Impact of EU GMPs on Australian GMP

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PharmOut

National GMP & Validation Forum

Hosted by PharmOut

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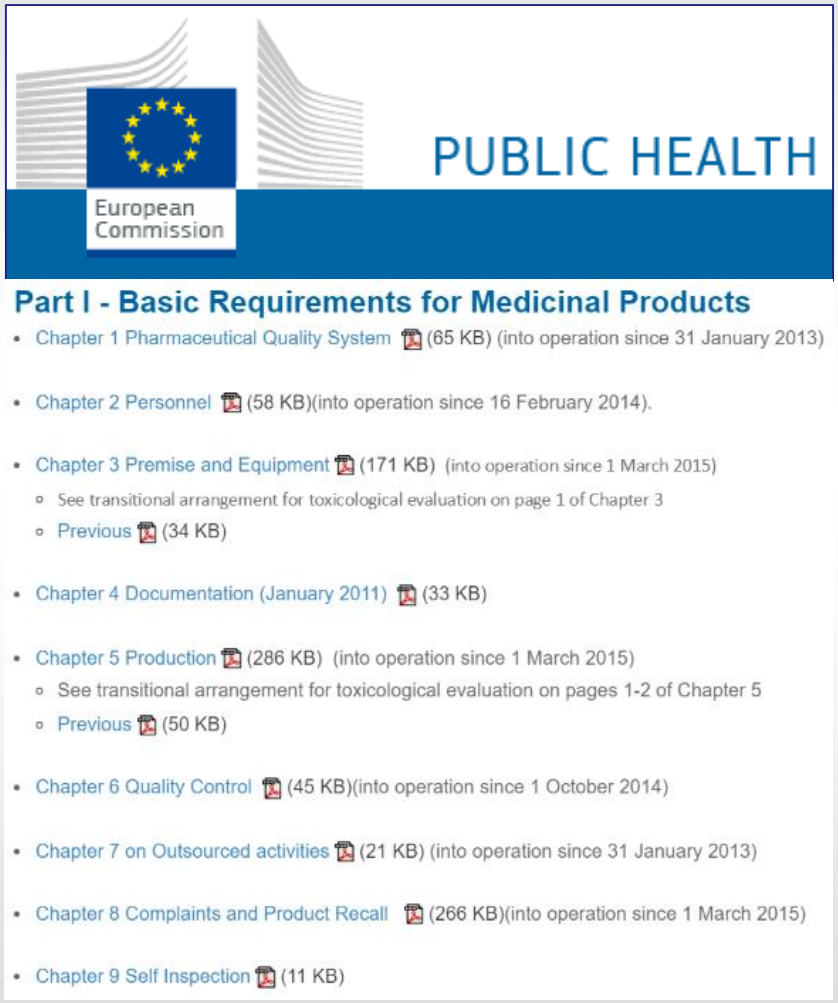
Part I – Basic Requirements for Medicinal Products



http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

- **Current TGA Version, 7 years out of date**
- **TGA are actively and publically talking about PE009-~~08~~13 & adopting it**
- **Validation**
- **Documentations**
- **Toxicology**
- **Cross contamination**
- **Design**

