FDA/CDER’s Focus on Surveillance

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Vision for 21st Century Manufacturing

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
Fundamental Drivers of Evolution

• One program for drug quality across generic, brand, OTC drugs. Same quality expectations for all marketed drugs = clinical performance

• Expertise-based standards development, review and inspection, surveillance, etc., e.g.,
  – Drug synthesis
  – Manufacturing processes and facilities
  – Policy development
  – Data and surveillance
  – Evaluation
Evolution of Roles

• Quality Review
  – Product Review – “What the product is and how designed”
    • Define effective clinically relevant product specifications… create standards that matter for patients
  – Process/Facility Review – “How and where it’s made”
    • Focus on process… conduct high risk PAIs, an integrated model

• Quality Surveillance
  – Monitoring -- “How products and firms perform over lifecycle”
    • Assess and make quality visible and impactful—for entire inventory of drug manufacturing facilities supplying US market
Vision for Surveillance

Renewed focus to answer the following questions:

• How many sites (that CDER regulate) are there and where are they?

• What do these sites do (products and processes)?

• How well do they do it (products and sites)?

• What are the tactical findings/implications and the strategic drivers/trends?
Quality Surveillance

We can’t conduct surveillance without reasonably reliable and accessible information related to drug quality
Informatics Strategy

Establish a set of strategic informatics capabilities leveraging best-in-class commercial off the shelf software packages that can be configured to address a wide range of business needs.
Required transformation of Informatics

Current State
- Many Databases
- One-off functionality
- Data entry centric
- Single use
- Custom-built
- User requirements
- Silos
- Acronyms

Future State
- Platforms
- Strategic Capabilities
- Work-flow centric
- Scalable
- Off-the-shelf
- Mapping & Matching
- Integrated
- Brands
CDER is Developing a Pharmaceutical Quality Platform (PQP)

• Set of strategic informatics capabilities
• Quality knowledge platform for CDER and ORA
• Manage an inventory of facilities involved in the manufacturing of human drugs
  – What is being made where and how?
  – Link between products, ingredients, facilities, processes and CMC supplements
• Understand the state of quality
  – Establish facility profiles and risk ranking
  – Enable risk-based review and surveillance
Inventory

• Inventory system consolidation, reconciliation, and correction
  – eDRLS
  – EES
  – FACTS
  – OASIS
  – User Fee Systems
  – Other

• Inventory list

• Inventory regulation enhancement

No perfect system or list
Center/Desk Assessment

- FARS evaluation
- Incident evaluation
- Adverse Events
- Recalls
- Sampling program
- Quality Metrics
On-Site Assessment

• New Inspection Protocol Project

• Policy directing surveillance inspections

• Evaluation of inspection reports
  – Enforcement cases forwarded to OC
Surveillance: Increasing Focus on Quality

- Quality Metrics

- Quality Surveillance Inspection
Quality Metrics

What

- Objective measures of the quality of a drug product or production process
- Objective measures of the quality of a site
- Objective measures of effectiveness of systems associated with the manufacture of pharmaceutical products

Why

- Inducing the right behavior and responsibility for industry—Enable better FDA surveillance of state of the firms’ quality
- Reduce product-related shortages and quality related recalls—Promote improved product and process capability
- Achieve product quality without extensive regulatory oversight
Metric Criteria

Regulations
- 706
- 704

Relevant

Unintended
Consequences

Patient

Intrusive (Industry)

Cross-Sectors

Relatable

Objective

Operationalize (FDA)

Quantitative
Drug Shortage – State of Quality?

Reasons for Shortage 2011

- Component Problems: 47%
- Delays/Capacity Issues: 19%
- Discontinuation: 12%
- Increased Demand: 6%
- Loss of Manufacturing Site: 2%
- Other/Unknown: 10%
- Quality Issue: 4%
- Raw Materials (API): 4%
- Other: 0%
- Unknown: 0%
Learning from Drug Shortages

FDA has concluded:

Our current drug inspection paradigm…
– focused on compliance with current Good Manufacturing Practice (cGMP) regulatory requirements

