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The essential tool for regulatory, compliance, & quality professionals

GMP Compliance Issues for Legacy Products

Jerry L. Chapman, Senior GMP Quality Expert

Agenda

- Legacy products and subsequent GMP guidance
- Potential GMP issues
  - FDA inspection models
  - CPGMs
  - ICH Q7
  - ICH Q3D, Q3C
  - Quality agreements
  - Data integrity
  - Process validation
  - *Combination products and medical devices*
- Summary and conclusions

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What is a legacy product”

Legacy product: “Previously approved and marketed drug, typically developed 10 to 20 years ago. Such products typically have multiple competitors on the market and are low-margin.”

- *Drug Shortages* a report from The Pew Charitable Trusts and ISPE Jan 2017

Companies need a good business justification to keep manufacturing these products.

And as you will see, there are GMP risks that need to be considered.

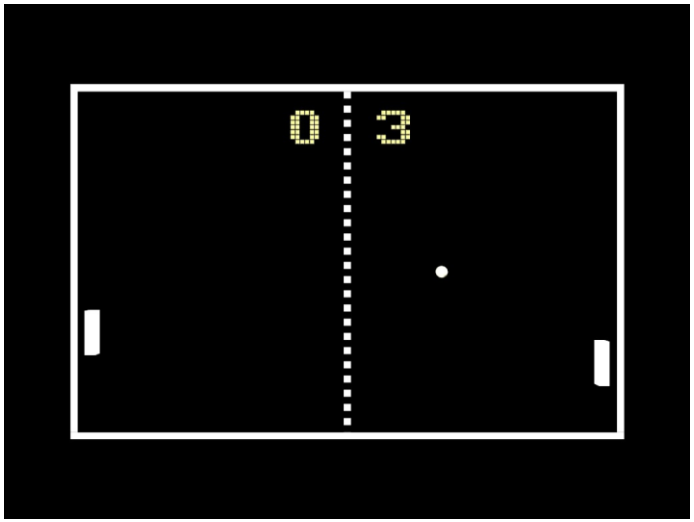
Subsequent GMP Guidance

- CGMPs date back to 1978.

1978

2019

1978



2019

Govzilla

1978 **2019**

Louise Joy Brown (born 25 July 1978) is an English woman known for being the first human to have been born after conception by *in vitro* fertilization, or IVF.

Subsequent GMP Guidance (cont'd)

• You must demonstrate conformance with the rules that were applicable when the product was approved for marketing.

Changes since 1978 to:

- Manufacturing technologies
- Lab analysis and detection methodologies and abilities
- Regulatory agency expectations, etc.

• In some cases, you may also have to conform to rules that went into effect ***after the product was approved***.

Key Recent GMP Guidance:

- ICH Q10, *Pharmaceutical Quality System*, 2008

- "Continual improvement" is used 25 times in the 22 pages of ICH Q10.

- Expectations for continual improvement of process performance, product quality, and the pharmaceutical quality system.

- Q10 applies to "new and existing products." *i.e.* – continual improvement is expected for all products.

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Potential GMP issues:
Changes to FDA Inspection models

- Legacy products, by definition, have been around a while
- Have been inspected many times
- Why be concerned now?
  - ✓ Program alignment
  - ✓ NIPP

Potential GMP issues:
Changes to FDA Inspection models

- Just concluded sterile products pilot
- Starting with other dosage forms this month
- A quality systems approach
- Six systems, 29 “elements,” six performance levels for each
- Will not impact NAI, VAI, OAI

