Supply Chain Compliance
meeting today’s FDA and EMA cGMPs

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Agenda

real-world challenges
new regulatory requirements
helpful harmonized guidance
defensible compliance techniques

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“I know the regs – isn’t that enough?”

When the GMPs were written....
When the GMPs were written....

And then the QSR was published....
And then the QSR was published....

Since 1999,
only 10% of all FDA requirements

Source: Hyman, Phelps & McNamara 2012
have made it into regulation form

Translation:

Relying on last century’s regulations leaves us blind to 90% of today’s rules
companies have an average of **651 suppliers** each

Source: International Journal of Purchasing and Materials Management
Institute for Supply Management, 2010

Multi-Tier Supply Chains…

1. Taixing Glycerin Factory (China)
   - Substituted DEG for glycerin
   - Labeled as “Glycerin USP”
   - Added indecipherable symbol to mean “substitute”
   - CoA reads 99.5% pure

2. CNSC Fortune Way (China)
   - Replaces mfg. name with its own on CoA
   - Translates to English
   - No testing

3. Rasfer International (Spain)
   - Replaces CNSC name with its own on CoA
   - No testing

4. Medicom Business (Panama)
   - Alters expiration date
   - No testing

5. Social Security Administration (Panama)
   - No testing
   - Makes cough medicine using tainted glycerine
...with very little leverage

More than 11% of the entire global workforce...

Source: Australian Virtual Business Network, 2011
...work for a **virtual company**

**Translation:**

1 out of 10 of your suppliers **is virtual**

...so which one?
Compliance-at-Any-Cost…?

$4,500

$18,000

$25,000

$20,000

$15,000

$10,000

$5,000

$0

Material / Services

Qualification / Oversight

- QC/CAPA/Verif.
- Track/Trend
- Onsite Audit/Travel
- Qualif. Prep/Report
- Legal Fees
- Purchase Price

$20,000
Product Liability Chain Gang

- Product liability lawyers sue name on label
- During “discovery,” uncover:
  - your suppliers (or you if hiding behind label)
  - your oversight (or lack thereof) of your suppliers
- Add additional names to litigation
- Failure to secure supply chain – to modern standards – is direct basis for liability*

*most recent example: see Triad Group, H&P Industries recalls (2012)
http://www.nbcnews.com/health/potentially-tainted-wipes-destroyed-embattled-firm-moves-forward-1C6436047
“…is responsible for…” ≠
“…is accountable for…”

Technology & science improve every 6 months
Regulations change every 10-14 years.

Eight **Daily** Challenges

- Latest FDA requirements are outside the CFRs
- Oversight process must handle 651 suppliers
- 10% of your suppliers are virtual companies
- Limited leverage in a multi-tier supply chain
- Cannot afford compliance-at-any-cost
- Litigation chain-gang approach to product liability
- Confusion over “accountability” v. “responsibility”
- Regulatory process cannot keep pace with today
FDASIA 2012  
EMA cGMP  
EU Falsified Medicines Directive  
EU Good Distribution Practices  

NEW REGULATORY REQUIREMENTS

“So ... if everything is open to interpretation ... does that mean my label translator or my printing company have to comply with GMPs or QSRs?”
FDASIA 2012

Title VII – Drug Supply Chain

• Clarifies types of suppliers that comprise the drug supply chain
  • Contract manufacture organizations (CMO)
  • Contract research organizations (CRO)
  • Contract clinical sites
  • Contract laboratories
  • Contract sterilizers
  • Contract label and product insert designers
  • Contract distributors
  • Contract active pharmaceutical ingredient (API) makers

FDASIA 2012

Title VII – Drug Supply Chain

• Registration system for ALL drug facilities
  • excipients: name, location, p.o.c. contact info, UFI
• Expands “adulterated” to include drugs or drug materials held/made in facility that:
  • refused, delayed or tried to limit FDA investigators
• Requires drug makers to provide FDA with supplier monitoring/qualification records
FDASIA 2012

