How to Build and Implement a QMS for Small Pharma and Biotech Firms

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Introduction & Background

Over 25 years of corporate and consulting experience in Pharma, Biotech, and related industries

ISO9001:2015 certified Lead Auditor

PDA Editorial Board member (JPST)

-QA Manager for OTC Contract Manufacturer

-QA Manager for biopharmaceutical (sterile product) manufacturer

-CMC team member for blockbuster parenteral product NDA

-design, construction and commissioning of sterile product manufacturing facility

-manufacturing operator in kilo-lab and pilot plant,

-numerous GMP and QMS remediation projects, domestic & international

Xcellarate
LOOK FORWARD

Founder, Managing Director & Principal at xCellarate & Associates

- based in Vancouver, British Columbia, Canada. We are a consortium of Associate consultants with seasoned career experience

- xCellarate is a trusted partner for providing consulting solutions to complex challenges in:
  - CMC Manufacturing/Product development (biologics, small molecule, aseptic processing)
  - Quality (QMS/GMP development & remediation, audits)
  - Regulatory (filings, applications, strategy)

- Provide solutions to the Biotech/Pharma, Medical Devices

- Clients in Canada/USA, Asia

Topics

1. Risk-based approach to QMS development
2. Quality mindset versus rules and regulations
3. QMS processes, -the chicken or the egg, which came first?
4. Pandemic impact on QMS

Some of the Basic Requirements for GMP

1. Clearly defined and systematically reviewed processes
2. Validation of critical steps/processes
3. Appropriate resources: personnel, buildings, equipment, materials
4. Clearly written procedures
5. Trained operators/personnel
6. Complete records
7. Complete, proper investigations
8. Proper storage and distribution
9. Clean, organized
10. Quality Approval

https://business.medicaldialogues.in/pharma-news/cdsco-updates-procedure-for-issuance-of-who-gmp-63901

Foundational Elements of a QMS

- Change Control
- Deviations/CAPA's
- Document Management
- Personnel Training
- Sample Retention
- Stability Program
- Facility Cleaning and Maintenance
- Equipment Maintenance
- Material Testing (raw materials, intermediates, finished products)
- Specifications

-Quarantine & Release

-Production Controls

-Packaging and Labeling Controls

-OOS

-Internal Audit Program

-Master Manufacturing Formulas, Master Batch Records

-Product Recall

-Consumer Complaints Handling

-others…

Typical Challenges for Small Companies

1. Immature culture of quality

2. Limited budget for suitably experienced Quality professional(s)/dept

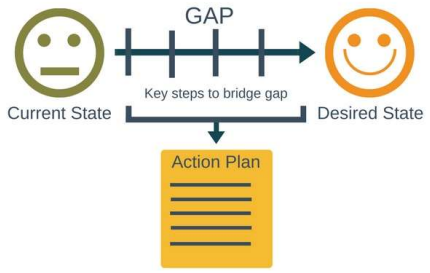
3. Grey area for how much (how little…) quality is needed for early stage product development (ie. specifications),

4. Building good/bad habits at the beginning

Where to begin?...

1. Conduct a gap analysis of existing QMS in your organization,

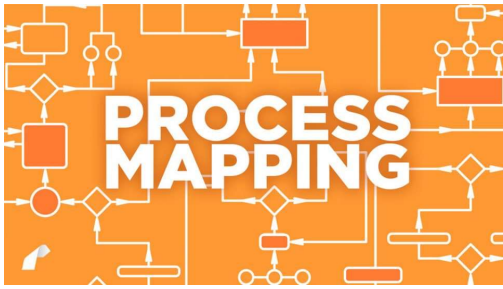
- Speak with key personnel in Quality, Engineering, Production, Management to understand roles, responsibilities and identify gaps in their tasks
- Reviewing existing documentation including, but not necessarily limited to:
  - -Master SOP list and GMP documents list
  - -SMF
  - -QA agreements
  - -Validation documents/VMP
  - -past inspection observation reports (if relevant)
  - -More and more…



https://www.questionpro.com/blog/gap-analysis/

Where to begin?... Cont'd

2. Identify and define all key processes in your organization



- Conduct physical walk-through of entire facility, including warehousing, utilities, gowning/changing, production areas, packaging/labeling, QC testing,
- Identify and map out all GMP-impact processes using flowcharts
- Involve a team of people with representation from all departments for input
- Identify gaps in the processes wrt to procedures, definition, responsibilities, risks/possible outcomes

Where to begin?... Cont'd

3. Evaluate findings from the first and second previous tasks

-Identify and define all major and minor gaps

-Identify a priority list for the gaps (devise a ranking system) (FMEA?)

-Identify and document an action plan with timelines for remediation and corrective actions to address gaps, create/expand existing QMS

-Assign responsibilities, create teams/sub-teams

THEN IT'S GO TIME!.....

Six system inspection model

Gemba walk

ISO Quality concepts

QTPP

Product lifecycle

PAT

QRM

Technology Transfer

Science-based

Risk-based

Design space

Risk methodologies

DoE

Key process parameters (KPP)

Quality by Design

Preventative/proactive vs reactive

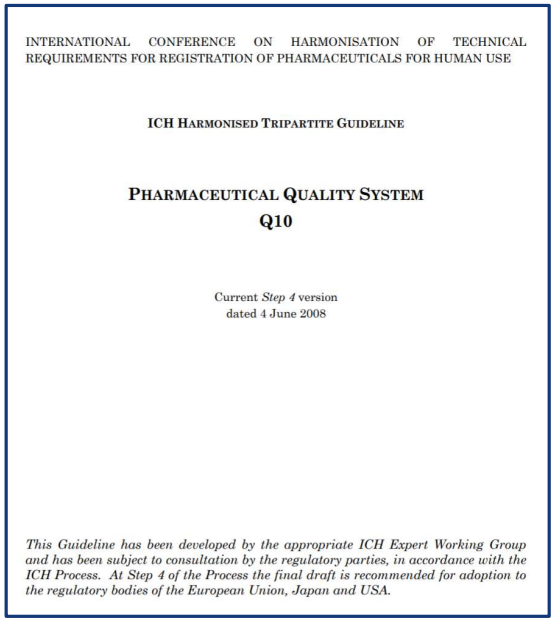
Background to ICH Q10 Pharmaceutical Quality System

	GMP	ISO 9000	FDA QS	Q10
GMPs	✓ ✓		✓ ✓	✓ ✓
Management	✓	✓ ✓	✓ ✓	✓ ✓
Continual Imp		✓ ✓	✓ ✓	✓ ✓
QRM		✓	✓ ✓	✓ ✓
Knowledge		✓	✓ ✓	✓ ✓
Lifecycle		✓	✓ ✓	✓ ✓
Opportunities			✓ ✓	✓ ✓