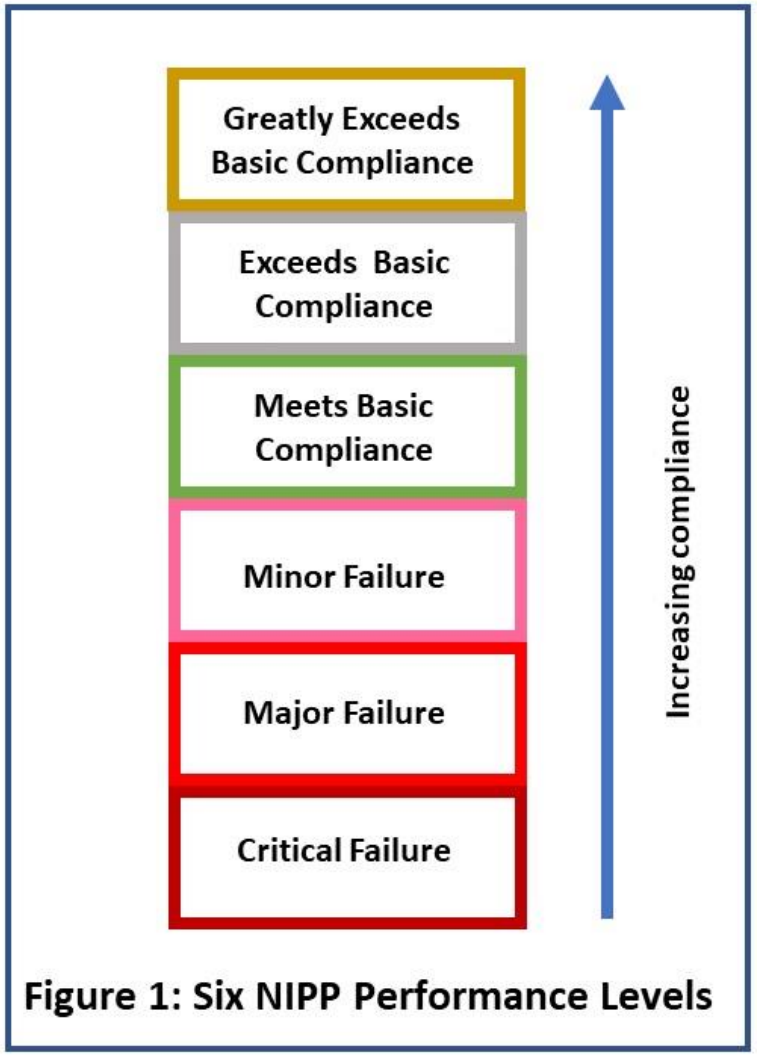
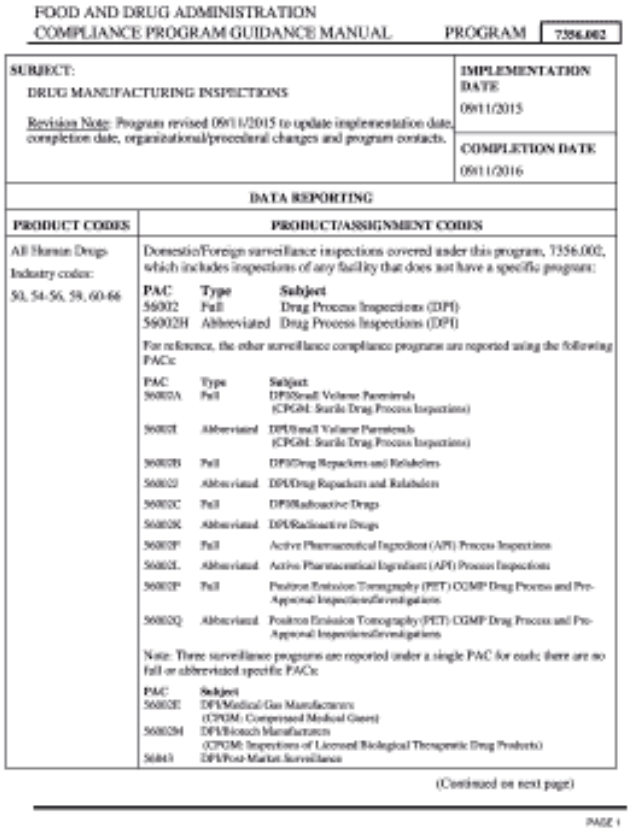


Figure 1: Six NIPP Performance Levels

Potential GMP issues:
Changes to FDA Inspection models

- Legacy products by definition have been around a while
- Have been inspected many times
- Why be concerned now?
  - ✓ **FDA investigators are not all the same**

Potential GMP issues:
CPGMs



FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL PROGRAM 7356.002

SUBJECT: DRUG MANUFACTURING INSPECTIONS Revision Note: Program revised 09/11/2015 to update implementation date, completion date, organizational/procedural changes and program contacts.	IMPLEMENTATION DATE 09/11/2015 COMPLETION DATE 09/11/2016