- **2016 Annex 1**

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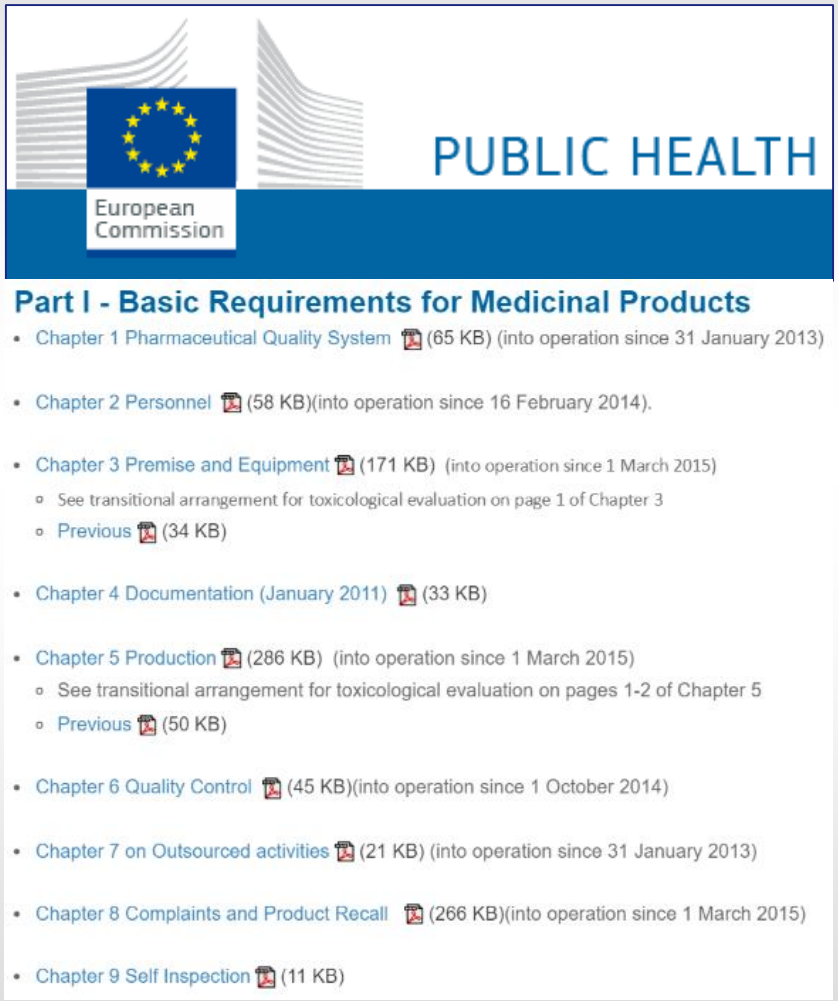
Covered in many other PharmOut events



http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

1. Dinner updates from 2011 to 2016
2. 2015 National GMP & Validation Forum – presentations
3. Spreadsheet tracking tool

https://www.pharmout.net/gmp-and-validation-forum/past-national-gmp-validation-forums/national-gmp-validation-forum-2015/

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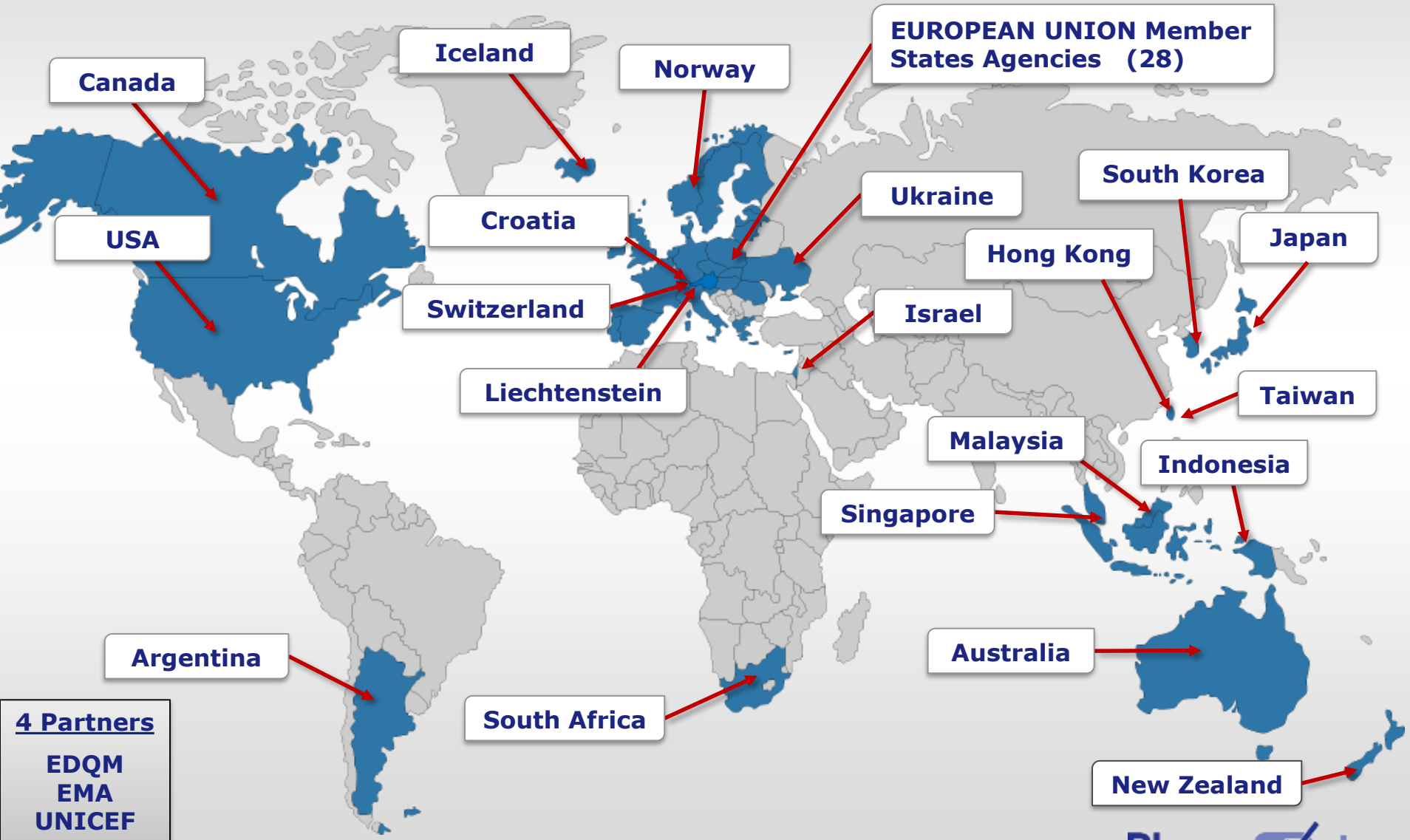
48 PIC/S member authorities

