PQRI Fall Conference October 5, 2015

How to Prevent, Detect and Respond to Data Integrity Events

People Aspects: Ensuring Training Resources, and Environment Promoting Good Documentation Practices

Joseph Famulare ‖ Vice President, Global Compliance and External Collaboration ‖ Pharma Technical Quality, Genentech, A Member of the Roche Group

Agenda

- Background
- War Stories
  - Data Integrity Problems
  - Regulatory Consequences
- Data Integrity Program - Success Factors
- Resources
- Sustaining Good Documentation Practices

Who Will Be the Next Poster Child

Source: Washington Post, Sept 26,2015

Background

- **Data Integrity** is "The degree to which a collection of data is complete, consistent, and accurate" Source: FDA Glossary of Computer Systems Software Development Terminology (8/95)
- **Two main areas of concern regarding data integrity in CGMP operations include:**
  - Providing data to a health authority as a result of an inspection
  - Providing data as part of a regulatory submission e.g., supplements, licensure verification supplement, Field Alert Reports, etc.

When and How Do Data Integrity Issues Occur?

- Data Integrity issues can occur at any time and in any place to any company
- Data may be unreliable due to sloppiness and inadvertent errors. A pattern of errors can raise question about the overall reliability of the data
- "A wrongful act also includes submitting data that are otherwise unreliable due to, for example, a pattern of errors whether caused by incompetence, negligence, or a practice such as inadequate standard operating procedures or a system-wide failure to ensure the integrity of data submissions." FDA AIP March 5, 1998

Data Integrity Problems– Common Causes

- The Quality System does not have adequate controls and oversight of manufacturing operations and processes

- Business and Performance Pressure
  - Time Pressure
  - Inventory Demands
  - Desire to meet metrics/goals

- Cultural Pressure
  - Deliberate attempt to hide errors
  - Desire to deflect accountability

- Inadequate processes and technology
  - Computer systems are not secure
  - Lack of training

Data Integrity is a Regulatory/GMP Requirement US

- US Code of Federal Regulations (CFR):
  - 21 CFR 211.180(d), "*Records required under this part may be retained either **as original records or as true copies** such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records".*
  - 21 CFR 211.194(a), "laboratory records shall include **complete data** derived from all tests necessary to assure compliance with established specifications and standards, including examination and assays"
  - *21 CFR Part 11 (FDA guidelines on electronic records and electronic signatures (ERES)) Sec. 11.10 Controls for closed systems requires "Use of secure, computer generated, time stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information"*
  - *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application*
- Submitting false data to the FDA can be deemed a criminal violation and can invoke FDA's Application Integrity Policy
  - *Title 18 U.S. Code-various sections*

New Q&A on Data Integrity Issues US FDA website

CGMP Questions and Answers on FDA's website include:

- Are shared login accounts OK for computer systems?
- Are electronic signatures OK for master production and control records?
- Can we use actual samples to perform system suitability testing?
- Detailed discussions online: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm

2015 CDER Guidance Agenda includes CGMP Data Integrity Questions and Answers.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf

Source: T. Cosgrove, FDA

MHRA GMP Data Integrity Definitions and Guidance for Industry, WHO Draft Guidance

- Published March 2015
- "Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality."
- "This document provides MHRA guidance on GMP data integrity expectations for the pharmaceutical industry."
- "The effort and resource assigned to data governance should be commensurate with the risk to product quality, and should also be balanced with other quality assurance resource demands"
  - Systems should be designed and operated to provide an acceptable state of control based on data integrity risk and which is fully documented with supporting rationale.

- From WHO: GUIDANCE ON GOOD DATA AND RECORD MANAGEMENT PRACTICES(SEPTEMBER 2015) DRAFT FOR COMMENT
  - http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidance-on-good-data-management-practices_QAS15-624_16092015.pdf?ua=1

War Stories

- Generic Drug Scandal (late 80's early 90's)
  - FDA employees accepted illegal gratuities (bribes)
  - Drug Manufacturers submitted false data in applications
  - Resulted (in part)
    - Generic Drug Enforcement Act (GDEA)
    - Pre-approval Inspection Program (PAI)
    - Application Integrity Policy (AIP)
- Consequences: Department of Justice actions
  - 22 Drug Company Criminal Convictions
  - 70 Criminal Convictions of Individuals (Industry and FDA Officials)
  - $50 million in Fines

Source: K. Takahashi, U.S. FDA,

Data Integrity Issues Examples

- Not recording activities contemporaneously
- Fabricating data
  - Backdating
  - Copying existing data as new data
  - Reporting only passing or unrealistic values (data is too good)
- "Testing into compliance"
  - Re-running samples
  - Basing results on non-scientific rationale
- Analyzing Standard for the Sample
- Discarding or altering data – not saving electronic or hard copy data
- Reported data is inaccurate and/or not supported by raw data
- Forging and/or unauthorized signatures
- Keeping and reporting un-official or private records "Off the Record Book"
- Selective Reporting
- Changing Batch Size
- Bioequivalence testing: "Innovator vs Innovator"