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
All Human Drugs Industry codes: 50, 54-56, 59, 60-66	Domestic/Foreign surveillance inspections covered under this program, 7356.002, which includes inspections of any facility that does not have a specific program: PAC Type Subject 56002 Full Drug Process Inspections (DPI) 56002H Abbreviated Drug Process Inspections (DPI) For reference, the other surveillance compliance programs are reported using the following PACs: PAC Type Subject 56003A Full DPI/Small Volume Parenterals (CPGM: Sterile Drug Process Inspections) 56003I Abbreviated DPI/Small Volume Parenterals (CPGM: Sterile Drug Process Inspections) 56003B Full DPI/Drug Repackers and Relabelers 56003J Abbreviated DPI/Drug Repackers and Relabelers 56003C Full DPI/Radioactive Drugs 56003K Abbreviated DPI/Radioactive Drugs 56003P Full Active Pharmaceutical Ingredient (API) Process Inspections 56003L Abbreviated Active Pharmaceutical Ingredient (API) Process Inspections 56003P Full Positron Emission Tomography (PET) CGMP Drug Process and Pre-Approval Inspections/Investigations 56003Q Abbreviated Positron Emission Tomography (PET) CGMP Drug Process and Pre-Approval Inspections/Investigations Note: Three surveillance programs are reported under a single PAC for each; there are no full or abbreviated specific PACs: PAC Subject 56003E DPI/Medical Gas Manufacturers (CPGM: Compressed Medical Gases) 56003M DPI/Biotech Manufacturers (CPGM: Inspections of Licensed Biological Therapeutic Drug Products) 56043 DPI/Post-Market Surveillance (Continued on next page)

PAGE 1

- FDA Compliance Program Guidance Manuals (CPGMs) are used by investigators to conduct inspections

- FDA CPGM 7356.002A, Sterile Drug Product Inspections (rev. 2016):

"Determine that validation of filter sterilization has been performed for all products. **Pay special attention to legacy products**."

Potential GMP issues:
CPGM, ICH Q7

- FDA CPGM 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection (rev. 2016)

- This CPGM also contains numerous references to ICH Q7, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*

- Boilerplate language in warning letter to API manufacturer:

"FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP."

Potential GMP issues:
ICH Q3D

- **ICH Q3D**, *Elemental Impurities*, was adopted by FDA in 2015.

- Establishes Permitted Daily Exposures (PDEs) for 24 Elemental Impurities (EIs) in drug products

- Revised periodically with new elements added

- FDAAA effective 2008

Potential GMP issues:
ICH Q3D, Q3C

- FDA assigned PMR 3332-1, gave 90 days, no response
- FDA sent a *Missed PMR Milestone Letter* then a *Failure to Respond Letter*
- Referred the matter to the Office of Compliance; warning letter.
- In January, FDA issued a warning letter to Lymol Medical Corp.
- J&J asbestos in talc verdict March 2019
- **ICH Q3C**, *Residual Solvents* was approved 2002 and updated frequently, most recently in October 2018, detailing acceptable levels of residual solvents in drug products.

Potential GMP issues:
Quality Agreements

- 2016 FDA guidance, *Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry*

- FDA's current thinking on defining, establishing, and documenting manufacturing activities of the parties involved in contract drug manufacturing subject to CGMPs.

- Numerous FDA warning letters for non-compliance (two examples follow)

Potential GMP issues:
Quality Agreements (cont'd)

- A May 12, 2017 warning letter to VitaPurity Corporation: "You state that you assume your contract manufacturer is responsible for preparing a master manufacturing record, exercising quality control functions, and verifying that the finished products meet specifications. You state that you assume your contract manufacturer is complying with 21 CFR Part 111 because you are unaware of any problems at the plant. You state that you do not have a written agreement with your contract manufacturer, and have not performed any audit or engaged in any other activity to determine the acceptability of the manufacturer…"

Potential GMP issues:
Quality Agreements (cont'd)

- A warning letter issued in July 2017 to Sage Products, Inc. cites the product owner for lax oversight of a **contractor that produced oral solutions using the same equipment in which it made toxic car washes and waxes**.

- FDA sent a similar letter **to the CMO**, ChemRite CoPac in Wisconsin, emphasizing its responsibility for the quality of drugs it producers for clients.

- "Twofer"

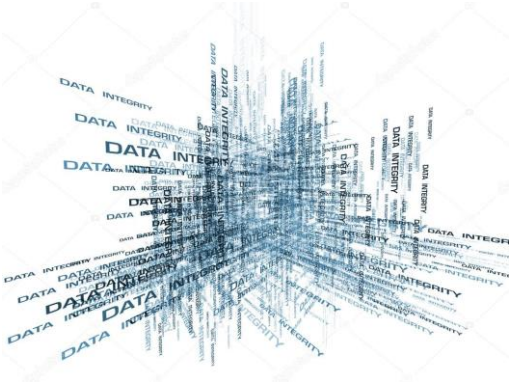
Potential GMP issues:
Data Integrity

- Draft Guidance for Industry, *Data Integrity and Compliance with CGMP*, 2016. The predicate rule was published in 1997. For all products.