*From: https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/west-coast/ich-quality-guideline-q10.pdf?sfvrsn=16c3a38e_8

ICH Q10 Pharmaceutical Quality System

- "*Comprehensive model for an effective pharmaceutical quality system*"
- Aims to promote a paradigm shift from discrete GMP compliance procedures at each stage of product lifecycle to a comprehensive quality systems approach over the lifecycle of the product**
- based on International Standards Organisation (ISO) quality concepts & applicable GMP regulations
- Not intended to create any new expectations beyond current regulatory requirements. …content of ICH Q10 that is additional to current regional GMP requirements is optional.
- Applies to DS and DP throughout product lifecycle
- Introduces concepts of:
  - -QRM
  - -continuous improvement (products/processes/QMS itself
  - -Management responsibility
  - -Knowledge management
  - -Science-based and risk-based thinking



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current *Step 4* version
dated 4 June 2008

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

*From: https://database.ich.org/sites/default/files/Q10%20Guideline.pdf

**Neil Wilkinson: Slide 1 (pda.org)

ICH Q8, Q9 & Q10 ("Trio")

- ICH Q8 Pharmaceutical Development,
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System

☑ Q8 - Q10 are linked together to provide a complementary, systematic, modern risk- and science-based approach to pharmaceutical manufacturing & development

☑ Good scientific development (Q8) in combination with QRM (Q9) and PQS (Q10) will improve drug quality and efficacy of pharmaceutical manufacturing.

☑ Comprehensive implementation of the three guidelines together is essential to achieve ICH Quality Vision

☑ High level guidance, not prescriptive

☑ Intended to work together to enhance pharmaceutical product quality*

*From ICH Q-IWG: https://studylib.net/doc/12159381/how-ich-q8--q9--q10-guidelines-are-working-together-throu...

ICH Q8(R2) Pharmaceutical Development*

- Guidance for pharmaceutical development content to have for 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in M3 of the Common Technical Document (CTD).

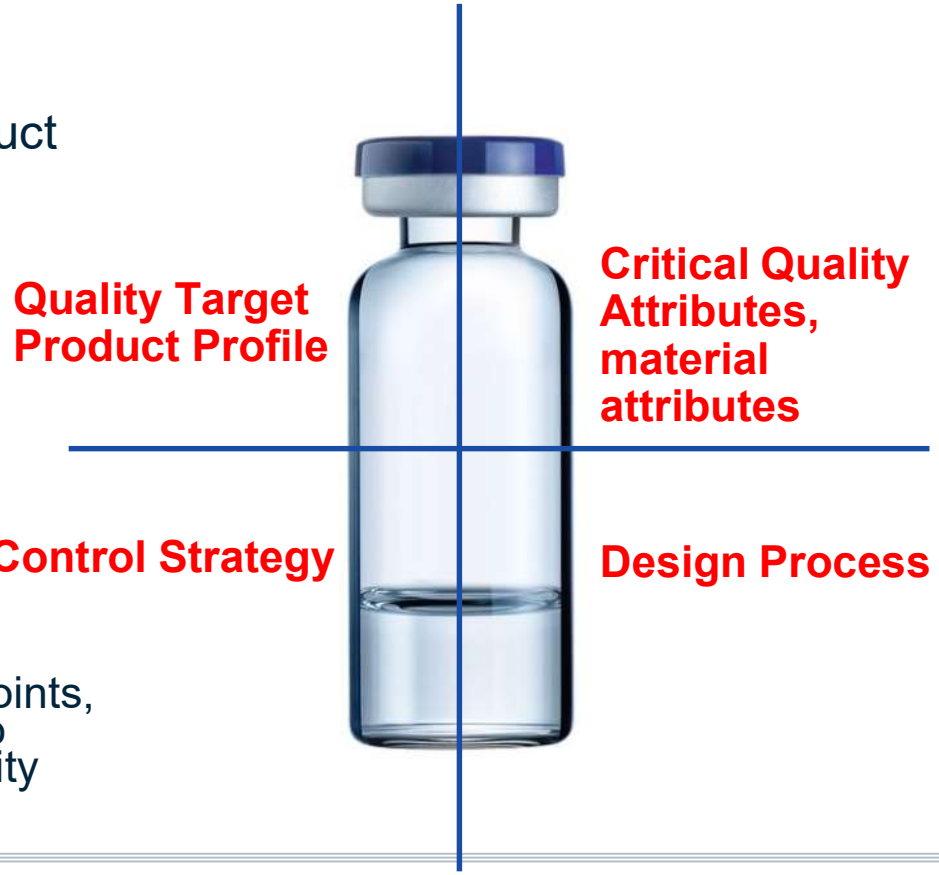
- Namely, aspects of drug substances, excipients, drug product, container closure systems and manufacturing processes that are critical to product quality should be determined and control strategies justified.

- Quality by Design (QbD)
  - systematic approach to drug development
  - Science-based
  - Risk-based
  - Versus “quality by QC”

*From:
https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf

ICH Q8 –Unified Concepts

Complete profile of intended drug product characteristics



Identifying all critical parameters and respective appropriate ranges to achieve desired product quality

Manufacturing unit operations, control points, control parameters to achieve desired quality

DoE's characterize relationship between CMA's, CPP's and CQA's

Design space (optional)

*Adapted from NSF: https://www.youtube.com/watch?v=7LNMTuQYN1k

ICH Q9 Quality Risk Management*

- QRM adoption and use in the pharma industry is growing and there is widespread use, -there is ample opportunity for improvement, especially for small/growing company's.

- Our industry [*traditionally*] lags behind similar and different industries for adoption of risk management**

  -ie. Medical devices reference ISO 14971 and the food industry uses hazard analysis and critical control points (HACCP).

