assess our performance against the standards
• Support both OPS/OC Policy Council and proposed re-instated cross-Agency Council on Pharmaceutical Quality (CBER, CDER, CVM, ORA)
Operations

• Would like to run the CMC review using centralized project management
• We are aware that the generic industry is concerned about getting, as early as possible, resolvable questions, and also an early indication of review status
• Difficult to accomplish all this while also clearing the backlog and getting a timely review process up and running
• We will make every effort to meet the needs of industry as this project evolves
Operations

• Assessing content and process of review and how quality assurance is conducted
• Aim for a more targeted and efficient process with fewer repetitive reviews
• QbR sought to standardize approach: can it be further refined?
• Aim for a more efficient process that also captures more of the clinically relevant quality problems
cGMP Standards and Inspections

• Would like to evolve to very clear, written standards and inspectional procedures
• Industry quality management system must be the mainstay of maintaining adequate quality
• Use of quantitative metrics should help in assessing which facilities are at risk, and which are operating in control based on a strong QMS
• Hope to use to direct inspections
• Hope to evolve towards new approaches towards manufacturing supplement requirements
Specific Issues for Generic Drugs

• Much less experience manufacturing a new generic at commercial scale than new drug, at time of approval
• Puts more emphasis on surveillance during marketing phase
• Some manufacturers have platform used for multiple products; experience in manufacturing at scale may be quite relevant
• I’m told many generics never marketed despite approval
Risks Associated with Initiative

• Internal and external stakeholders may be concerned with direction: it represents a change in approach
• Magnitude of effort required for GDUFA requires major focus on accomplishing those goals; changing FDA approach to drug quality also a heavy lift
• Further government cutbacks, “sequestration”, etc, may diminish resources available for effort
Role of Industry

- FDA plans to be transparent and engage external stakeholders as we initiate changes.
- Technical experts in industry and professional societies have been and will continue to be consulted.
- We are interested in your ideas.
- This is likely to be a multi-year process; there will be ample opportunity for input.
- Now only in early stages.
Next Steps

• We will be working on a proposed organizational structure over the next months
• Putting this in place will require ~6mths
• In parallel, will develop relevant procedures and processes
• Also, will be developing some changes in approaches concurrently
• At the same time, working to implement GDUFA
Summary

• FDA has made some progress in improving its overall approach to regulating pharmaceutical quality, but major challenges remain
• We are looking at this again, and taking a comprehensive approach to change
• We are planning to make coordinated organizational, process, and policy changes that will move us more towards our articulated vision
“A MAXIMALLY EFFICIENT, AGILE, FLEXIBLE PHARMACEUTICAL MANUFACTURING SECTOR THAT RELIABLY PRODUCES HIGH QUALITY DRUGS WITHOUT EXTENSIVE REGULATORY OVERSIGHT.”