Title VII – Drug Supply Chain
- Allows FDA to adopt risk-based inspections relying on:
  - compliance history of the site
  - record, history, and nature of the recalls linked to the site
  - inherent risk of the product manufactured, prepared, propagated, compounded, or processed at the site
  - inspection frequency and history of the site, including whether the establishment has been inspected w/in the last 4 years
  - whether the site has been inspected by a foreign government recognized as having standards similar to the FDC Act
  - any other criteria that FDA deems are necessary and appropriate
- Tells FDA to craft GDP-esque regulations by July 2014

EMA cGMP

New Chapter 1: GMP – Pharmaceutical Quality System

Specifies role of senior management (e.g., officers of company):
- Senior management of “Contract Giver” (i.e., purchaser) accountable for supplier oversight
- Senior management of Contract Giver must periodically review:
  - supplier/outsourced service provider performance
  - supply chain traceability
EMA cGMP

New Chapter 1: GMP – Pharmaceutical Quality System

Clarifies supplier management as part of quality system:
– Selection and monitoring of suppliers (materials and services) for medicinal products falls under QS of Contract Giver
– Requires adherence to Good Distribution Practices (GDPs)
– Contract Giver must specify – in contracts with CMOs – responsibilities for each portion of the Product Quality Review

EMA cGMP

Chapter 5: Production

Requirements in context of starting materials:
– Purchase materials only from approved suppliers
  • if possible, purchase directly from original producer of material (i.e., avoid off-the-shelf where possible)
– Supplied materials should have documented specifications
– Staff dealing with suppliers should be trained and knowledgeable
EMA cGMP

New Chapter 7: GMP – Outsourced Activities

For Non-Off-the-Shelf Materials/Services:

- Requires written contracts
- Contract must:
  - specify responsibilities AND communication
  - clearly define which party is responsible for each step of outsourced activity
- Contract should allow Contract Giver to audit the supplier
- Contract should specify that records are to be kept (or otherwise given to) the Contract Giver and not retained by the supplier

Responsibility of Contract Giver

- Accountable for all supplied materials and services
  - includes any records required by regulation/law or to prove conformance
- Prior to contract, Contract Giver must assess supplier
- Throughout contract, Contract Giver must monitor and continuously evaluate supplier performance
EMA cGMP

New Chapter 7: GMP – Outsourced Activities

Responsibility of Supplier
– Responsible for carrying out terms of contract
– Not directly accountable for compliance with cGMPs unless part of normal operations (e.g., Contract Giver cannot delegate accountability for cGMP compliance to supplier)

EMA cGMP

Updated FAQs on cGMP and cGDP
www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp

Qualification of API makers
– Content of audit reports
– Qualification of auditors
EU Directive 2011/62/EU

New Falsified Medicinal Products Directive


Overall
– does not apply to research/investigational drug products
– creates public database of compliance status/certificates issued by Member States for entities by end of 2013
– clarifies that WHO and ICH standards are equivalent to EU

Responsibility of MAA Holder
– verify compliance of contract manufacturers and API distributors
– conduct onsite audits at CMOs and API distributors

EU cGDP

Revised Good Distribution Practices


Published March 2013 (repl 1994 version)

Applies to pharma/biotech firms, wholesalers, brokers

Inspections:
• wholesalers and brokers every 5 years
• pharma firms – cGDP questions added to routine cGMP inspections
EU cGDP

Pharma-specific inspection components:

• SOPs and environ
  – how will you detect/investigate/handle suspected falsified medicines?
  – is your environment/site set up to handle suspected medicines?

• Job descriptions and staff training
  – how are your staff trained to recognize falsified medicines?
  – who is authorized to stop production, stop shipments, etc.?

• Supplier assessments
  – did you verify the cGDP status of your brokers? your wholesalers?
  – do you have on-file a current copy of the GDP certificate?