Regulatory Consequences (US)

- Patient Harm
- Recall
- Warning or Untitled Letter
- Import Alert
- Injunction
- Seizure
- Application Integrity Policy Invocation
  - Review of pending applications is halted
  - FDA conserves review resources while validity assessment and corrective actions are implemented
  - Possible withdrawal of affected applications

Reference: K. Takahashi, Senior Policy Advisory, FDA/CDER/Office of Compliance at ISPE Annual Meeting Nov. 2013

Regulatory Consequences (Europe and ROW)

- Recalls, withdraw of products from the market
- Rejection of data (+ withdrawal of approved applications)
- Sanctions, legal actions, fines and prison
- 'Black-listed' (SFDA)
- Refusal to issue GMP certificate or revoke previously awarded one
- Re-inspection, Seizure and Forfeiture
- Warning letters, import alerts, product alerts and notices (suspension, prohibition, restriction)

Consequences of Data Integrity Issues

US regulators banned imports from 39 laboratories in India

- Indian companies make around 30-40% of the generic medicines taken in the US (a 44 billion dollar market)
- Grand total of 39 drug facilities, owned by 27 different companies in India, cannot import to the US (six included last year alone)
- 2014 Recall of 40,000 bottles of medicine due to deviations from cGMPs and laboratory testing
- July 2015, FDA issued an import alert for all drugs manufactured by plant

Source: Financial Times. Sept. 9, 2015

Consequences of Data Integrity Issues

- Ranbaxy Laboratories
- Once India's largest drug company
- 2013 - Fined $500 million by US Dept. of Justice
  - Plead guilty to seven criminal charges including:
    - Selling adulterated drugs
    - Failing to report that drugs did not meet specifications
    - Making false statements to the US government
    - Violations took place between 2004-2007
- Japan's Daiichi Sankyo bought Ranbaxy for $4.2 billion in 2008, weeks before case was filed
  - Took a $3.7 billion write-down on the acquisition six months later

Source: Financial Times. Sept. 9, 2015

Consequences of Data Integrity Issues

- July 2015 – European Union banned 700 Indian-made generic drugs, citing doubts about the credibility of clinical trials conducted by GVK Biosciences.
- Inspection conducted by the French medicines agency (ANSM) cast doubt on the integrity of the conduct of the trials and on the reliability of data generated at the site including:
  - Data manipulations of electrocardiograms over a 5yr period
  - Systemic manipulation of clinical trial data
  - Extended period of time
  - Number of members of staff involved
- Became effective on August 21 and it will be applicable to all 28 member nations

Source: The Economic Times July 25, 2015: http://articles.economictimes.indiatimes.com/2015-07-25/news/64850225_1_gvk-biosciences-french-medicines-agency-generic-drugs

Consequences of Data Integrity Issues

- August 2015 – The World Health Organization (WHO) warned Svizera Laboratories (Mumbai, India), that inspections in July revealed "serious concerns about the integrity, reliability and accuracy of data generated and available at your manufacturing site…"
- Svizera Laboratories is one of four manufacturers with a long-term contract to supply tuberculosis medicines to the "Stop TB Partnership," a WHO-backed organization set up in 2001 to fight tuberculosis in more than 100 developing countries
- Inspectors also criticized the quality of drug testing and said some of the results may have been manipulated
- Svizera will not be allowed to submit new products under the WHO pre-qualification approval process until the notice of concern is lifted
- WHO said approvals would be suspended and it would recommend that agencies stop buying from Svizera if the problems are not rectified within a reasonable time.

Source: Reuters. Sept 4, 2015. http://in.reuters.com/article/2015/09/04/india-pharmaceuticals-svizera-idINKCN0R41JW20150904

Data Integrity Program Success Factors

Executive Sponsorship

- Requires active involvement and support of senior management
- Senior management with executive authority
  - Promotes the data integrity cause
  - Provides appropriate resource allocation
  - Settles difference of opinion and priorities
  - Ensures DI expectations are carried out across all levels of the organization

Data Integrity Program Success Factors

Executive Sponsorship

- **Key benefits** that a DI program can deliver, including:
  - **Reputational**
  - **Financial**
  - **Risk reduction**
  - **Regulatory**
  - **Legal product liability**

Data Integrity Program Success Factors

Cross-Functional Ownership:

- Consists of the firm's functional leaders and departmental supervisors
  - Ex.: Quality, Regulatory, IT, Records and Information Management, Purchasing/Vendor Management
- An effective DI program requires a wide variety of functional inputs across multiple departments, e.g., business functional leaders by department
- Data needs to be controlled across the data lifecycle (creation, disposition, destruction)
- Data also crosses regulatory boundaries that have unique regulatory requirements, e.g., GCP, GLP, cGMP, and GDP

