EU and US Joint Inspections: Data as the Cornerstone for the Future

FDAnews' 8th FDA Inspections Summit
Washington
October, 2013
What we will see

THREADS

COUNTERFEIT

ADULTERATION

SERIALIZATION

PRODUCT REVIEW

QUALITY METRICS

QUALITY AGREEMENTS

DATA INTEGRITY

MITIGATION MEASURES

ULTIMATE NEED
QUALITY OF MEDICINES IN XXI CENTURY: NEED FOR DATA INTEGRITY AS RESULT OF GLOBALIZED REGULATIONS
Need for data integrity as results of globalized regulations

• International integration arising from the *interchange of world views, products, ideas and other aspects of culture*

• Advances in *transportation, telecommunications, infrastructure*

• “Globalization has fundamentally altered the economic and security landscape and demands a major change in the way Regulators/Drug Products Manufacturers, Distributors, Suppliers fulfill their mission”.
The process for creating global coalition, avoiding rules interpretation, relying on each other and relying on data is on going!

<table>
<thead>
<tr>
<th>PIC/S membership</th>
<th>In continuos expansion!</th>
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<tr>
<td></td>
<td>• 2013 - The latest entries: Taiwan; New Zealand</td>
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<td>• 2013 - The latest applications: Mexico; Japan; Iran; Korea; Philippines</td>
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<th>Inspectional Cooperation Program</th>
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<tr>
<td></td>
<td>• 2011: Jointly announced by FDA &amp; EMA</td>
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<td>• 2012: EMA, Member Authorities and FDA announce further evolution of program to rationalize international GMP Inspections</td>
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<td>• 2013: Now in extension and maintenance phase</td>
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<th>Assessors / Inspectors guidelines</th>
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<tr>
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<td>• Formal incorporation of ICH Quality Guidelines into assessor/inspector guidelines (both EU and US Sides)</td>
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Create Global Coalitions (2/2)

... The process for creating global coalition, avoiding rules interpretation, relying on each other and relying on data is on going!

| APIs for human use: equivalence to EU Regulations of different regulatory framework | • The process is on going! (as per 2011/62/EU)  
• 2013, Sept. - Countries Listed: Switzerland, Australia, Japan, United States (*)  
• 2013, Sept – Contacts on going: Israel, Brazil, New Zealand |

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Note (*): “The FDA’s Listing Request sends a clear and strong message that recognition of equivalent scientifically-based standards better protects the public and provides a greater level of protection for more people. (...) Working with the EU under this Directive is evidence of the FDA’s commitment: to meet the challenges of globalization, to rely on our trusted partners in other countries, and to better use our resources where there is greatest risk” (FDA web-site)
Globalization: New challenges for Regulators

- more outsourcing manufacturing
- greater complexity in supply chain
- imports coming from countries with less developed regulatory systems

- New Technologies are more and more supporting any Actor of the Supply Chain

- fight counterfeit
- create global coalition, avoid rules interpretation & rely on each other
- rely on data (i.e. ensure that data are trustworthy)
Fight Counterfeit

Counterfeit drug incidents – as per Feb., 8th 2010
**WHO**: there is *no agreed international definition of a falsified medical product* and this issue continues to be subject to debate at the WHO.

**EU parliament**: in 2011/62/EU defines a *falsified medicine* as: any medicinal product with a false representation of:

- *Its identity*, including its packaging, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients
- *Its source*, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder
- *Its history, including the records and documents* relating to the distribution channels used

**Council of Europe**: defines *counterfeit within the Medicrime Convention* as meaning: “a false representation as regards identity and/or source”, extending this definition to include both human and veterinary medicines and medical devices.

