#sharing challenges
and solutions in practice

Update on Annex 1 Revision …

GMP/FDA Compliance Conference

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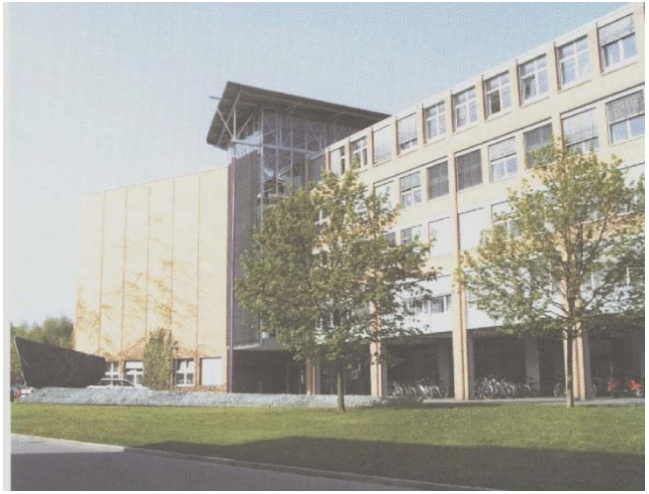
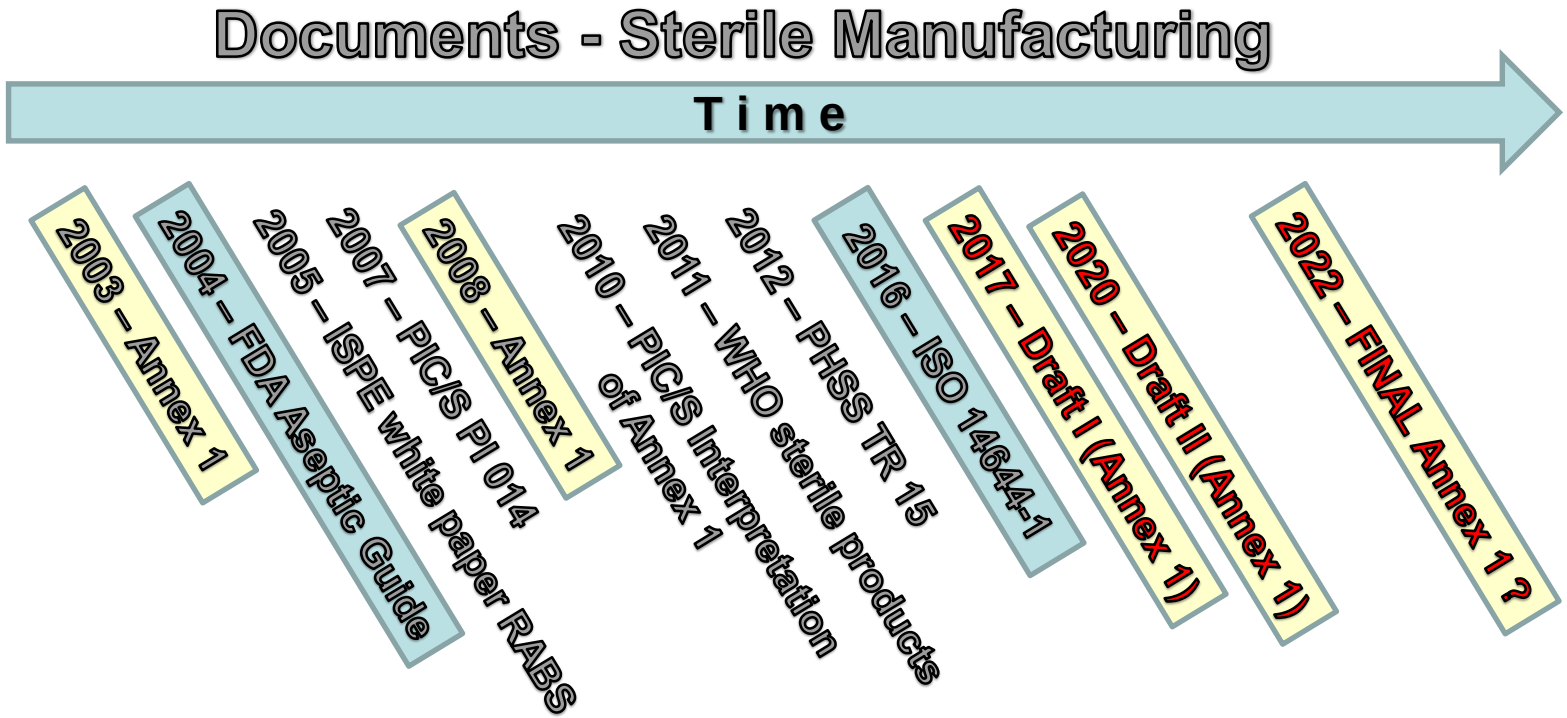