As of 1st January 2016

NEW! Croatia

Hong Kong



4 Partners

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Current TGA GMP vs EU GMP

Parts I and II

Chapter	PIC/S Guide to GMP PE009-08	EU GMP Guidelines	Degree of change
1	Quality management	Pharmaceutical Quality System (Jan 2013)	**Major**
2	Personnel	Personnel (Feb 2014)	Minor
3	Premises and Equipment	Premise and Equipment (Mar 2015)	**Major**
4	Documentation	Documentation (Jan 2011)	**Major**
5	Production	Production (Mar 2015)	**Major**
6	Quality control	Quality Control (Oct 2014)	**Major**
7	Contract manufacture and analysis	Outsourced activities (Jan 2013)	Minor
8	Complaints and product recall	Complaints and Product Recall (Oct 2014)	**Major**
9	Self Inspection	Self Inspection	Same
Part II	no clause 2.2		

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Current TGA GMP vs EU GMP

Annex	PIC/S Guide to GMP PE009-08	EU GMP Guidelines	Degree of change
1	Manufacture of sterile medicinal products	Manufacture of Sterile Medicinal Products (Nov 2008)	Same
2	Manufacture of biological medicinal products for human use	Manufacture of Biological active substances and Medicinal Products for Human Use (Jan 2013)	**Major**
3	Manufacture of radiopharmaceuticals	Manufacture of Radiopharmaceuticals	**Major**
6	Manufacture of medicinal gases	Manufacture of Medicinal Gases (Feb 2010)	**Major**
7	Manufacture of herbal medicinal products	Manufacture of Herbal Medicinal Products (Sept 2008)	**Major**
8	Sampling of starting and packaging materials	Sampling of Starting and Packaging Materials	Same
9	Manufacture of liquids, creams and ointments	Manufacture of Liquids, Creams and Ointments	Same

Current TGA GMP vs EU GMP

Annex	PIC/S Guide to GMP PE009-08	EU GMP Guidelines	Degree of change
10	Manufacture of pressurised metered dose aerosol preparations for inhalation	Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation	Same
11	Computerised systems	Computerised Systems (Jan 2011)	**Major**
12	Use of ionising radiation in the manufacture of medicinal products	Use of Ionising Radiation in the Manufacture of Medicinal Products	Same
13	Manufacture of investigational medicinal products	Manufacture of investigational medicinal products (Feb 2010)	Minor
15	Qualification and validation	Qualification and Validation (in draft)	**Major**
16	Qualified person and batch release	Certification by a Qualified Person and Batch Release (in draft)	**Not adopted, yet?**
17	Parametric release	Parametric Release	Same
19	Reference and retention samples	Reference and Retention Samples	Same
20	Quality risk management	*Refer to Q9 in Part III (Jan 2011)*	Same

Chapter 1
Pharmaceutical Quality System

- Complexity of PQS
- **Technical Transfer**
- Product and process knowledge
- All lifecycle stages
- Root cause analysis
- **Data Integrity**
- **Continuous PQR**

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Chapter 3: Premises & Equipment

The reasons for changes:

"The **only** change is to **section 6** as part of the improved guidance on **prevention of cross-contamination** involving also Chapter 5."

But…small changes can make a BIG difference!

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Chapter 3: Premises and Equipment
Cross-contamination

Cross-contamination **should be avoided** for all products by **appropriate** design and operation of manufacturing facilities.