*From: https://database.ich.org/sites/default/files/Q9%20Guideline.pdf

**From: https://www.theauditoronline.com/qbd-for-pharmaceuticals-assessing-quality-through-risk/

Risk Assessment

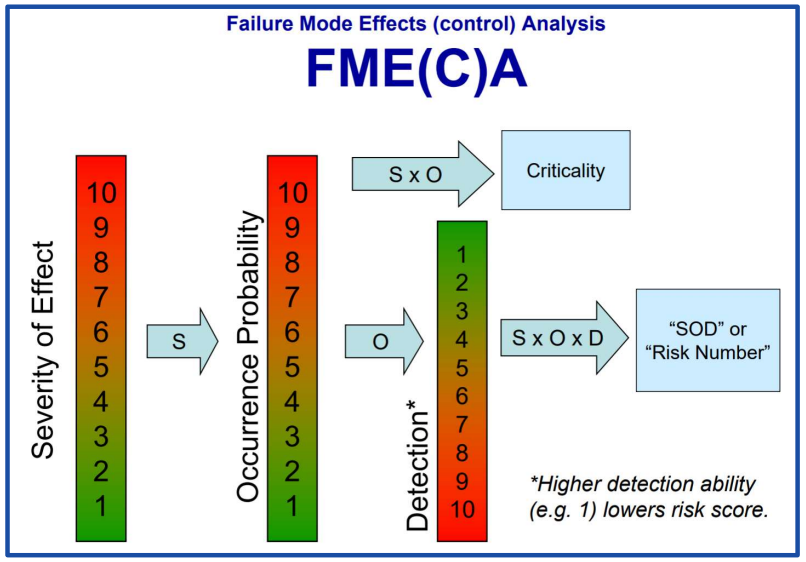
-Adopt concept of risk-based thinking

-Brainstorming, SWOT's, FMEA's, Ishikawa's, Fault Tree Analysis, HACCP, PHA, others…

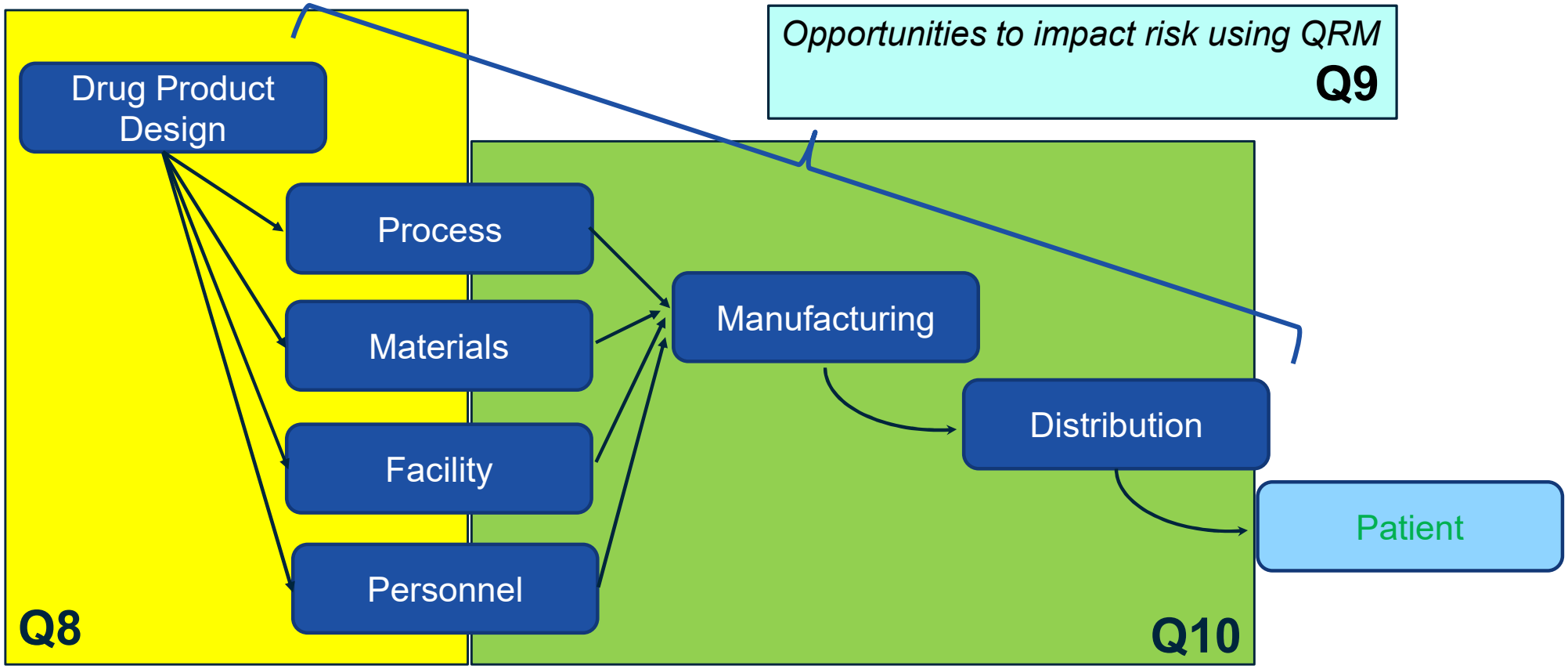
-There's no ONE way to conduct a RA, no one-size fits all!

-All methods and approaches have a degree of subjectivity and uncertainty!

-What's important is that you document that the RA took place and the thinking that went behind it to arrive at what/why you did it. Risk Register