This presentation represents the personal view of the author and not necessarily the view of (all) competent authorities or regulatory bodies.

Update on Annex 1 Revision

- **Timelines on Annex 1-revision process**
- Old- (2008) versus new Annex 1 version (2022)
- Important changes, disussion points

Regulatory documents



Annex 1 (2008) vs. 2017, 2020 drafts & final version

Current version (2008)	Draft 12/2017 (Rev.)	Draft 02/2020 (Rev.)	FINAL version (2022)
16 pages	50 pages	52 pages	**57 pages**
127 clauses	269 clauses	292 clauses	**285 clauses**
Major changes (in 2008): - Cleanroom classification versus -monitoring - Bioburden testing - Media fill - Capping of vials	Major changes: - (completely) new structure - QRM principles introduced - Pharm Quality System (PQS) - New aseptic techniques (e.g FFS, SUS, …) = „new“ guideline		Major changes: - (completely) new structure - QRM principles introduced - Pharm Quality System (PQS) - New aseptic techniques (e.g FFS, SUS, …) = „new“ guideline

Update on Annex 1 Revision

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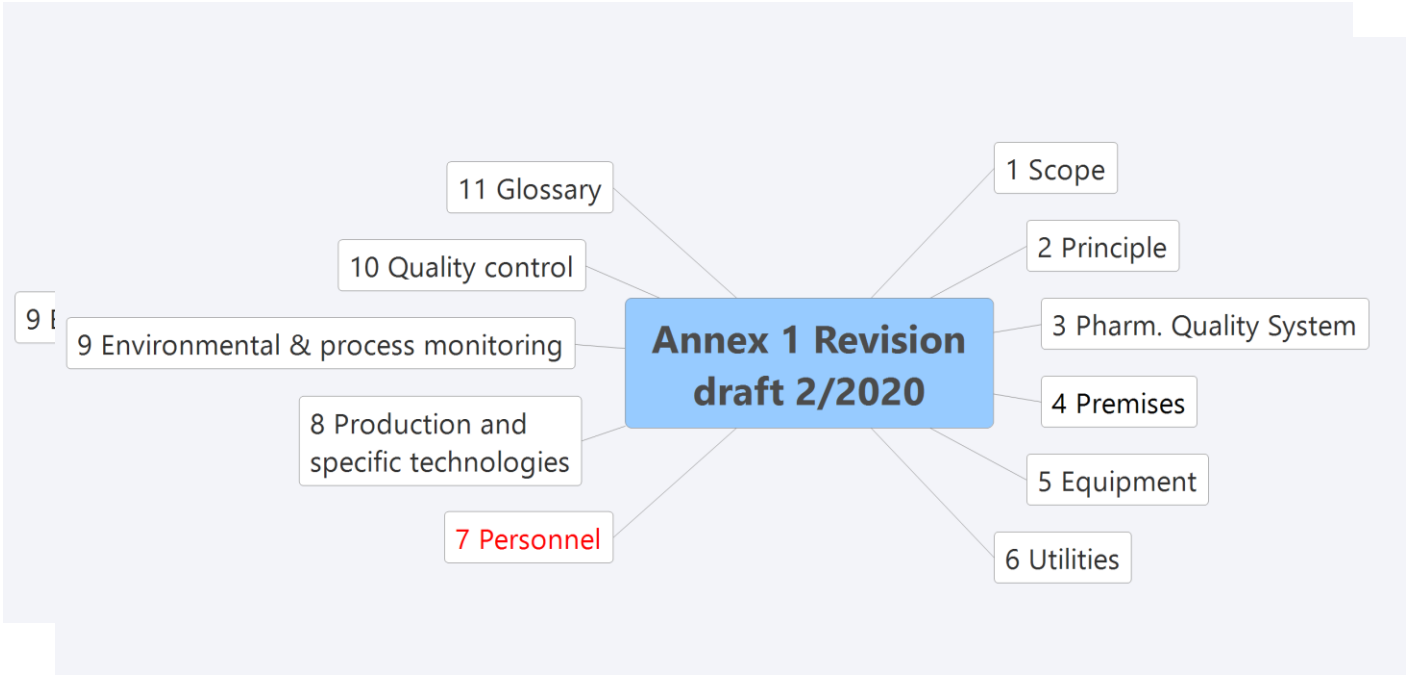
Annex 1 (final, 2022)

