Medical Product Quality Paradigm and FDA Program Alignment Efforts

Howard R. Sklamberg
Deputy Commissioner
FDA Office of Global Regulatory Operations and Policy

GMP Conference
March 11, 2014

Quality Focus for FDA

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

Current problems

- Need for ongoing innovation in manufacturing
- Drug shortages, recalls: lack of indicators of quality cross-industry that make it difficult to focus FDA inspections on quality issues; can we predict these problems?
- Compliance with FDA regulations becomes the low bar to meet rather than industry efforts to hit the highest quality mark on a maturity matrix

FDA Mission

- Make sure beneficial drugs are available, and substandard or harmful drugs are not
- FDA in general has a *health promotion* as well as *health protection* mission
- Clinical review results in a *risk-benefit* assessment
- Need to make *risk-based assessment* of product quality as well

Mission of our Drug Quality Organization

- Help expedite availability of new beneficial Rx (e.g., breakthrough drugs) and needed drugs (e.g., shortages)

- Ensure all US marketed drugs are of adequate quality (will perform clinically) through
  - establishing standards
  - premarket review
  - surveillance

Vision for 21st Century Manufacturing

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

- Are we there yet?

Field Alert Reports (FARs) are Increasing

- FARS increased from approximately 250 in 2005 to 1,560 in 2011.
- The purpose of the New Drug Application (NDA) Field Alert Program is to quickly identify drug products that pose potential safety threats. All drug manufacturers with approved New Drug Applications ((NDAs) and Abbreviated New Drug Applications (ANDAs) are required to submit Field Alert Reports to the FDA if they find any significant problems with an approved drug. Reports must be submitted to district FDA offices within three days of a problem being identified. Information that must be reported in a Field Alert Report includes:
- any incident that causes the drug product or its labeling to be mistaken for or applied to another article,; bacterial contamination,; a significant chemical, physical, or other change, deterioration in the distributed drug product, and failure of one or more distributed batches of the drug product to meet the specifications established in its application..
- The division determines whether drug firms are complying with the NDA Field Alert Report requirements by evaluating the reports and any investigational information that is sent to the division by the eistrict offices, coordinating investigational and regulatory actions with FDA headquarters and the district offices, issuing assignments to investigate NDA Field Alert reports, and providing guidance on enforcement issues, and recommends regulatory action.

Supplements to Post-Approval

- The number of supplements that come in post-approval is a concern.
- The Agency continues to see a high number of supplements that come in shortly (1-3 years) post-approval.
- Our goals, as noted in the decade old 21st Century Initiative, is to lower the number of supplements.
- With our renewed focus on pharmaceutical quality we would like to see robust applications that don't need supplements shortly after approval.
- This type of improvement is going to take work on the industry and FDA side.

Why Are We Not There Yet?

- **Industry**
  - Has ultimate responsibility and authority over the product it manufacturers
  - QbD should be positively impacting quality
    - Quality = Knowledge + Systems + Culture/People
    - QbD = Knowledge of product and process
      - Perhaps not an ideal regulatory tool, but a critical aid to quality
- **FDA/CDER conducted an internal assessment**

Smart Regulation

- Obligations as a Regulator:
  - Consistency, cannot be arbitrary or capricious
  - Transparent processes
  - Clear standards that the “regulated” must conform to, that are no more burdensome than needed to achieve the objectives
  - To be effective
  - To be efficient (not our money)

What This Means within GO?

- Need to align with all medical product Centers on quality initiatives
- Work with Centers to implement a risk-informed approach that incorporates assessment of quality performance:
  - Require corrections where standards not met
  - Enforce against those who (severely or repeatedly) violate standards
  - Enforcement also should have clear standards and policies
  - Not arbitrary or capricious

Addressing emerging drug quality issues

- FDA will improve its overall approach to regulating pharmaceutical quality
- We will be 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
  - Office of Pharmaceutical Quality (OPQ)
  - Program Alignment Initiative

Program Alignment across FDA

- Transition to distinct commodity-based and vertically-integrated regulatory programs with:
  - Well-defined leads
  - Coherent compliance policy and enforcement strategy development
  - Well-designed and coordinated implementation
  - De-layered management structure
  - Investigators, compliance officers , import reviewers, laboratory personnel, and managers to become more specialized in a particular regulatory program

Quality Safety Initiative from a GO Perspective

- Specialized investigators who are better trained and can focus on critical to quality factors
- Team approach with Centers to speak with one FDA voice, provide consistency across multiple districts for same firm
- Comprehensive and up-to-date standards to inform compliance policy and enforcement strategies
- Clear risk-based resource allocation to direct investigational attention to firms that do not demonstrate maturity in quality systems

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

Quality Focus for Industry

Commitment to quality

- Essential… from the top down and bottom up
- Cannot settle on "meeting regulators standards"
  - Must meet ***YOUR*** standards to reliably produce high quality products
- What Dr. Woodcock has said…
  - proactively identify & promptly correct issues
  - design/qualify robust operations
  - maintain equipment and facilities
  - Implement robust quality management systems
- Significant impacts to the public's health
  - Cost of poor quality – $$$$$$$$$$$$$
  - Cost to patients – shortages, adverse events, etc.

A quality system creates real fixes

- A robust quality system is:
  - Science and risk-based
  - Vigilant and Proactive
  - Culture-focused
  - Able to identify issues while they are still small
  - Responsible for assuring any contracted site is qualified to do the function, and performed it satisfactorily
  - Supportive of business needs because it creates dependability and sustainability, as well as efficiency and effectiveness!
- It should not be:
  - Reactive or defensive (issues should be surfaced)
  - Solely a procedural approach (only “plan-do”)

An effective quality system…

- Yields quality and business benefits
  - Cost of poor quality survey published in December 2012
- Support and ownership of quality goes beyond the Quality/Compliance units
- Scientific risk management throughout the process lifecycle yields many benefits:
  - Enhanced process stability drives productivity and performance
  - Prevention reduces compliance risks and costs
  - Fewer significant complaints and investigations and therefore more efficient QA release of batches
  - Protection of brand

Thank You!

Howard R. Sklamberg
howard.sklamberg@fda.hhs.gov