Tripartite guidelines in harmony…

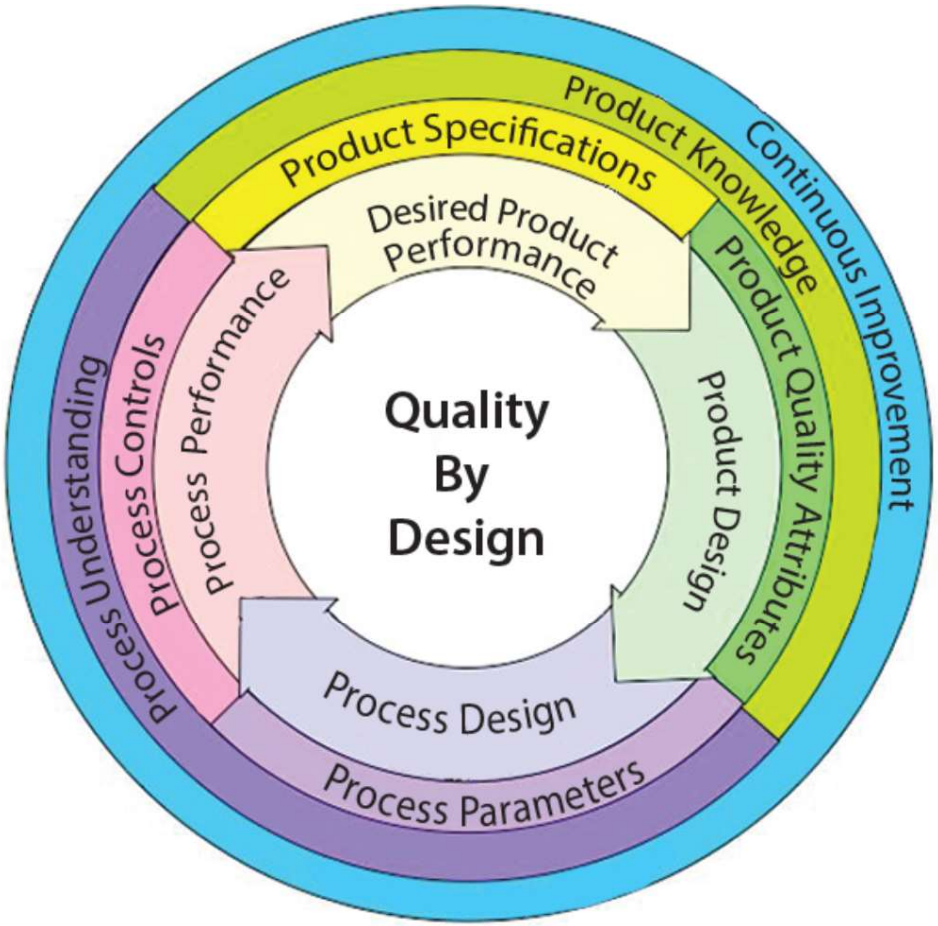


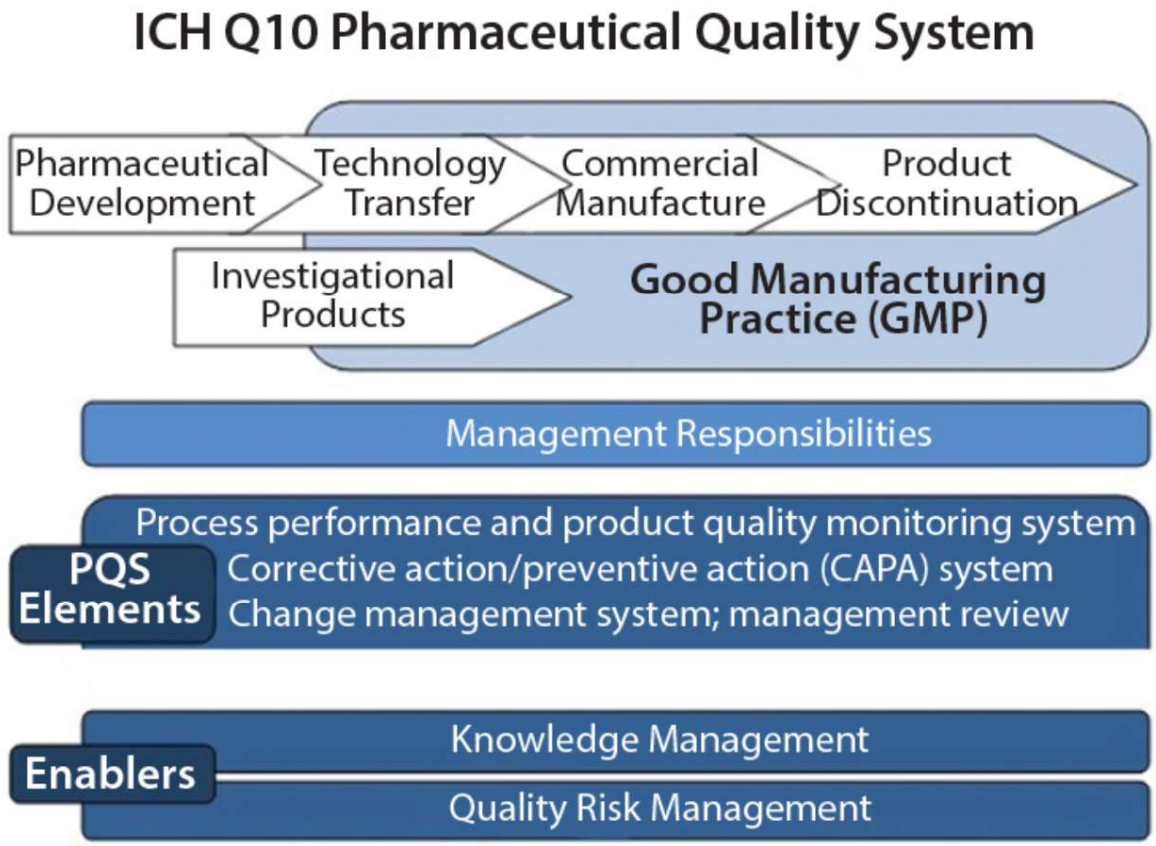
Based on: G. Claycamp, FDA, June 2006

References from Different Guidance Sources

- FDA's *Quality Systems Approach to Pharmaceutical CGMP Regulations Guidance for Industry* states "Quality risk management is a valuable component of an effective quality systems framework. Quality risk management can, for example, help guide the setting of specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a process or specification, and determine the extent of discrepancy investigations and corrective actions."

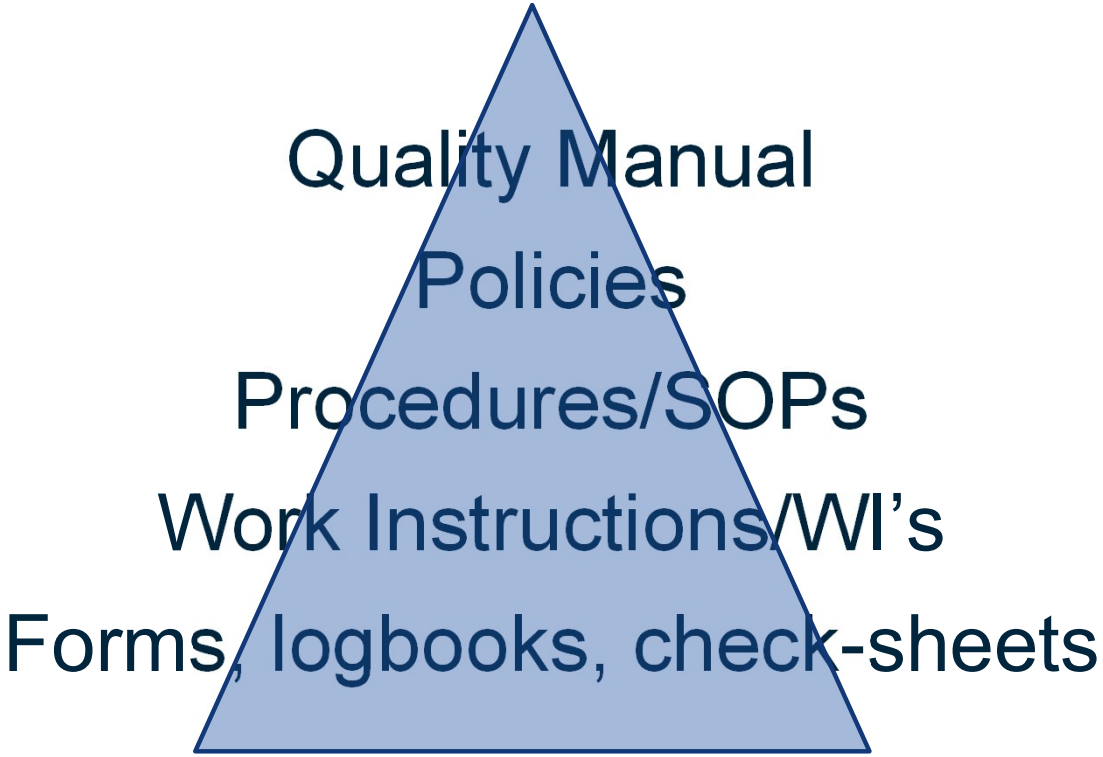
- ISO 9001:2015
- ISO 13485: 2017
- QbD





From: https://bioprocessintl.com/wp-content/uploads/2015/06/Figure1A_1.jpg

GMP Documents Hierarchy



Quality Documents in a QMS

Your QMS should include:

- Master List of Controlled Documents
- Procedures (SOPs)
- Work instructions
- Templates for different doc types
- Forms
- Registers (signatures, etc)
- Manuals & Policies

- Lists
- Training assessments
- Test methods
- Specifications
- Master manufacturing formula
- Batch records, etc.

- More…….

SOP tips

- ☑ Use flowcharts & images as much as possible, not just verbiage. Pictures tell a thousand words!
- ☑ Use Tables, bullets, effective indentation (max 3 levels)
- ☑ Write simply, succinctly, use verbs and be imperative
- ☑ Good balance of white space
- ☑ Don’t include version numbers in cited documents within an SOP
- ☑ It all starts with your template
- ☑ Include an effective date that is min 14 days after the approval date in order to build in training period.

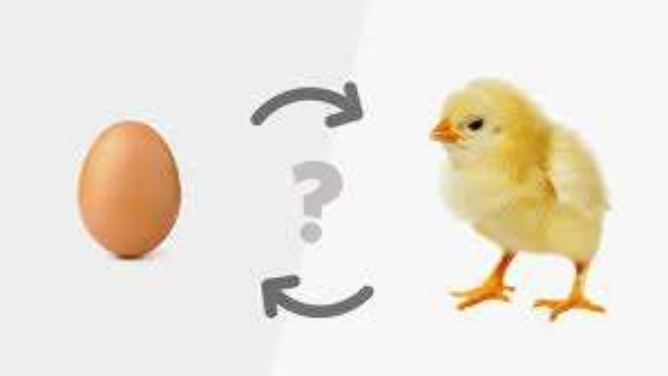
Unique opportunity of starting from a clean slate….

-Usually starting from an existing QMS system that's already in place

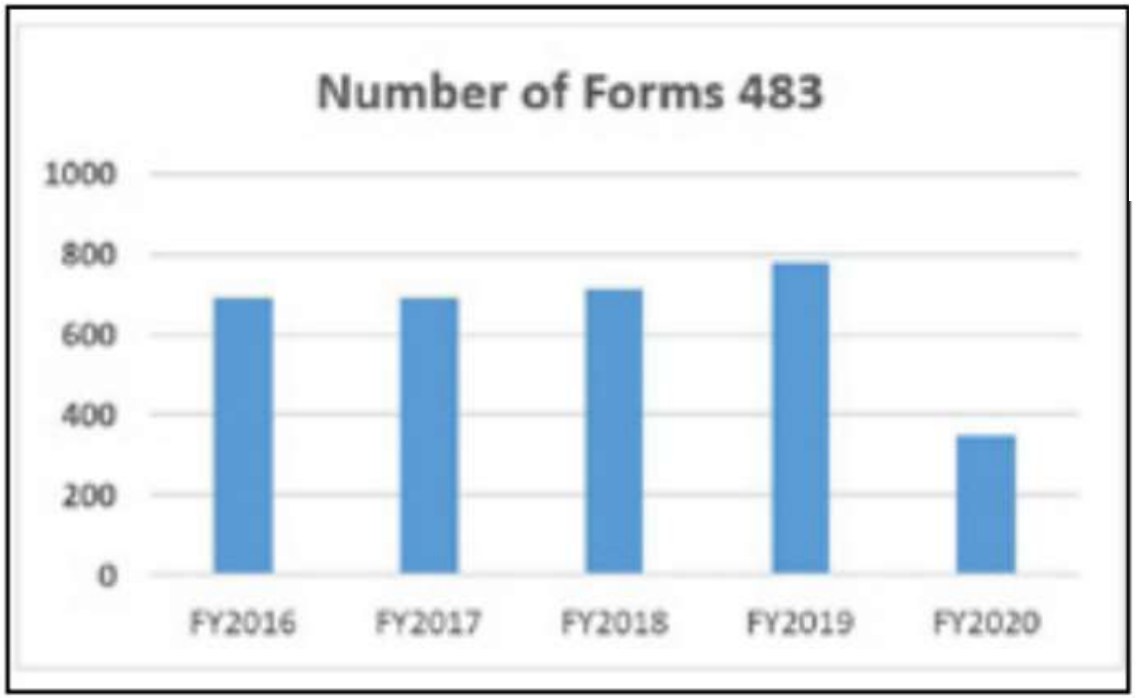
1. Document Management System (numbering, version control, signature register)
2. Personnel Training
3. Change control
4. Quality Manual
5. SOP on how to write a SOP/SOP template
6. Vendor Management
7. QA responsibilities

QMS processes, -the chicken or the egg, which came first?!

- What to prioritize first, over others?
- What is appropriate for each stage of company growth?
- Do you have enough manpower/resources to take on new processes?



Inspection Metrics….



REDICA Systems

FDA FY2020 Drug Inspection Observations and Trends

REPORT

* Data from: REDICA systems –report by Barb Unger: FDA FY2020 Drug Inspection Observations and Trends

FY2020…

#2
Responsibilities & Procedures for the QA Unit are not in writing or fully followed. (21 CFR 211.22 (d))

* Data from: REDICA systems – Webinar by Barb Unger: FDA FY2020 Drug Inspection Observations and Trends

FIGURE 2: DRUG GMP INSPECTIONS, §211 CITATION FREQUENCY BY FISCAL YEAR

CITATION	SHORT DESCRIPTION	2016	2017	2018	2019	2020
Total Form 483s issued using the FDA tool for Drug Inspections		691	694	716	779	349
§211.192	Investigations of discrepancies	227	278	183	167	128
§211.22 (d)	Procedures applicable to the quality unit shall be in writing and shall be followed	153	185	208	215	111
§211.160 (b)	Lab controls should include scientifically sound specifications	133	207	209	145	84
§211.100 (a)	Production and process controls shall be supported by written procedures	110	116	102	129	59
§211.68 (b)	Appropriate controls shall be exercised over computer systems	*	*	*	*	57
§211.42 (c)	Facilities shall include defined areas of sufficient size	227	148	134	156	56
§211.188	Master production and control records	100	208	93	123	54
§211.166 (a)	Stability testing	124	72	111	135	42
§211.67 (b)	Equipment cleaning and maintenance	102	91	112	124	45
§211.113 (b)	Control of microbiological contamination	118	92	71	121	43
§211.67 (a)	Equipment shall be cleaned/sanitized or sterilized	94	54	81	99	42
§211.25 (a)	Personnel qualifications	99	113	47	113	39
§211.160 (a)	Following/documenting laboratory controls					38
§211.68 (a)	Automatic, mechanical, and electronic equipment	80	67	60	67	33
§211.110 (a)	Sampling and testing of in-process materials and final product	65	68	86	94	33

*211.68(b) and 211.160(a) were not in the top group in previous years, so i did not go back and calculate the earlier values.

