Evolution in FDA’s Approach to Pharmaceutical Quality

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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 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 Quality for 21st Century Initiative

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

• 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?
Clinical Relevance

- 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
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
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)
Principles for 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
- Overall QMS and evaluation system
Quality Metrics

• Quality metrics can be useful
  – Surveillance using both leading and lagging indicators

• Considering two major buckets of quality metrics
  – Risk rank sites and products
  – Better structure inspections

• FDASIA Title VII a potentially useful regulatory mechanism
  – Sec. 706 allows FDA to collect information that would have been available on inspection “in advance or in lieu of an inspection”
  – Sec. 705 requires FDA to do risk based inspection (i.e. site stratification schedule)
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
Thank You!

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