**MHRA**: no specific definition of counterfeit medical product exists within English law and the MHRA adopts the definition contained within the EU Falsified Medicines Directive.
Counterfeiting

• Etymological meaning: “the fraudulent copy of another’s product without their consent”

• WHO definition: a medical product is counterfeit “when there is a false presentation in relation to its identity (e.g. any misleading statement with respect to name, composition, strength, or other elements), its history or source (e.g. any misleading statement with respect to manufacturer, country of manufacturing, country of origin, marketing authorization holder)”
Adultered Product

the term is **used any time a Company is not complying with cGMP Regulations**. Any medicines that such Company manufactures are considered to be “adultered” under the law. In other words, its medicines are not manufactured under conditions that comply with cGMP. It does not mean that the medicine is necessarily substandard (ref. Barry A Friedman, “What is the meaning of “adultered”?, posted on July 10, 2013)

*also deems a product to be adultered if drugs have been manufactured, processed, packed or held in an establishment by an owner or operator who has delayed, denied or limited an inspection*
Across the globe, drug and food contamination are on the rise.

Counterfeit drugs are infiltrating the life sciences industry at such a rapid rate that, by 2010, it has been estimated that the market value of all counterfeit drugs in circulation exceeded US$300B.
2011/62/EU amending 2001/83/EC and focused on medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified Med. Prods.

- It also provides EU requirements for serialization
- Among the Expected results: a EU Community data base for tracking each packaging unit

→ Whichever system will be implemented, it is supposed to manage the data of more than 10 billion pharmaceutical packs in the 27 countries of the EU per year (ref. EFPIA, 2013)

→ Adopted SW by EFPIA: cloud-based platform

**Italy**: vignettes / “bollini” are used. Such labels provide information on Product Licence Number (AIC/Marketing Authorisation number) and serial number
Technological implications of new Rules

Unrelated Regulations for Serialization

Babel Tower for Rules!!

NEED FOR NEW TECHNOLOGY
From the Manufacturer Point of View

- what is Quality Culture for? Preventing or remediating regulatory compliance violations

- Which are the elements most essential to establish a culture of quality?
  - company’s quality values and principles
  - systems used to support these values
  - people accountable to these values
  - establishing metrics to define success.

- What are Quality Metrics for?
  - they can tell you if you have a competent quality system
  - they can provide you hints for improvement

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Note (1): Ref. Establishing a Culture of Quality for Pharma Compliance, by R. Johnson
From the Regulatory Authority Point of View (2)

- What are Quality Metrics for?
  - Surveillance, using both leasing and lagging indicators
  - Identification of risk rank sites and products
  - Better structure inspections

- FDASIA Title VII “Drug Supply Chain Provision”
  - allows FDA to collect information that would have been available on inspection “in advance or in lieu of an inspection” (ref. sec. 706)
  - requires FDA to di risk based inspection, i.e. site stratification schedule (ref. sec. 705)

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EU

- EU GMP Part I, 1.10-11 (drugs) - EU GMP Part II, 2.60-61 (API) requires Regular periodic (annual) or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, (...). for

- **starting materials** including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances.

- **critical in-process controls and finished product results.**

- **all batches** that failed to meet established specification(s) and their investigation.

- **all significant deviations or non-conformances**, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.

- **processes or analytical methods**

- **stability** monitoring programme and any adverse trends.

- The qualification status of relevant equipment and utilities

- **Returns, complaints and recalls**

US

- **21 CFR 211.180 (e)**: Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.
Need for integration of different Data Sources
Ensuring product supply in the requested timeframe and in any Country
Ensuring that product quality and compliance to applicable regulations is still granted
Saving Costs
Relying more and more on
  new technologies (e.g. virtualization, cloud computing)
  outsourcing
    Costs & efficacy savings
    Focus on your business
    Scalability
    SaaS, PaaS, IaaS
  Security Aspects: back up, disaster recovery
  Highly skilled staff
What these Rules implies

COMPLEX PROCESS
(e.g. anti-Counterfeit, Serialization)