Top Citations from 21 CFR Part 211

§211.192 Production Record Review Investigations of discrepancies moved from third place in FY2018 to second place in FY2019 and is in first place in FY2020. It has historically been among the most frequently cited regulations.

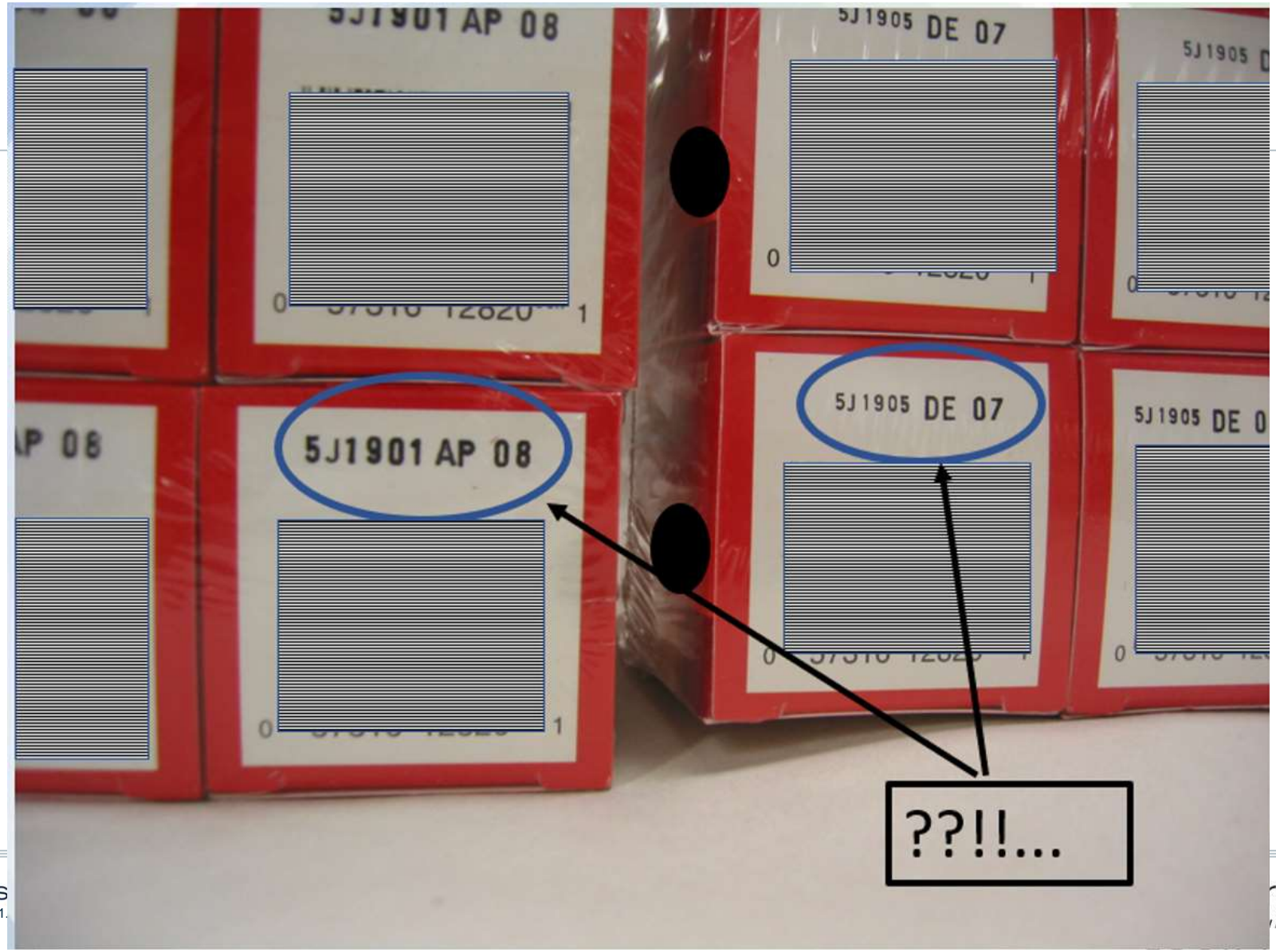
§211.22(d) Responsibilities of quality control unit -The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed Procedures applicable to the quality control unit shall be in writing and shall be followed moved from first place in FY2019 to second place this year. Again, this is another regulation that has been among the top group for many years.

§211.160(b) Laboratory controls –Among many requirements here, should include scientifically sound specifications was fourth place last year and third place this year.

§211.100(a) Written procedures; deviations -Production and process controls shall be supported by written procedures is a common observation issued to OTC manufacturers who frequently have not conducted process validation for some or all products.

Case Study

Mismanaged Stability Study & Raw Materials release


5J1901 AP 08
5J1905 DE 07
5J1905 DE 07
5J1901 AP 08
??!!...

Aside from the FDA…

Analysis of inspection findings from 2 other regulatory agencies (*Russia SID&GP*, *UK-MHRA*) aside from the FDA, for FY2019*.

Found that ~70% of all citations can be covered under 6 common themes:

1. Data Integrity
2. Deviation and failure investigations **<FDA 21 CFR 211.192>**
3. Lack of established lab controls **<21 CFR 211.160 (b)>**
4. Finished product testing
5. Stability program
6. Equipment cleaning and maintenance

* Data from: REDICA systems –Webinar by Jerry Chapman: Comparing and Analyzing Russian, US and US Top 10 Inspection Findings FY19

Highlights of xCellarate's Findings from Past Projects and Remote Audits in 2020

- Same theme's of FDA's FY's…

  -lack of written procedures

  -lack of control

  -lack of testing

- What about 2021 and vaccine rollout?....