The measures to **prevent** cross-contamination should be commensurate with the **risks**.

Quality Risk Management principles should be used to assess and control the risks.

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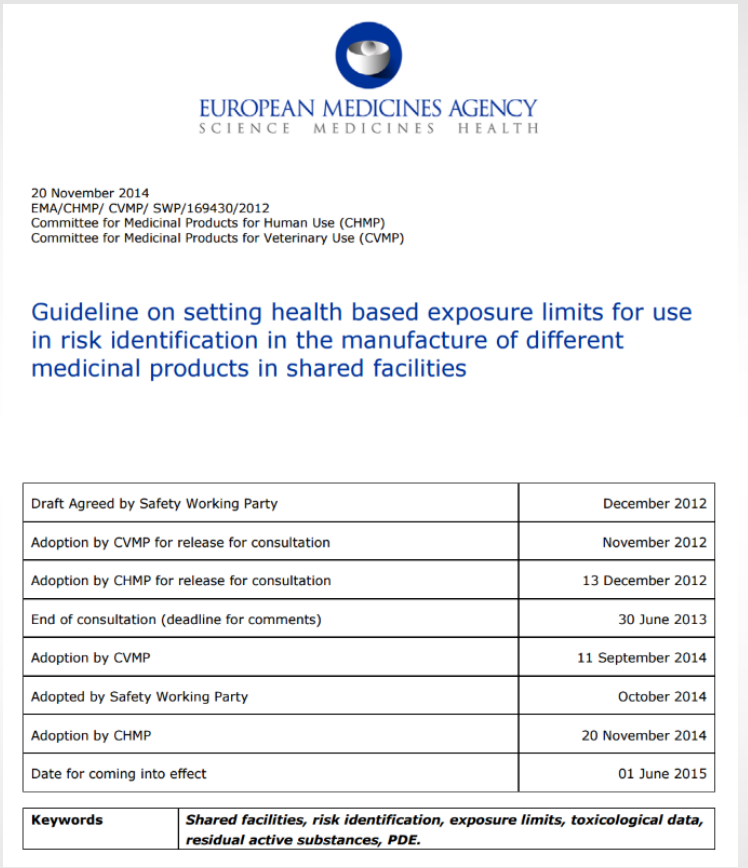
Chapter 3: Premises and Equipment Toxicological Evaluation

- Risk assessment should include among other parameters a **toxicological evaluation** of the products being manufactured (see **Guideline** on setting **health based exposure limits** for use in risk identification in the manufacture of different medicinal products in shared facilities).



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/ CVMP/ SWP/169430/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

Draft Agreed by Safety Working Party	December 2012
Adoption by CVMP for release for consultation	November 2012
Adoption by CHMP for release for consultation	13 December 2012
End of consultation (deadline for comments)	30 June 2013
Adoption by CVMP	11 September 2014
Adopted by Safety Working Party	October 2014
Adoption by CHMP	20 November 2014
Date for coming into effect	01 June 2015

Keywords	***Shared facilities, risk identification, exposure limits, toxicological data, residual active substances, PDE.***

http://ec.ehttp://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdfuropa.eu/health/files/gmp/2013_gmp_pc_en.pdf

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Chapter 3: Premises and Equipment Dedicated facilities?

Dedicated facilities are required for manufacturing when a medicinal product presents a **risk**:

a) Which cannot be adequately controlled by **operational** and/ or **technical** measures or

b) **Scientific data** does not support **threshold values** (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

c) Threshold values derived from the **toxicological evaluation** are below the levels of detection

Removed the "certain" products that must be produced in dedicated facilities.

Chapter 4: Documentation Principle

Good documentation constitutes an **essential part** of the quality assurance system and **is key** to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's **Quality Management System**.

Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.

Chapter 4: Documentation

The main objective of the system of documentation utilized must be to **establish, control, monitor and record all activities** which directly or indirectly impact on all aspects of the quality of medicinal products.