ULTIMATE NEED

DATA RELIABILITY

NEW TECHNOLOGY

MORE RELIANCE ON SW SUPPLIER / OUTSOURCED PROCESS

RULES TO MEET
Main concerns

INTEGRITY
• Data is accurate and reliable

CONFIDENTIALITY
• limiting information access and disclosure to authorized users and preventing access by or disclosure to unauthorized ones

AVAILABILITY
• Ability of a user to access information or resources in a specified location and in the correct format
Global Rule for IT Compliance

Annex 11

21 CFR Part 11

Part 11 Guidance

Warning Letters

US 21 CFR Part 11 & EU GMP Annex 11 are the equivalent Global standards

CHINA CFDA Computer Rule

BRASIL Anvisa Title VII: Computer information systems

CANADA Health PIC/S Annex 11: Computerised Systems
Conclusions: 2 different approaches, but together...

TARGET: Records reliable

STRATEGY: key Rule for reliability

21 CFR Part 11

TARGET: Records reliable

STRATEGY: key Rules for reliability

TACTIC: how to achieve reliability

Annex 11
Conclusions: 2 different approaches, but together…

MEET THESE RULES  DATA ARE RELIABLE
Ultimate Purpose of Computer Regulations

21 CFR Part 11

Annex 11

ULTIMATE PURPOSE

DATA RELIABILITY

INTEGRITY

SECURITY

ACCOUNTABILITY

TRACEABILITY
Increasing Regulatory Pressure on Data Integrity Requirements

- **Europe:**
  - based on our experience, compliance to Annex 11 is routinely verified by Inspectors moving the focus on data integrity and Computer System Validation

- **US:**
  - “imperative that the data generated and used to make manufacturing and quality decisions at your firm is trustworthy and reliable” (WL Fresenius Kabi Oncology Ltd - India, Jul 1 2013)

  - “no protection of the data from alteration and deletion and no audit trails to detect if such alteration or deletion had occurred” (WL Posh Chemicals Private Ltd - India, Aug 2 2013)
HOW TO RELY ON SUPPLIERS ENSURING COMPLIANCE
Caveats: Who is accountable for Compliance?

FDA is clearly stating that outsourcing accountability is not only illegal, but that if companies try to get around this by mutually negotiating a transfer of accountability in a Quality Agreement, this will also be held by the agency as a violation of the Food, Drug and Cosmetic Act (FDCA).

FDA cites the Park Doctrine (from United States v. Park, 1975) to hold the firms and their management accountable for criminal wrongdoing even though they delegated cGMP work task responsibilities to their suppliers through contracts.

Accountability ALWAYS relies within Regulated Company.

To the FDA then, the Contracted Facility is only responsible for completing the actual work tasks as delegated by the product Owner. The product Owner is accountable for the compliance of those work tasks and for the quality, safety, and efficacy of any resulting drug product.
What is IT Outsourcing

IT Services delivered as
Service may greatly vary

HOSTING SERVICES
The Supplier provides/manages
IT Infrastructure Component(s) in
its Data Center (Servers, Networks, Clients)
SW Application(s) are completely
under the control of Regulated

APPLICATION MANAGED SERVICES
Service provided by the Supplier may
include the management and tuning of
databases, the configuration of
applications or general performance monitoring

CLOUD-BASED SERVICES
Service provided by the Supplier
may include the management and
tuning of databases, the
configuration of applications or
general performance monitoring
Cloud Computing Models: a clarifying view

IaaS
- Configuration
- Applications
- Data
- Runtime
- Security, Clustering
- Operating System
- Virtualization
- Servers
- Storage
- Networking

Vendor Manages

PaaS
- Configuration
- Applications
- Data
- Runtime
- Security, Clustering
- Operating System
- Virtualization
- Servers
- Storage
- Networking

Client Manages

SaaS
- Configuration
- Applications
- Data
- Runtime
- Security, Clustering
- Operating System
- Virtualization
- Servers
- Storage
- Networking