- Completely new structure (compared to version 2008)



New structure

Chapter	FINAL version, 2022
Principle	7 clauses
Pharmaceutical Quality System (PQS)	2 clauses
Premises	36 clauses
Equipment	9 clauses
Utilities	22 clauses

New structure

Chapter	FINAL version, 2022 [pages]
Personnel	10 clauses
Production & specific technologies	139 clauses
Environmental & process monitoring	49 clauses
Quality control	11 clauses
Glossary	71 terms

Annex 1 (2008) vs. final version (2022)

Key words	Current Version (2008)	FINAL version (2022)
Contamination Control Strategy „CCS“	--- ---	3 51 !!!
Barrier	1	16 !
Isolator	7	48 !!!
Robotic	3	2
„automat“	---	13 !

Annex 1 (final)

- Completely **new chapters** / subchapters
  - Utilities
    - ⇨ water, steam, gases, vacuum- / heating- / cooling- hydraulic systems
  - Form fill seal (FFS)
  - Lyophilisation
  - Closed systems
  - Single use system
  - Environmental & process monitoring
    - ⇨ General, environm. & process monitoring, EM total particle / - viable particle, aseptic process simulation (APS, formerly „media fill“)

Annex 1 (final)

- Completely **new glossary**, e.g.
  - 71 terms defined!
  - Barrier / restricted access barrier system (RABS) / isolator (closed, open) / … Rapid transfer port (RTP)
  - Bio-decontamination / decontamination / disinfection / sporicidal agent / … cleaning
  - Cleanroom classification / - qualification / classified area / clean area / cleanroom / airlock / pass-through hatch / … critical zone / critical surfaces
  - Turbulent airflow / unidirectional - / unidirectional – unit (UDAF, formerly „LAF“) / first air / grade A air supply / HEPA filter

Annex 1 (final)

- Completely new glossary, e.g.
  - Operator / gowning qualification
  - Closed system / single use systems / „intrinsic sterile connection device“ / extractables / leachables
  - Filter integrity test / sterilising grade filter
  - Aseptic process simulation (APS, formly „media fill“) / corrective - / critical - / inherent intervention, aseptic preparation, processing /

Annex 1 (final)

- Scope & principle:
  - For a **wide range** of **sterile products** (api/ds, excipient, primary packaging material, ds/api, dp/finished dosage form)
  - General guidance for „**hardware**“ (facility, equipment) and **operations** (procedures, processes) for all sterile products …
    … to ensure **prevention** of „any kind“ of **contamination** (microbial, particulate, endotoxin/pyrogen)
  - **QRM applies** … in its entity to the whole guide.
  - Contamination Control Strategy (**CCS**) = major tool

Annex 1 (final)

- Contamination control strategy (CCS):
  - „new“ requirement - since first draft (12/2917)
  - Implemented across the facility
  - Establish robust assurance of contamination prevention
  - Actively reviewed, updated … drive continual improvement
  - Periodically reviewed, managment review
  - **CSS** should **consider all aspects of contamination control** … with ongoing **periodic review** … **changes** should be **assessed** …

