# 2020 PDA Asia Pacific Pharmaceutical Manufacturing & Quality

## Regulatory Update: Annex 1

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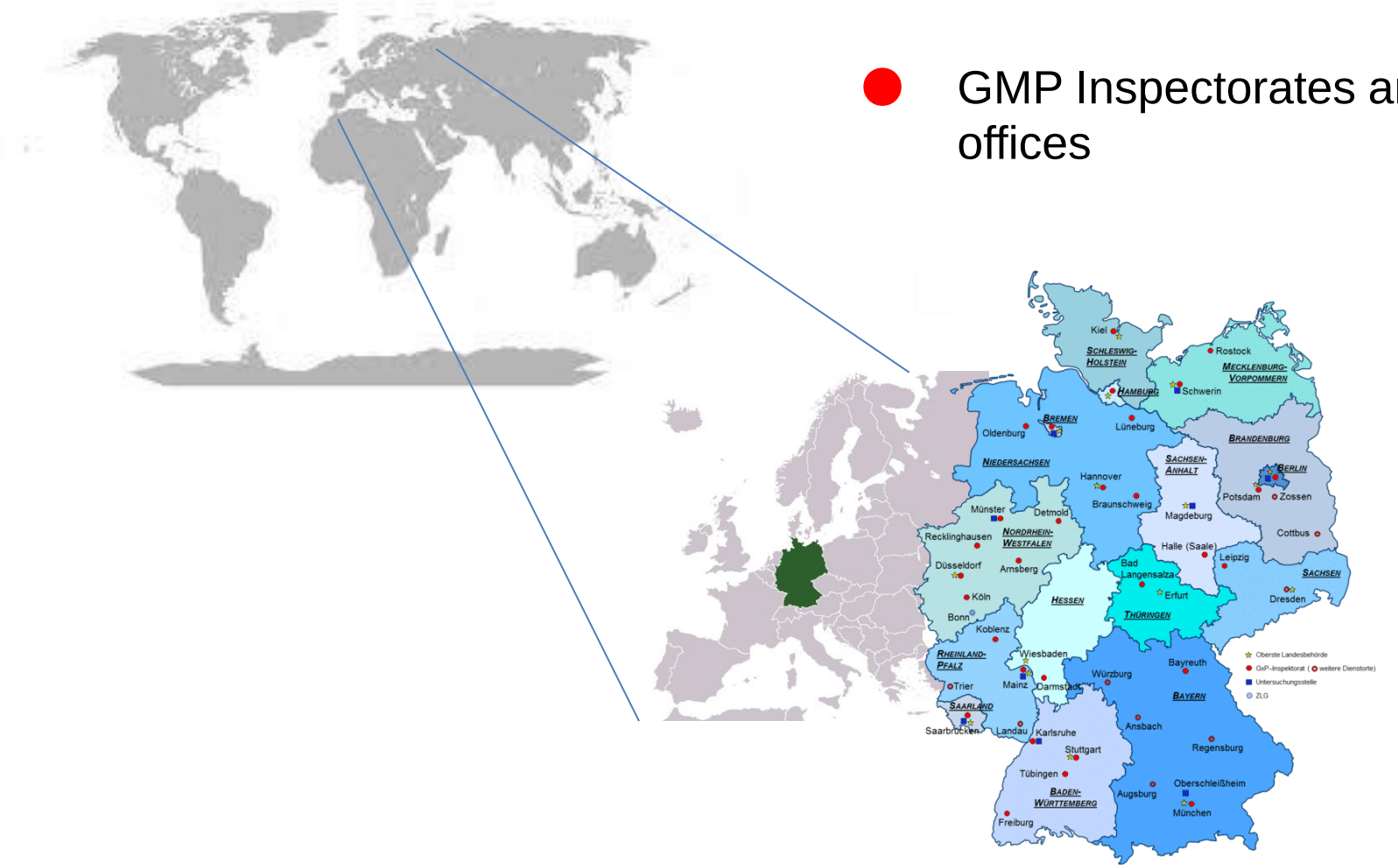
# GMP Supervision in Germany




- GMP Inspectorates and field offices

# Annex 1

## Manufacture of Sterile Medicinal Products

History (I):

- First issued in 1971/1989
- Revisions in 1996, 2003, 2005, 2007 and 2009 (no full revisions)
- Proposal for full revision in 2012, concept paper issued in 2015
- Draft for comment issued in December 2017
- End of consultation period March 20, 2018: more than 140 companies/organizations commented, more than 6,200 lines of comments

# Annex 1
## (cont'd)

History (II):

- Annex 1 Working Group (A1 WG) reviewed and suggested approach to comments and accepted or suggested alternatives
- Problems: "Brexit", Head of A1 WG left UK MHRA, a number of topics still under discussion
- Draft version no. 12 issued for a 3-months "targeted stakeholder consultation" on February 12, 2020
- Because of COVID-19 extension of consultation period until July 20,2020

# Annex 1

## A global approach

World Health Organization

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH


Australian Government
Department of Health
Therapeutic Goods Administration

Health Canada Santé Canada

Ministry of Food and Drug Safety


… and many others

# Section 1

## “Scope”

More than “sterile dosage forms”:

- **All sterile products** from API through to finished dosage forms – including excipients and primary packaging
- And: “May be used to support the manufacture of **other products** that are not intended to be sterile but where the control of microbial, particulate and pyrogen contamination is considered important”

# Section 2

## “Principle”

Key words:

- Application of “**quality risk management**” (QRM) principles
- “A **contamination control strategy** (CCS) should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed”

# Section 2
## (cont'd)

CCS "should include but not be limited to":

- Design of both plant and process
- Equipment and facilities
- Personnel
- Utilities
- Raw materials control
- Product containers and closures
- Vendor approval
- Mgmt of outsourced activities
- Process risk assessment
- Process validation
- Preventative maintenance
- Cleaning and disinfection
- Monitoring systems
- Continuous improvement
- Prevention – Trending, investigations, CAPA, root cause determination

# Section 4

## “Premises”

Structure:

- General requirements
- Clean room design (e.g., airlocks, air supply and air-flow)
- Barrier technologies
- Clean room and clean air device qualification
- Disinfection

# Section 4
## (cont'd)

Main topics of discussion:

- "~~For RABS used for aseptic processing (grade A) and open isolator, the background environment should meet at least grade B.~~" ▸ "4.21 For RABS used for aseptic processing, the **background environment** should meet at least grade B. The background environment for open isolators should meet grade C or D, based on a risk assessment."
- 4.25 and 4.26 Classification of cleanrooms: glossary definition of **classification and qualification**
- "4.29 For cleanroom classification, the **airborne particulates** equal to or greater than 0.5 and 5 µm should be measured"
- "4.34 The **requalification** of cleanrooms and clean air equipment should be carried out periodically following defined procedures" (see table 3)

# Section 7

## “Personnel”

Key requirements:

- **Training** for aseptic gowning and aseptic practices
- Unsupervised access to grade A zone and grade B areas where aseptic operations will be conducted is restricted to appropriately qualified personnel who have passed gowning assessment and participated in a successful **aseptic process simulation** (APS) test
- Systems for **disqualification of personnel** from entry into cleanrooms based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring program and/or after participation in a failed APS; once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices

# Section 8

## “Production and Specific Technologies”

Structure:

- Terminally sterilized products
- Aseptic preparation
- Finishing of sterile products
- Sterilization (by heat, moist heat, dry heat, radiation, ethylene oxide)
- Filtration of products which cannot be sterilized in their final container
- Form-Fill-Seal; Blow-Fill-Seal
- Lyophilization
- Closed systems; Single use systems

# Section 8
## (cont'd)

Main topics of discussion (I):

- Containers closed by fusion, e.g. […] **Small and Large Volume Parenteral bags** should be subject to **100% integrity testing**
- "Integrity of the sterilized filter assembly should be verified by testing before use and by on line testing immediately after use" (**PUPSIT**) ▸ "8.88 … It is recognized that PUPSIT may **not always be possible** after sterilization due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility. Points to consider in such a risk assessment should include …"

# Section 8
## (cont'd)

Main topics of discussion (II):

- "~~Bioburden samples should be taken prior to the first filter and the sterilizing filter~~" ▸ "8.94 **Bioburden samples** should be taken from the bulk product and immediately prior to the final sterile filtration"
- "8.95 **Liquid sterilizing filters should be discarded after the processing of a single lo**t and the same filter should not be used for more than one working day unless such use has been validated" – transition period most likely longer than 6 months
- "~~The lyophilizer should be sterilized before each load~~" ▸ "8.112 **Lyophilizers** that are manually loaded or unloaded should normally be **sterilized** before each load. For lyophilizers loaded by automated closed systems or located within systems that exclude operator intervention, the frequency of sterilization should be justified and documented as part of the CCS"

# Section 9

## “Viable and non-viable environmental & process monitoring”

Structure:

- General requirements
- Environmental monitoring (EM)
- EM - non-viable particles
- EM and personnel monitoring - viable particles
- Aseptic process simulation (also known as media-fill)

# Section 9
## (cont'd)

Another component of a CCS:

- Appropriately designed facilities
- Qualified premises and equipment
- Validated processes
- Suitable procedures
- Trained and qualified staff
- Only then: Monitoring

# Section 9
## (cont'd)

Main topic of discussion:

- **APS – "The target should be zero growth**. Any contaminated unit should result in a failed process simulation and the following actions should occur …"

  Root Cause Analysis; determination and implementation of corrective measures; prompt review of all records relating aseptic production since last successful APS; probably affected batches should be placed under quarantine; demonstration of successful "process revalidation" (minimum 3 successful, consecutive repeat media fills) before resuming production

# Section 10

## “Quality Control”

Main topics of discussion:

- “**Sterility test** should be performed under aseptic conditions~~, which are at least consistent with the standard of clean room required for the aseptic manufacture~~”
- “~~Each sterilized load should be considered as different batches and require a separate sterility test~~“ ▸ „Where the manufacturing process results in sub-batches (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed.”

# And now?

## A look into the crystal ball

Thank you for listening

Questions, comments, ideas?