Vendor Manages

Client Manages
### Outsourcing Services (examples)

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<tr>
<th>SERVICE</th>
<th>HOSTING SERVICES</th>
<th>APPLICATION MANAGED SERVICES</th>
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<tbody>
<tr>
<td>SW Release Management</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SW Application Configuration/Build</td>
<td></td>
<td>(X)</td>
</tr>
<tr>
<td>SW Application Customization</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SW Application Testing</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SW Change Management</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Logical Security Management</td>
<td></td>
<td>(X)</td>
</tr>
<tr>
<td>Physical Security Management</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Disaster Recovery</td>
<td>(X)</td>
<td>X</td>
</tr>
<tr>
<td>Backup &amp; Restore</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Server Management &amp; Qualification</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Network Management &amp; Qualification</td>
<td>X</td>
<td>X</td>
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Outsourced Service can be used for GxP Systems provided that

- Providers are formally qualified to ensure that adequacy of internal IT quality management system (including appropriate GxP awareness training) for each delivered Service

- Formal Service Level Agreement (now explicitly required by Regulations) for each delivered Service (at each relevant location)
Cloud Computing Models

- **IaaS**: Infrastructure as a Service
  - host
  - higher IT management cost

- **PaaS**: Platform as a Service
  - build

- **Saas**: Software as a Service
  - use
  - lower IT management costs

Abstraction
Cloud for Regulated Companies: enablers or blocking?

BEWARE THAT

- CLOUDING INCREASE RISKS
- THE IMPLEMENTED CLOUD MODEL/DEPLOYMENT/SERVICE
- (EFFECTIVE) PROVIDER QUALIFICATION IS A MUST

(*) D.Stokes - July/August 2013 PHARMACEUTICAL ENGINEERING
Developers / Computerised Systems providers

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Computerised System Validation Suppliers

Validation with the SW supplier should be performed only in case the Supplier can demonstrate the independence of validation service from SW development / management
Provider Continuous Audits and Qualification is Key to use this technology.

It’s a challenging task as it requires new approaches and a vast knowledge in different topics:

- GxP and CSV
- IT technology
- IT certifications
- Legal

Each location shall be verified.

Without a know how in IT Infrastructure it’s quite impossible to achieve a meaningful Audit!
Suppliers Selection & Supplier Audit should take into consideration:

- SW development
- Infrastructure
- Application management

Do not commit to “Black Box-Suppliers”
Europe EU GMP, Chapter 7 “Outsourced Activities”

- “Prior to outsourcing activities, the Contract Giver is responsible for assessing the **legality**, **suitability** and the **competence** of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this Guide are followed.” (EU GMP, Ch. 7, 7.5)

- “The **Contract Giver** should be responsible for **reviewing and assessing** the records and the results related to the outsourced activities.” (EU GMP, Ch. 7, 7.8)

- “The **Contract Acceptor** should ensure that all **products, materials and knowledge delivered to him are suitable for their intended purpose.**” (EU GMP, Ch. 7, 7.10)

US

- **21 CFR 111.75**: pharmaceutical, biotechnology and even dietary supplement makers must **qualify and monitor** any supplier providing GxP-relevant services or materials

- From 2003 on: 170 WLs citing firms for **inadequate qualification and supervision of suppliers** such as **consultants** and **auditors** firms (ref. Cerulean, Vol 7, No. 72, 2013)
Suppliers & Computer System Validation:

• Define the kind of service you are purchasing and verify Suppliers’ knowledge
  • Is the Supplier a SW developer?
  • Is the Supplier a Computer System Validation Expert?
  • Is there any conflict of interest between purchased service and Suppliers’ expertise?

• Does the supplier know your requirements?
• Check Supplier Competence on Computer System Validation

• Does the Supplier have a Quality System in place?
• What kind of technology are they using?