HELPFUL HARMONIZED GUIDANCE

ICH
GHTF
EFfCI
WHO
PIC/S
ICH Q9 Guidance

*Quality Risk Management* 
([www.ich.org](http://www.ich.org))

- Members of the supply chain are partners - which contributes to assuring success
- Recommends a comprehensive evaluation of suppliers and contract manufacturers including audits and supplier quality agreements
- A manufacturer’s quality system will drive the management of outsourced processes and entities (risk and quality management used in selecting suppliers)

*FDA and EMA will cite in enforcement actions!*

GHTF SG3:N17 Guidance

*Guidance on the Control of Products and Services Obtained from Suppliers* 

- Harmonized definitions
- Six stage process
  1. Planning (requirements gathering)
  2. Supplier selection (preliminary evaluation)
  3. Supplier evaluation and acceptance (auditing)
  4. Finalization of controls (internal v. external, contracts, quality agreements, etc.)
  5. Delivery, measurement and monitoring (ongoing review, CAPA, re-evaluation, etc.)
  6. Feedback and communication (communication matrices, CAPA, etc.)
GHTF SG4:N84 Guidance

Guidelines for Regulatory Auditing of QMS of Medical Device Manufacturers – Audits of Manufacturer Control of Suppliers (www.imdrf.org/documents/documents.asp)

- Supplier agreements
- Change management SOPs
- Specifications, requirements, procedures & work instructions
- Documented list of the risks identified for the products and services supplied, and linkages to design, development and production/distribution planning
- Documented supplier requirements
- Capability assessment of the supplier (e.g., qualification)
- Contracts (and amendments)
- Purchase orders
- Audits reports of supplier
- Correspondence with supplier
- Minutes of meetings with suppliers
- CAPAs relating to products and services supplied
- Verification that received products match requested products
- Acceptance procedures for incoming products

EFfCI cGMP Guide


- OTC APIs
- Incorporates
  - IPEC-PQG GMP
  - EXCiPACT and ANSI NSF-363
  - Annex aligns against ISO 9001
- 29-page audit checklist for suppliers and supply chain management http://www.effci.org/assets/files/Audit_Checklist.pdf
**WHO cGMP for APIs**

WHO TRS-957 Annex 2 Good Manufacturing Practices for APIs

http://apps.who.int/medicinedocs/en/m/abstract/Js20119en/

- Use this in your supplier audits
- Show this to API-makers
- Reference standards in contracts and quality agreements as needed

**WHO cGDP for Pharma**

WHO TRS-957 Annex 5 Good Distribution Practices

http://apps.who.int/medicinedocs/en/m/abstract/Js18678en/

- Use this in supplier audits (CMO, API, distributors)
- Reference standards from this in your contracts
PIC/S

Pharmaceutical Inspectorate Co-operation Scheme (PIC/S)

Inspection aides for inspectors/auditors/investigators:
- aide-memoire on inspection of quality control laboratories
- aide-memoire on inspection of biotech
- aide-memoire on inspection of packaging
- aide-memoire on inspection of APIs

Inspection guidelines for inspectors/auditors/investigators:
- good practices for computerised systems in regulated GXP environments
- pic/s recommendation on risk-based inspection planning

Overall Process Flow
FDA’s SOP Suggestions
Using Guidance for Checklist Items
Records to Retain
Preparing a Supplier for FDA or EMA

DEFENSIBLE COMPLIANCE TECHNIQUES
Overall Process Flow

- Six overall phases
- 22 distinct activities
- Each phase ≈ 1 SOP
- Each SOP = 1+ records

Re-Use FDA Publications

- Guidance documents
- Federal register publications
- Compliance program manuals
- FDASIA 2012, Title VII
- Warning letters
  example: March 2011 letter to Ningbo Smart Pharmaceutical Co.
  www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm249425.htm
FDA’s Suggested SOP List

Federal Register, Vol. 76, No. 188 (2011)

- SOP on receipt, testing and approval of product components, containers and closures
- SOP on reviewing, examining and verification of labeling and packaging materials
- SOP on warehousing
- SOP on drug product distribution

List of SOPs and Policies

- Supplier management and purchasing controls overview (policy)
- Supplier selection
- Supplier remote evaluation
- Supplier onsite audits
- Supplier quality/technical agreements
- Supplier monitoring
- Supplier re-evaluations
- Supplier dossiers
- Review of supplier validations
Turn Guidance into Checklists

Draft Quality Agreement
Guidance Examples:

- has supplier conducted some level of acceptance testing or qualification on its equipment?
- are supplier’s personnel trained or otherwise qualified to operate the equipment?
- does the supplier retain records of production?
- does the supplier have a records retention policy or schedule?