…Cannot not succeed in shifting the drug industry’s focus as needed to achieving and maintaining a state of acceptable product quality
– to ensure clinical effectiveness and patient access to protect public health.
GMP Inspection Findings have not been a reliable predictor of state of quality
Example: Inspection History (October 1999 – December 2011)

<table>
<thead>
<tr>
<th>Inspection Date</th>
<th>Agencies</th>
<th>Inspection Classification</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 December 2011</td>
<td>FDA</td>
<td>OAI</td>
<td>Support Injunction Recommendation</td>
</tr>
<tr>
<td>29 May 2011</td>
<td>FDA</td>
<td>VAI</td>
<td>Injunction Recommended, F/up to 2 FARs</td>
</tr>
<tr>
<td>28 March 2011</td>
<td>MHRA, TGA, AFSSAPS</td>
<td>NAI</td>
<td>FDA classification was NAI, Foreign inspectorate issued significant findings</td>
</tr>
<tr>
<td>27 February 2011</td>
<td>FDA</td>
<td>NAI</td>
<td>No FDA-483 issued, Final classification was NAI. 48 item FDA-483 Pending injunction?</td>
</tr>
<tr>
<td>26 September 2010</td>
<td>MHRA, TGA, FDA</td>
<td>NAI</td>
<td>FDA class NAI based on previous inspection</td>
</tr>
<tr>
<td>25 December 2009</td>
<td>FDA</td>
<td>VAI</td>
<td>For-Cause inspection to follow up on FAR, incorrectly labeled product</td>
</tr>
<tr>
<td>24 July 2009</td>
<td>FDA</td>
<td>OAI</td>
<td>F/up on 1 FAR, F/up to objectionable conditions found during 2009 EMEA inspection</td>
</tr>
<tr>
<td>23 April 2009</td>
<td>FDA</td>
<td>OAI</td>
<td>F/up on significant GMP findings from 2008 inspection</td>
</tr>
<tr>
<td>22 June 2008</td>
<td>FDA</td>
<td>VAI</td>
<td>F/up on recall, ORA Inspection Branch recommended OAI, Regulatory meeting held</td>
</tr>
<tr>
<td>21 February 2008</td>
<td>FDA</td>
<td>VAI</td>
<td>cGMP Inspection, ORA Inspection Branch recommended OAI, Regulatory meeting held</td>
</tr>
<tr>
<td>20 May 2007</td>
<td>FDA</td>
<td>NAI</td>
<td>WL issued for the product for failing endotoxin levels and for failure to thoroughly investigate unexplained discrepancies</td>
</tr>
<tr>
<td>19 May 2006</td>
<td>FDA</td>
<td>OAI</td>
<td>Limited directed inspection</td>
</tr>
<tr>
<td>18 May 2006</td>
<td>FDA</td>
<td>OAI</td>
<td>Biologics inspection</td>
</tr>
<tr>
<td>17 February 2006</td>
<td>FDA</td>
<td>OAI</td>
<td>Pre-approval inspection</td>
</tr>
<tr>
<td>16 December 2005</td>
<td>FDA</td>
<td>OAI</td>
<td>F/U to recall of XXX specific sterile product</td>
</tr>
<tr>
<td>15 April 2005</td>
<td>FDA</td>
<td>OAI</td>
<td>F/U to 6 FARs</td>
</tr>
<tr>
<td>14 June 2004</td>
<td>FDA</td>
<td>OAI</td>
<td>Pre-approval inspection and F/U to 2 FARs and recall of two lots of XXX</td>
</tr>
<tr>
<td>13 November 2003</td>
<td>FDA</td>
<td>NAI</td>
<td>Biologic inspection</td>
</tr>
<tr>
<td>12 November 2003</td>
<td>FDA</td>
<td>NAI</td>
<td>Routine, F/U to one FAR</td>
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<tr>
<td>11 July 2003</td>
<td>FDA</td>
<td>VAI</td>
<td>F/U to Consumer complaint and pre-approval Sample collected, in compliance</td>
</tr>
<tr>
<td>10 April 2003</td>
<td>FDA</td>
<td>VAI</td>
<td>Samples collected, in compliance</td>
</tr>
<tr>
<td>9 May 2002</td>
<td>FDA</td>
<td>VAI</td>
<td>GMP and pre-approval inspection</td>
</tr>
<tr>
<td>8 February 2002</td>
<td>FDA</td>
<td>OAI</td>
<td>Limited Device inspection, no longer manufacturing medical devices</td>
</tr>
<tr>
<td>7 October 2001</td>
<td>FDA</td>
<td>NAI</td>
<td>Biologics Inspection</td>
</tr>
<tr>
<td>6 June 2001</td>
<td>FDA</td>
<td>NAI</td>
<td>F/up to contamination of XXX IB recommended OAI and warning letter not supported by center</td>
</tr>
<tr>
<td>5 October 2000</td>
<td>FDA</td>
<td>OAI</td>
<td>GMP inspection &amp; evaluation of new line</td>
</tr>
<tr>
<td>4 June 2000</td>
<td>FDA</td>
<td>OAI</td>
<td>Routine GMP inspection</td>
</tr>
<tr>
<td>3 March 2000</td>
<td>FDA</td>
<td>VAI</td>
<td>Biologics Inspection, Warning letter recommended</td>
</tr>
<tr>
<td>2 March 2000</td>
<td>FDA</td>
<td>NAI</td>
<td>Pre-approval and GMP inspection</td>
</tr>
<tr>
<td>1 October 1999</td>
<td>FDA</td>
<td>NAI</td>
<td>Route GMP inspection, Warning letter recommended, ORA Compliance Branch changed to VAI</td>
</tr>
</tbody>
</table>
Quality-focused Surveillance Inspection