• Do they outsource any activity?
HOW NEW TECH MAY FACILITATE
IT tools: simple and key Enablers

Nowadays a number of IT SW tool (e.g. Winlock™, Verdasis™, Desklock™) allows fast and cheap solution to common Compliance-related Security issue

What you can get for 30 $

- Security tool - allows to restrict access to important system resources like Control Panel, desktop, system registry, disable Windows hotkeys (such as Alt-Ctrl-Del, Alt-Tab, Ctrl-Esc, etc.) and hide the Start button and taskbar
- Deny access to selected files, applications, and Explorer windows (Recycle Bin, My Computer, etc.) and USB removable storages and hard drives
- System restrictions - disable command prompt, Desktop, Control Panel, Safe Mode etc.
- Restrict Start Menu - hide the selective Start menu items, block context menus
- Installation blocker - prevent users from installing the software
- Hide drives - hide your system and network drives in Windows Explorer
- Window blocking - block virtually any application or any part of it: window, popup message, dialog box
- Logging - monitor changes to the Windows shell and writes these changes to the log file

Consider also stable, low-cost EDMS (e.g. Sharepoint™, Alfresco™)
Electronic Document Management System are currently available embedded in the OS (e.g. Sharepoint™) or Open Source (e.g., Alfresco™)

EDMS may greatly facilitate IT Compliance
⇒ Version History
⇒ Robust Archiving
⇒ Easy-to-use Approval Workflows
⇒ Paperless Regulated Records allowed
Virtualization: good news for Compliance

Virtualized approach allows a feasible, cost effective facilitator for following compliance processes:

- Retirement
- Equivalent Testing environment
- Disaster Recovery
- Clients Management
Retirement through Virtualization

THE WHOLE COMPUTER SYSTEM, INCLUDING SW APPLICATION, DATABASE AND OPERATING SYSTEM IS RECREATED ON A VIRTUAL MACHINE ENVIRONMENT

ORIGINAL WORKSTATION CAN BE DISMISSED

USERS CAN ACCESS THE SW APPLICATION IN THE VIRTUAL ENVIRONMENT TO RETRIEVE DATA AND TO ELABORATE USING AN IDENTICAL COMPUTER SYSTEM NO INSTRUMENT CONNECTED (NO NEED FOR THAT)
Ultimate results of the Virtualization process

**DIRECT VIRTUALIZATION**
A virtual machine is created directly from System through a standard converter tool

**IMAGE BASED VIRTUALIZATION**
The image of the original hard disk is created through a standard tool and then loaded in Virtual Machine

**VIRTUAL REINSTALLATION**
The SW application is installed on a Virtual Machine with the same original HW/SW elements
Data are copied from the original system to the virtualized one

- **IDENTICAL**
  - COMPUTER
  - VIRTUALIZED SW APPLICATION

- **EQUIVALENT**
  - COMPUTER
  - VIRTUALIZED SW APPLICATION
CASE FOR LIVE SYSTEMS

CHANGE CONTROL

ARCHIVING

PROCESSES FACILITATED BY THE VIRTUALIZATION
Virtualized application can be used to:

- implement and test changes before the installation in the effective environment
- To archive data
OPC Server may be included to make data retrieved from PLCs available to superior level Systems.

Virtualization of OPC Server.

Packaging Lines (e.g. PLCs)
Conclusions

- New Challenges are triggered by Global Supply Chain Process
- A number of different Regulatory measures have been defined by Regulatory Bodies to mitigate Risk to Product Quality
- Compliance to new Regulatory is ultimately based upon Data Integrity
- Regulatory Requirements for new New Technology can provide robust Enablers for IT Compliance
- Outsourcing & Cloud Computing can be used by Regulated Companies provided that a strict Provider Qualification/Monitoring process is in place

The complexity of Technology might be the only chance we have to face the current challenges for pharmaceutical industry (globalization, cost reduction) ...

.. Complex answers to complex problems
If you have any question, feel free to contact me.

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