Supplier Audit (Onsite) Checklist

FDA’s Heparin Guidance

Heparin for Drug and Medical Device Use - Monitoring Crude Heparin for Quality (2013)

- See suggestions on pages 5-6
- Substitute “raw heparin” for your “raw ingredient” or your “API”
FDA Tissue Bank CMO Guide

Guidance for Industry
Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements

Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements (2006)

- See recommendations on pages 2-3
- Handling process validation between you and CMO
- Initial v. on-going due diligence

Records to Retain

- Supplier agreements
- Change management SOPs
- Specifications, requirements, procedures & work instructions
- Documented list of the risks identified for the products and services supplied, and linkages to design, development and production/distribution planning
- Documented supplier requirements
- Capability assessment of the supplier (e.g., qualification)
- Contracts (and amendments) – including list of industry standards referenced/identified
- Purchase orders
- Audit or qualification reports of supplier
- Correspondence with supplier
- Minutes of meetings with suppliers
- CAPAs relating to products and services supplied
- Verification that received products match requested products
- Acceptance procedures for incoming products
Prepare Supplier for Inspection

Prioritize on critical suppliers (CMOs, CROs)

Cover 3 topics
1. Logic behind FDA/EMA supplier inspections
2. Overall inspection process
3. How to prepare and respond (including coordination with you)

“How to Prepare” points:
• responsibilities under the contract
• industry cGMP and/or cGDP standards agreed to in contract
• key documents to have on hand
• best practices for inspectional logistics
• best practices for behavior during the inspection (responding to questions, etc.)
• verify you will be involved in any formal response
• timelines for follow-ups with your organization (weekly meetings and teleconferences, etc.)
• consider conducting a “dry run” using an independent party as a mock auditor
Agenda Recap

- real-world challenges
- new regulatory requirements
- helpful harmonized guidance
- defensible compliance techniques

download a copy of this presentation –
including working URLs for all items – at:
www.Ceruleanllc.com/proof
(available until Nov. 8th)

About Your Presenter

John Avellanet gives practical, compliance solutions and streamlines quality systems for clients around the world. Winner of the 2009 & 2011 Best of Business Services award by the Small Business Commerce Association, Mr. Avellanet has earned international acclaim for his business-savvy, pragmatic FDA compliance advice.

His latest book, Get to Market Now! Turn FDA Compliance into a Competitive Edge, was featured at BIO 2011 and has garnered multiple five-star reviews from industry publications, blogs, Amazon.com readers, and former FDA officials.

He has a breadth of experience designing, implementing, and being accountable for quality systems and compliance programs for FDA, DEA, ICH, GHTF, and ISO. For more than 15 years, John was directly accountable for regulatory compliance, records management, and information technology, most recently as a C-level executive for a Fortune 50 combination device subsidiary.

In 2006, Mr. Avellanet founded his independent lean compliance consulting and training firm, Cerulean Associates LLC.
About Your Presenter

Recent Resume Highlights

• 2011-2015 IRO for Dr. Comfort Consent Decree
• 2010 and 2011 Top 10 FDA Compliance Blog
• 2010 Top 50 Pharma/Biotech Blog
• 2009 and 2011 Best of Business Services Award
• 2008-2012 Guest Lecturer at NIH
• 2006 Lifetime Achievement Award – Who’s Who of Biopharma & Device Executives
• Lead author of 2 certification courses for RAPS

FDA Lean Compliance Consulting Services

• Process map and streamline SOPs and policies
• Perform audits for compliance and cost-effectiveness
• Develop records management policies and RRS
• Write and improve Part 11 protocols and reports
• Conduct QS & compliance training and workshops
• Serve as consent decree IRO and litigation support

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