…Still a significant percentage of the industry that approaches the QMS largely via discrete GMP compliance procedures

versus

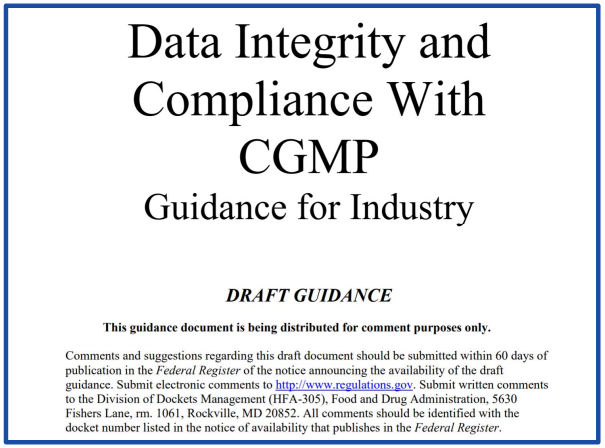
A comprehensive quality systems approach over the product lifecycle (ICH Tripartite guidelines)

Data Integrity – ALCOA, ALCOA+

Concept from 1990's and earlier, broad and applicable across different industries

Resurgence of this concept due to dramatic evolution of our industry:

- Emergence of new technologies (automation, robotics, biologics (ATMP's, mRNA-based vaccines, cell/gene therapy, biosimilars, etc)
- Increased reliance on electronic records (vs paper, handwritten)
- Emergence of new business models, globalization,
- Increased/repeated citations of data integrity issues…



Data Integrity and Compliance With CGMP

Guidance for Industry

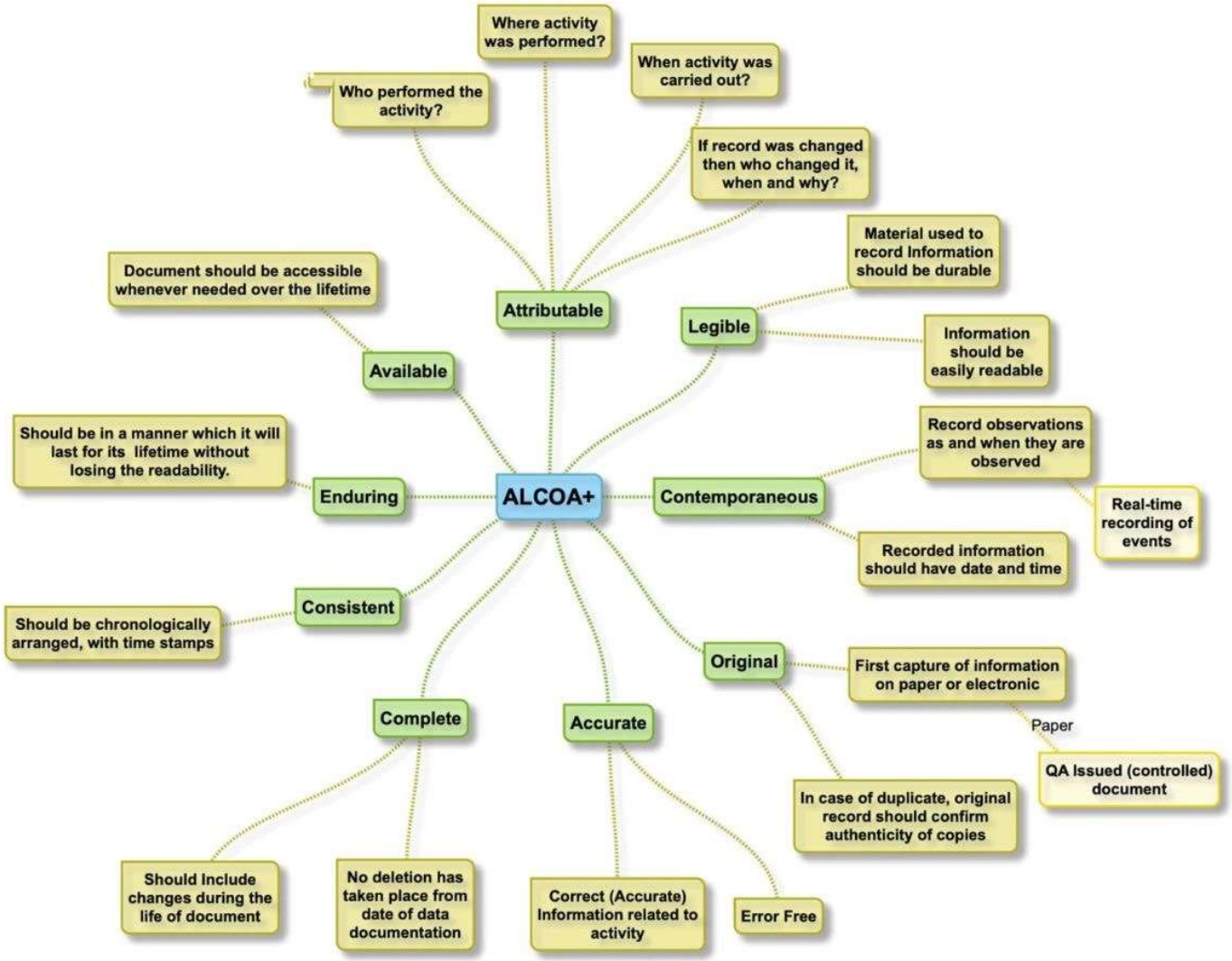
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf

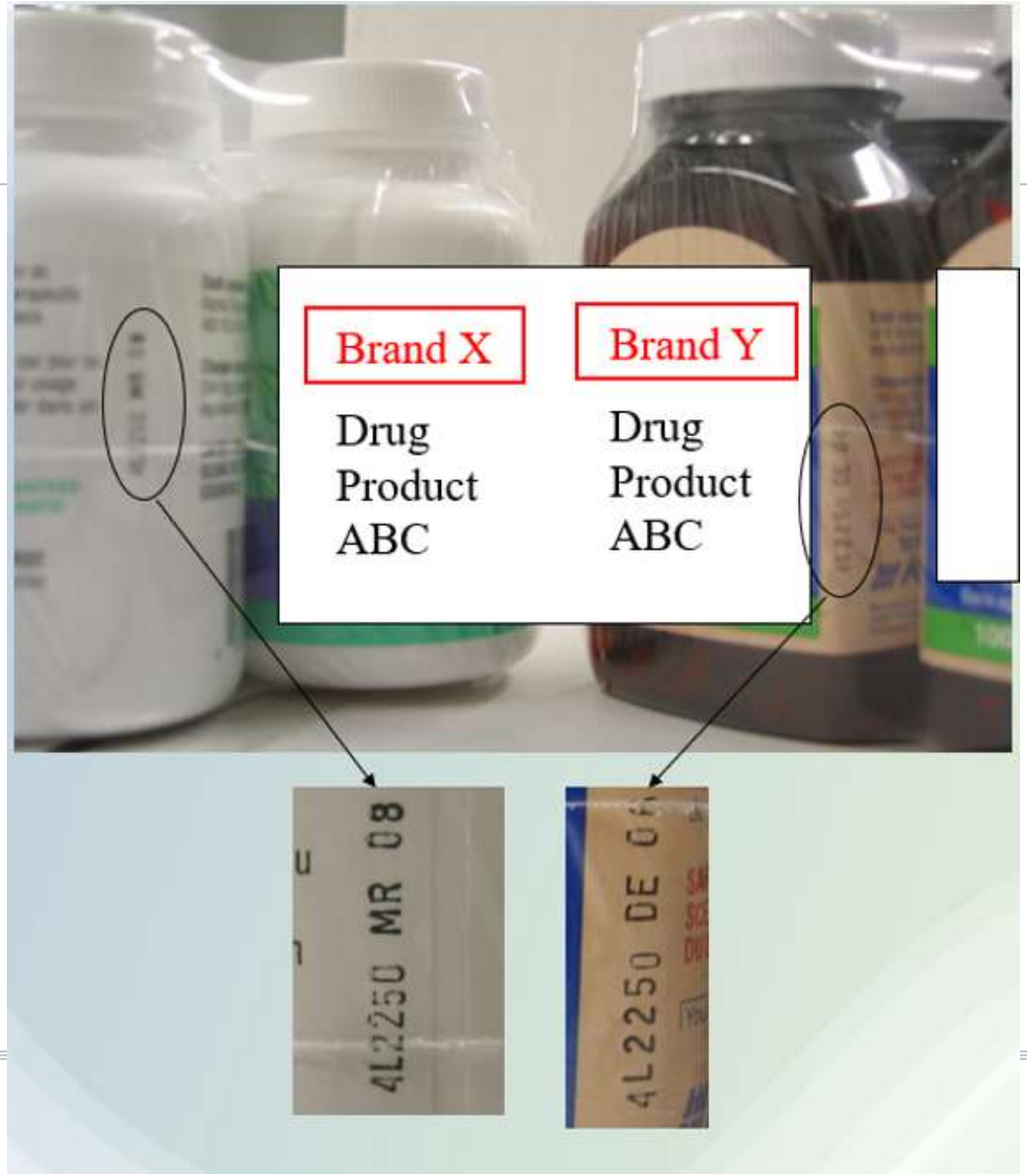
Also: FDA Q&A: https://www.gmp-compliance.org/files/guidemgr/UCM495891.pdf



Adapted from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry

Case Study

Master Batch Record & Labelling Errors



These “industry-isms” are clichés for a reason!….

…”do what you say, say what you do”

…”you can’t test quality into a product, it has to be built in”

”…if it isn’t documented, it didn’t happen”

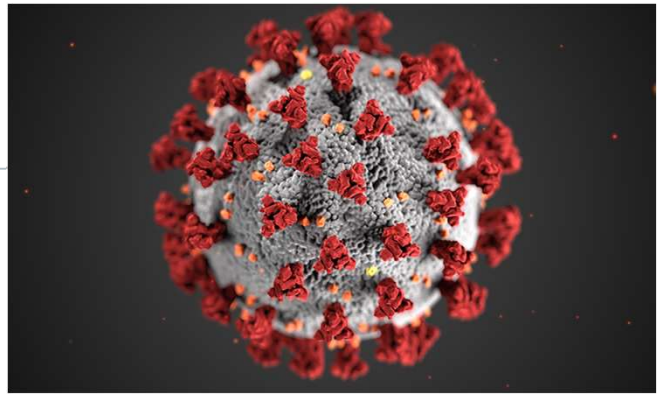
Impact of the Pandemic

- General slowdown of all typical/daily Quality group activities (internal/external audits, extended time for CAPA resolution, batch record/doc review/approval, etc, etc)
- Layoffs due to loss of business/staffing shortages, increased work for fewer people, staggered shifts and coffee/lunch breaks, remote work
- Online training, further shift away from paper-based QMS
- Additional work for daily health checks/health assessment, additional PPE, documenting it
- Visitor Control Policy/Questionnaire, employee health and hygiene, plexiglass screening

and more….

https://www.computerworld.com/article/3534478/tech-pitches-in-to-fight-covid-19-pandemic.html

Impact of the Pandemic …cont'd



- Defined response to incidences of positive testing (ie. self-isolation, fumigation, sanitization, etc), lost time, cooperation with regional health authority

- noted from several different remote audits that there were empty hand sanitizer bottles in wash-up stations and bathrooms. Need more frequent checking for refill as they're being used much more often now

- Remote auditing --Recommend face to face on zoom, it's not a requirement but it adds to building rapport; There's essentially total loss of non-verbal communication if the auditee is unwilling to have their camera turned on

- Efficient management of info and documents –ultimate test of this efficiency is during an audit

Health Canada/EU/WHO definition of Quality…

"Quality management is a wide-ranging concept. It covers all matters that individually or collectively influence the quality of a drug. It is the total of the arrangements made to ensure that drugs are of the quality required for their intended use."

* https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gui-0001-en.pdf

The Challenge…

The hard part about GMP, is not understanding the requirements, concepts, written regs. That's easy!

…It's interpreting them and implementing them in a suitable fashion in your Organization, versus Organization B and Organization C, etc...

Each company and environment is different.

Maintaining the QMS. How?

-Regular Quality Management Reviews

-Annual product reviews,

-Trend analysis & Quality metrics

-Internal audits (as well as external audits)

My thoughts on the “Culture of Quality”

- ☑ Senior Management –power to the people!
- ☑ Relationship building vs policing
- ☑ Quality functions daily tasks
- ☑ Prioritizing the right things in the QMS
- ☑ Business Objectives vs Quality Objective
- ☑ Mistakes, and the hidden opportunity

https://www.linkedin.com/feed/update/urn:li:activity:6772120918731882497/

Guiding principles for you…

GMP's tell you WHAT to do, not HOW to do it. Big difference!

GMP's and QMS's are about ACCOUNTABILITY and TRACEABILITY.

-Anything that can potentially impact product efficacy and safety is important for consideration!

How to Build a Pharmaceutical Quality System?...

Use highest quality bricks!

One at a time!…

https://www.carloscamara.es/en/blog/2019/09/05/the-three-little-pigs-is-a-fairy-tale/
https://www.raps.org/news-and-articles/news-articles/2020/6/fda-reports-on-drug-quality-oversight-trends-in-fy
https://gharpedia.com/blog/good-clay-bricks/

Thank You!

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