Annex 1 (final)

- Contamination control strategy (CCS):
  - **CCS** should include („should **assess**“)
    - ⇨ Design of plant & process
    - ⇨ Premises & equipment
    - ⇨ Personnel
    - ⇨ Utilities
    - ⇨ Raw material, IPC
    - ⇨ Containers & closures
    - ⇨ Vendor approval
    - ⇨ Outsourced activities
    - ⇨ Process risk management
    - ⇨ Process validation
    - ⇨ Validation of sterilisation processes
    - ⇨ Preventive Maintenance
    - ⇨ Cleaning & disinfection
    - ⇨ Monitoring systems
    - ⇨ Prevention mechanisms (… CAPA)
    - ⇨ Continuous improvement

Update on Annex 1 Revision

- Timelines on Annex 1-revision process
- Old- (2008) versus new Annex 1 version (2022)
- **Important changes, disussion points**

Some selected aspects

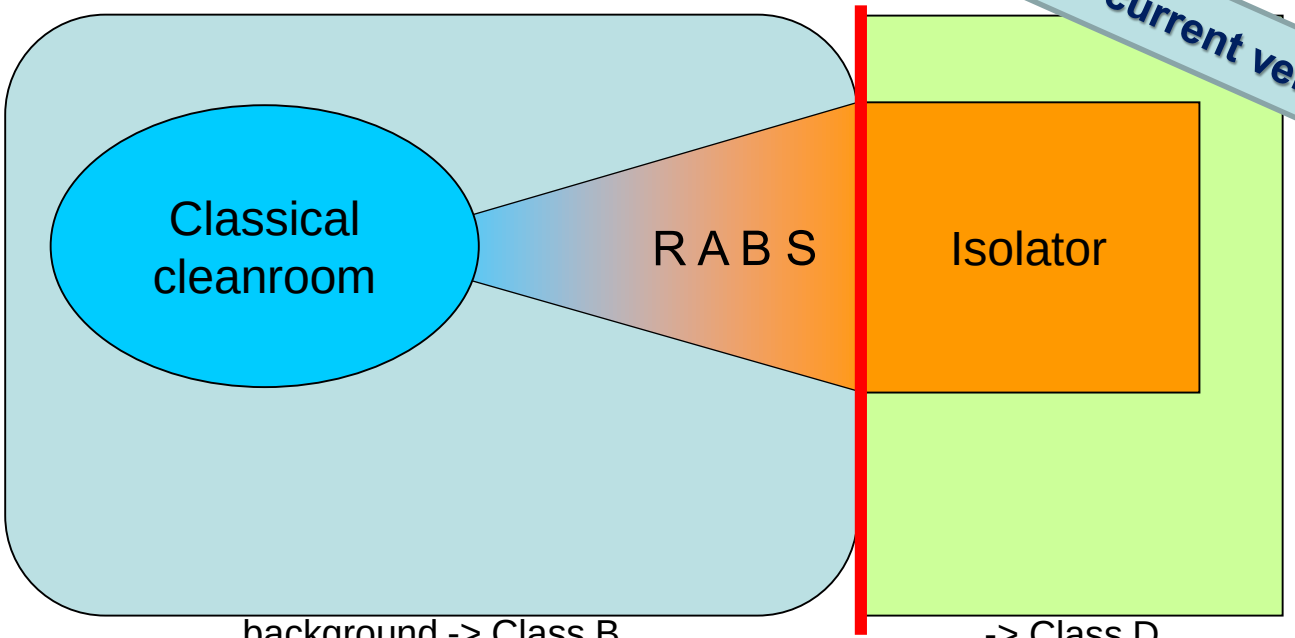
- Cleanrooms / premises
  - **Classification**
    - ⇨ cf. to ISO 14644-x Standards (values, sampling points
    - ⇨ Particles >= **5um still part of classification**,
      BUT for class A/B „at rest“ & class A „in operation“ **not specified**, classification including 5um particles **may** be considered (mentioned in CCS, historical data)
    - ⇨ Definitions of „at rest“ and in operation given in text (not in glossary)
  - Classification is part of cleanroom qualification
    - ⇨ Qualification -> cf. to Annex 15
  - Env. Monitoring
    - ⇨ Acceptance criteria for >= 5um particles, alignement with ISO 14644-1 (?)