Data Integrity Program Success Factors

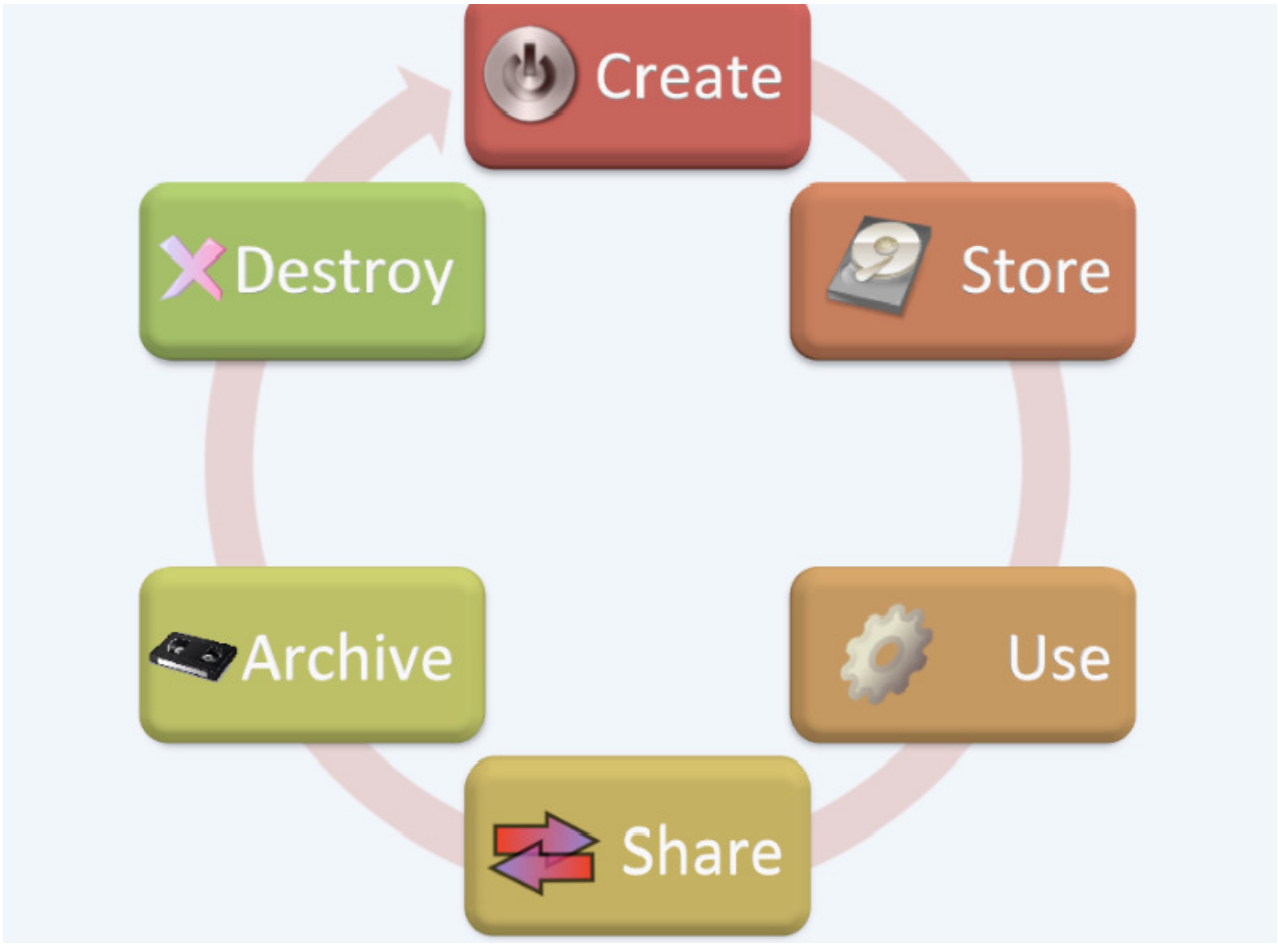
Training and Knowledge Sharing

- Education and Communication on Recognizing DI issues
- Training courses beginning with a sponsor, then functional leaders across the organization are essential
- Communicate that DI is everyone's responsibility
- Mindset shift; DI impacts product quality and ultimately patients' safety
- Outside expertise early is helpful particularly for training workshops and identifying organization habits that need to be changed – ISPE GAMP
- Can result in remove individuals responsible for problems from CGMP positions
- Plan for continual improvement – metrics, reporting, auditing

Resources

- Assure adequate staffing is available throughout the organization
- Quality oversight is essential to assure adequate controls and oversight
- Laboratory overcapacity may lead to “cutting corners”
  - Not all required tests are conducted
  - Testing of release samples may often take precedent over testing of stability samples
- Production understaffing and Inventory Demands
  - May lead to manufacturing short cuts

Sustaining Good Documentation Practices



Doing now what patients need next