FDA recognizes the need to clarify the inspection process and work product requirements
- to provide the needed focus on measurement and ascertainment of the state of quality of production and quality systems in the inspected facility
- to support quality risk assessment and risk based inspection as envisioned by FDASIA and required to achieve meaningful mutual reliance.
Drug GMP Surveillance Inspections

Current Objectives:

• Conduct inspection in accordance with FD&C Act and cGMP regulations (and follow established Compliance Programs)

Current Focus of investigator*: 

• Evidence that a violation exists
  – Adulteration
  – Misbranding

• CGMP violations
  – Poor employee practices
  – Poor equipment and facilities
  – Lack of process control

• Application departures
• Data integrity issues

*FDA Drug Manufacturing Inspections: A Collaborative Effort between CDER and ORA, Jan. 9, 2014
Drug Quality Surveillance Inspections

• General principles
  – Inspections should gather analyzable data where possible—to inform on-going quality assessment and “intelligence”
  – Develop an effective and efficient process for quality surveillance inspection [e.g., a new surveillance inspection module]
  – Develop standards for consistently gauging and “grading” state of quality observed by investigator, e.g., across the 6 systems*
    • Specify positive range to build on /expand on current structure of observations focused on failures and deviations
  – Develop an abbreviated (data rich) inspection format and more structured, standardized inspection report.
    • More readily accessible, interpretable, and analyzable post-inspection, to maximize downstream use to inform FDA (and potentially other regulators)
  – Scope: pre-inspection prep through post-inspection follow-up

* Quality; materials; production; facilities and equipment; packaging and labeling; and laboratory control
NIPP

• What is the recipe for a successful inspection, one that adds value and encourages manufacturing quality?

• Inspections should yield semi-quantitative assessments on the state of quality at inspected facilities

• While continuing to document observed deficiencies, inspections should also identify practices that exceed basic compliance.
New Inspection Protocols Project

• FDA-driven internal analysis and modernization of inspection protocols

  Explicitly address manufacturing quality and have the inspection include analyzable observations that will enable us to assess the state of quality in the inspected facility.

  Develop a clearer set of requirements for recognition and reliance on other inspectorates, and provide the kind of information from inspections that will enable reduced regulatory oversight and the related burden for industry.

  For FDA this does not exist today and it will be challenging to develop. We estimate that it will take 2 years to achieve this milestone (i.e., by the end of CY 2015).
Near Future: Envisioned Work

• Following internal analysis, propose work to develop an internationally harmonized basic protocol for the inspection and basic structure for the inspection report
  – This could essentially be a “common technical document” for drug quality surveillance inspection reports—will facilitate sharing with other inspectorates
  – If there is a piece for further standardizing industry reporting to support this there might be a parallel effort undertaken in ICH
Questions?