Some selected aspects

- Barrier technologies
  - Isolator // RABS are different technologies
  - Design
    - ⇨ Isolators: closed or open; negative pressure (containment)
    - ⇨ RABS: grade A air conditions, unidirectional airflow, … [= open]
  - **Background**
    - ⇨ Isolator: **min. grade C** (RA, justify in CCS = **„opener clause“** if grade D is used)
    - ⇨ RABS: **min. grade B**
  - Glove systems (-> leak testing strategies)
  - Decontamination methods (cleanig & bio-decontamination)

Cleanroom – RABS – Isolator

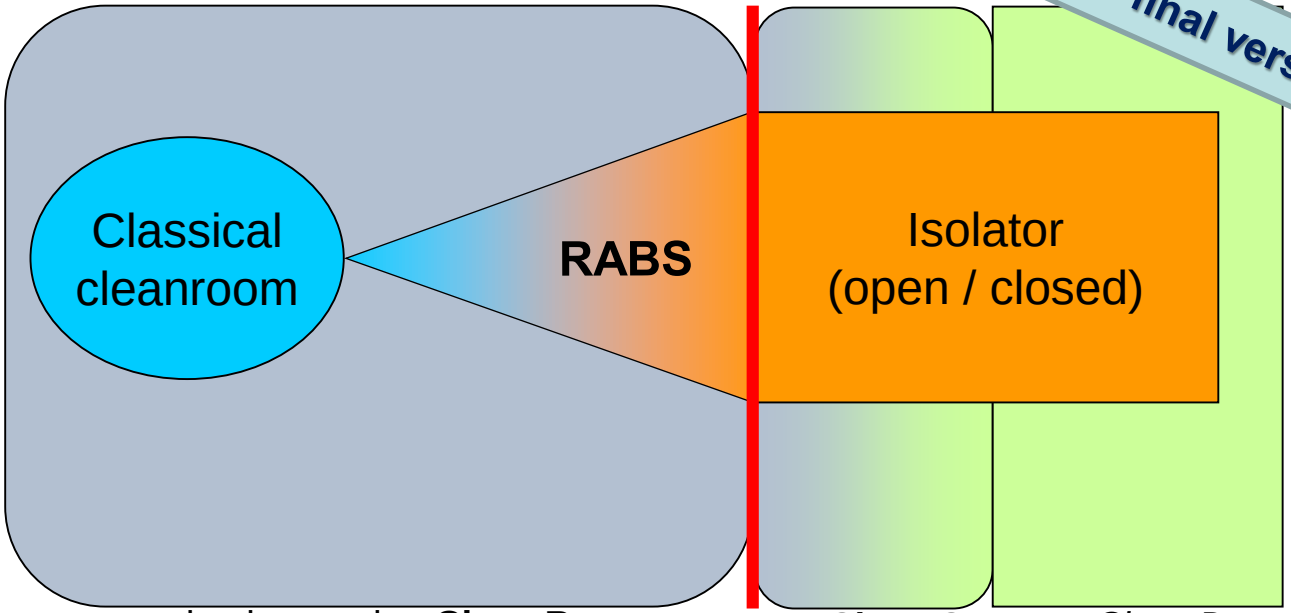
Annex 1 – current version (2008)



„Regulatory line“

Cleanroom – RABS - Isolator

Annex 1 – final version (2022)



„Regulatory line“

Some selected aspects

- Personnel / Gowning / Monitoring
  - **Gowning qualification**
    - ⇨ Defined in glossary and requirements given in text
    - ⇨ Assessment & confirmation of aseptic gowning procedures
      - initailly & periodically (at least annually)
      - Visual & microbial asessment (sample positions listed)
      - (Action) limits given in clause 9.30 (Env. & personnel monitg. – viable particle)
  - Personnel monitoring programme including **trend** analysis
  - System for **disqualification**