The Quality Management System should include **sufficient instructional detail** to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

Chapter 5: Production

The reasons for changes:

"…to improve the guidance on prevention of **cross contamination** and to refer to **toxicological assessment**…the qualification of **suppliers**… **supply chain traceability**… the testing of **starting materials**… guidance on notification of **restrictions in supply**"

Chapter 5: Production
Cross-contamination

- Reference to those "**certain**" products removed
- "Cross contamination should be avoided by **robust design** of the premises, equipment and processes which take place within a manufacturing facility. This should be supported by **appropriate procedures** and **technical or organizational measures**, including **reproducible** cleaning and decontamination processes of **validated effectiveness**."
- Section contains reworded & additional technical and organizational measures that can mitigate the risks of cross-contamination in greater detail

Chapter 5: Production
Cross-contamination

Technical Measures:

- **Dedicated** facilities & **self-contained** facilities rather than just segregation
- **Design** of facilities, equipment & processes to mitigate risks
- Using physical **barrier systems**
- Localised **extraction** of dusts
- **Dedicating** equipment
- Use of **disposable technologies**
- **Effective use** of airlocks and pressure cascades
- Use of **automatic** cleaning processes or **isolation** of equipment during cleaning

Chapter 5: Production
Cross-contamination

Organisational Measures:

- **Campaign** manufacturing in shared facilities
- **Cleaning verification** after each product campaign instead of a cleaning validation as a **detectability tool**
- Additional to use of **air samplers**, the use of **swab or wipe samples** from adjacent areas to confirm effectiveness of mitigation strategies

Chapter 5: Production Suppliers

Recognition that the **supply chain** needs to also be considered as part of the risks to materials

Preference to **purchase direct** from manufacturers of materials

Detailed quality agreement should be **documented** with suppliers

Chapter 5: Production
Supplier audits

- Audit duration and scope should be based ensuring that **full assessment** of GMP is made
- Particular attention to the **potential of cross-contamination** from other materials should be addressed during the audit
- **CAPA approach** should be used by the supplier to address findings
- Audit schedule for suppliers should be based on **risk** and ensure standards are maintained.

GMP

CAPA

RISK

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Chapter 5: Production
Starting Materials

- Material received should include a **check** of the containers for **integrity** and documentation/ labelling checked against standard documentation maintained by the manufacturer
- Material sampling should be in line with **MA requirements** including packaging material
- **Identity** of each batch of excipients must **be proven**

Chapter 5: Production Starting Materials analysis

Audits of outsourced test laboratories is required to ensure compliance of the lab with GMP and that testing is in **compliance** with the methods defined in the MA dossier

The COA should **be formally checked** against the agreed product specifications and **signed** by a suitably experienced designated person.

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Chapter 5: Production
Starting Materials analysis

Reduced testing can be considered once **suitable experience and history** of supply is assessed and confirmed. Significant changes should be considered in the testing schedule

Full testing of supplied material should be conducted on **a periodic basis** based on **risk**. If issues are identified, acceptance of CoA's should be discontinued until rectified

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Chapter 5: Production
Product Shortage

Notification of MAH should occur if the there are **abnormal restriction** of supply of products so that the **competent authorities can be notified**.

Chapter 6: Quality Control

The reasons for changes:

"Inclusion of a new section on **technical transfer** of testing methods and **other items** such as **Out Of Specification** results."

Chapter 6: Quality Control Technical Transfer

- Original validation method **should be compliant** with ICH requirements
- A **gap analysis** should be performed to identify additional validation requirements
- Transfer should be described in a **written protocol**