- Increased data integrity issues during CGMP inspections.

- High number of warning letters citing data integrity or data handling and governance

Potential GMP issues:
Data Integrity (cont'd)



- For legacy products, the company may have a problem locating old documentation for inspections

- "Know-how" that is plant or operator-related

- May be little or no documentation on the pharmaceutical development.

- Pay special attention to the analytical labs.

Potential GMP issues:
Process Validation

- In FDA 2011 guidance, *Process Validation: General Principles and Practices*, legacy products are specifically mentioned.

- "Manufacturers of **legacy products** can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. **Implementation of the recommendations in this guidance for legacy products** and processes would likely begin with the activities described in Stage 3."

Resource: Process validation

ISPE has good resources to help guide these activities.

“Process Validation Lifecycle Implementation for Existing (‘Legacy’) Products” discussion paper

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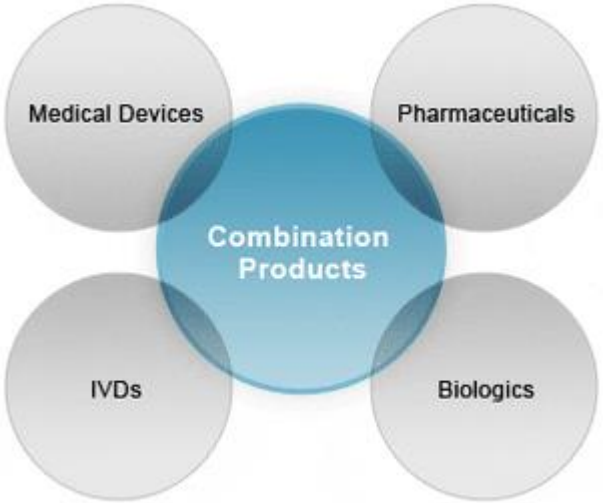
Potential GMP issues: Combination Products, Medical Devices



We will discuss a few potential issues specific to:

- combination products (2013 rule [*GMP Part 4]* explained by 2017 guidance), and

- medical devices (EU MDR 2020, no grandfathering)

Combination Products

• Combination products are defined by FDA as products that are some combination of drugs, biological products and/or devices.

• 2013 rule (*GMP Part 4*) explained by 2017 guidance

• No new GMP requirements; guidance details that how existing rules apply to combination products depends on the specific circumstances under which the combination product is produced, packaged and marketed.

• If the product includes a medical device component, a Design History File (DHF) is expected (since 1990).

Combination Products (cont'd)

- Even if no DHF, will have basic information on the product, especially if it was patented, that will likely be sufficient

- FDA does not expect sponsors to recreate information that did not exist previously

- The preamble to the GMP rule allows for flexibility in design controls

Combination Products (cont'd)

- From the January 2017 guidance:

"Although products developed prior to promulgation of part 4 are frequently termed "legacy" combination products, FDA deliberately does not use this terminology in this guidance because it could be inappropriately interpreted to indicate that products developed prior to promulgation of part 4 are therefore subject to fewer CGMP obligations than products developed after promulgation of part 4."

- Case study: FluMist

Medical Devices

- Not technically a GMP issue, but an issue if a company wants to keep medical devices on the market in the EU: The EU 2017 *Medical Device Regulation* (MDR)

- May 2020, no grandfathering, May 2024 expiration

- Changes to the classification of some medical devices, as well as more prescriptive guidance on the content of technical documentation and, in some cases, more clinical data required.

- Notified Bodies, cost of compliance

- In Vitro Diagnostic Regulation (IVDR)

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Summary and Conclusions

- Rules applicable when the product was approved for marketing

- In some cases, rules that went into effect ***after the product was approved***.

- ICH Q10

- Changing nature of FDA inspections presents risk

- Specific examples of regulation and guidance

- FDA warning letters

Proposed Action Item:

Review the presentation and determine if there is possible impact to your legacy products.

For more information

- Explore the links in the presentation

- Check the FDAzilla blog at least weekly for a wide variety of content of interest in the pharma and medical device landscapes – for example:
  - Weekly warning letter analysis
  - Analysis of important new regulations and guidance
  - Industry initiatives
  - Conference coverage

- Get a Free FDAzilla PRO account for access to search, sites, inspections, and warning letters – that is where the inspection information in this presentation came from

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