Some selected aspects

- Cleanroom clothing
  - Cleanroom clothing: company socks & goggles!
    [all the rest is well known standard]
  - **Qualification of garments**, holding times (sterilised), check of clothing before usage
  - Max. period of usage during shift (-> CCS!)
  - **Reusable clothing**: qualified laundry [& validated sterilisation], …
    … no shedding, no risk of contamination, max. laundry & sterilsation cycles = part of garment qualification [outsourcing: vendor audit, change control, qualified / validated processes as well]

Some selected aspects

- Sterile filtration
  - Bioburden reduction prefilter**s** possible, but additional filtration through sterilising grade filter as close as possible to pint of fill (-> part of CCS!)
  - Design of filtration system, validation & worst case conditions, bacterial retention testing with product/matrix, filtration parameters, … [well known standard]
  - **PUPSIT** = will be **kept** as requirement !!!, BUT an **„opener clause“** for **alternative approaches** introduced
    - ⇨ RA and justification
    - ⇨ Points to consider for such RA listed!
  - Routine filter integrity testing: PUPSIT & post use

Some selected aspects

- Sterile filtration
  - Multiple filter system = considered to be a „single sterilising unit“
  - **Redundant filtration systems** adressed
    - ⇨ when to perform filter integrity test on which filter (primary „sterile filter“, backup sterilising grade filter)
  - Bioburden sampling adressed in detail
  - Sterile filters used **batchwise**, continuously not more than one day
    - ⇨ unless otherwise justified [= „opener clause“]
  - Campain manufacture adressed with requirements

Some selected aspects

- Closed Systems / Single use systems
  - **Aseptic connections** in grade A/B
    - ⇨ Unless subsequently sterilised in place
      or with **„intrinsic sterile connection devices“** [two „opener clauses“]
      - defined in glossary & text: designed to mitigate risk of contaminatnion, reducing risk of contamination during process (mechnical or sealing)
  - Connection of sterile equipment to sterilised product pathway after final sterilising grade filter -> aseptic connection, e.g. by „intrinsic sterile connection devices“

Some selected aspects

- Closed Systems / Single use systems
  - Background environment
    - ⇨ Based on their design & the process [question: how „open“ is the process?]
    - ⇨ General rule: **aseptic processing** located in **grade A,** ...
      … BUT if there‘s proof that systems remains integral at every usage (e.g. pressure testing monitoring) -> lower classification possible [= **„opener clause“**, -> RA, justification needed!]
    - ⇨ If system is considered „open“ at a certain time (e.g. maintenance) -> cleanroom grade appropriate for materials / product
      - e.g. class C for terminal serilisation, grade A for aseptic procesing
  - Appropriate measures to ensure integrity of components
  - Integrity maintained throughout processing

Some selected aspects

- Container closure integrity / visual inspection
  - Containes closed by fusion: 100% container cloure integrity testing (CCIT)
  - Concept for integrity testing of other containers
  - Vacuum test if product sealed under vacuum

  - Parenteral products subjected to visual [optical] inspection of each container (for extraneous contaminations or defects ⇔ CCIT)
  - Manual & automated visual inspection techniques adressed

=> Alignement with USP <1790> and EP 5.17.2!

Annex 1 revision (… 2022)

- Major, basic requirements are known since first draft (12/2017)
  - e.g. contamination control strategy (CCS)
- Relevant changes from draft 12/17 to draft 2/20,
- After draft 2/20 changes are not to be called „major“, smaller changes happened in
  - Structure, details, terms & wording
- But no real changes in „new basic“ requirements for maunfacturing of sterile products (like CCS) since draft 2/20

Annex 1 revision (… 2022)

- „Bad news“
  - ⇨ No, I unfortunately do not know what will be the day of publi
  - ⇨ No, I unfortunately can‘t tell you which timefram ation of all new requirements
- „Good news“:
  - Most probab year, and will probably
  - is about „some requirements / details“, but the overall be a „up-to-date state of the art“ for sterile manufacture
  - You had already time to prepare for major new requirements, event if some details may have changed during the drafting phase

It‘s TIME for the final version of Annex 1 – NOW!

Thank you for your attention

QUESTIONS ?