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US FDA Inspection Trends

QikSolve
www.qiksolve.com

FDA Inspection Trends by Subpart Details

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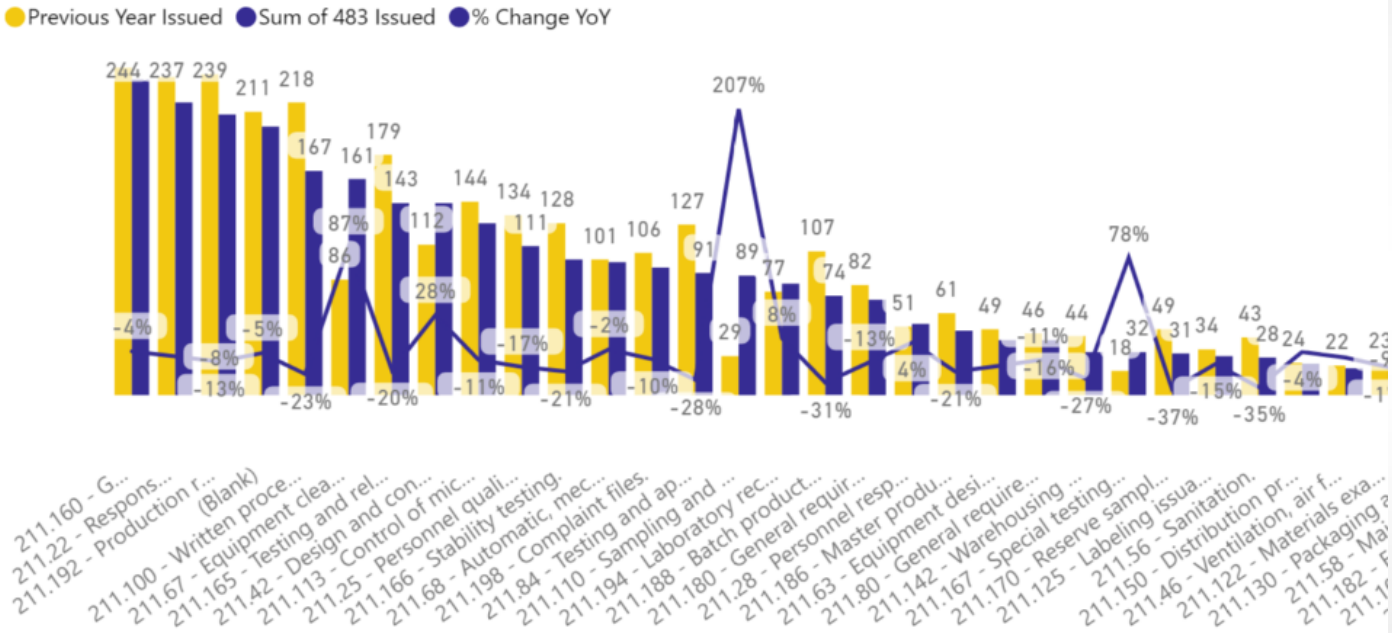
Data Source http://www.fda.gov/ICECI/Inspections/ucm222557.htm

Previous Year Issued, Sum of 483 Issued and % Change YoY by Section



483 Issued	Cite Id	Ref No	Long Desc
160	1105	21 CFR 211.22(d)	The responsibilities and procedures applicable to the quality control unit are not [in writ
130	3603	21 CFR 211.160(b)	Laboratory controls do not include the establishment of scientifically sound and approp
124	2027	21 CFR 211.192	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a ba
104	1451	21 CFR 211.113(b)	Procedures designed to prevent microbiological contamination of drug products purpo
95	1361	21 CFR 211.100(a)	There are no written procedures for production and process controls designed to assur

https://www.pharmout.net/services/gmp-consultants/fda-483-inspections-citations-drugs/

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Chapter 8: Complaints, Quality Defects and Product Recalls

The reasons for changes:

"Extensive changes…now reflect that **Quality Risk Management** principles should be applied…the need for the **cause(s)** of **quality defects** or complaints to be investigated and determined…appropriate **preventative actions**…clarifies expectations and responsibilities in relation to the **reporting of quality defects** to the Competent Authorities."

Chapter 8: Complaints, Quality Defects and Product Recalls

More specific guidance on the importance of **addressing product issues**

Inclusion of **product defects** to Chapter 8

Investigation of issues should be in line with standard methodologies used for **issue management and CAPA**

Outsourced activities are still the **responsibility** of the MAH or sponsor

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Chapter 8: Complaints… Investigation and Decision Making

New Clauses

- Introduces quality defects as **part of the investigation** of complaints
- Decision-making should address the **level of risk** to patient and be **timely**
- Accepts that early stage investigations have limited data, but risk-reducing activities should be determined as part of the **decision making life -cycle**
- Defects should be reported in a **timely manner** and **competent regulators notified**
- **Restriction of supply** should also be communicated to the Regulator

Chapter 8: Complaints… Root Cause Analysis

- Introduction of **Root Cause Analysis and CAPA's required**
- Processes & Systems should **not be overlooked** if human error is suspected early in the investigation
- Quality defect records should be **reviewed and trend analyses** should be **performed regularly**

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Chapter 8: Complaints… Product Recalls

New Clause:

- Relevant Regulators should be **consulted** regarding the extent of a recall
- Relevant Regulators should be **notified** of issues affecting expired product where no recall is initiated

Key Changes:

- Regulators should be notified in advance if a recall is imminent (except for serious cases)
- Regulators should agree with the recall strategy prior to execution

Chapter 8: Complaints… Product Recalls

Key Changes:

- Recall procedures should be **reviewed periodically** for both in and out of hours situations
- Evaluation should be **documented**
- **Mock recalls** should be considered as part of the review

New Clause:

- Other actions besides recall should be considered
- This should be discussed with the relevant regulator

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Regulatory Knowledge, Practically Applied.

Thank you for your time.
Questions?

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