Update on the revision of Annex 1 – Sterile Medicinal Products

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Background – the Annex 1 ~~Story~~ Saga

Update to 2008 revision of Annex 1 announced in 2015, with an estimated 2 year timeframe for publication

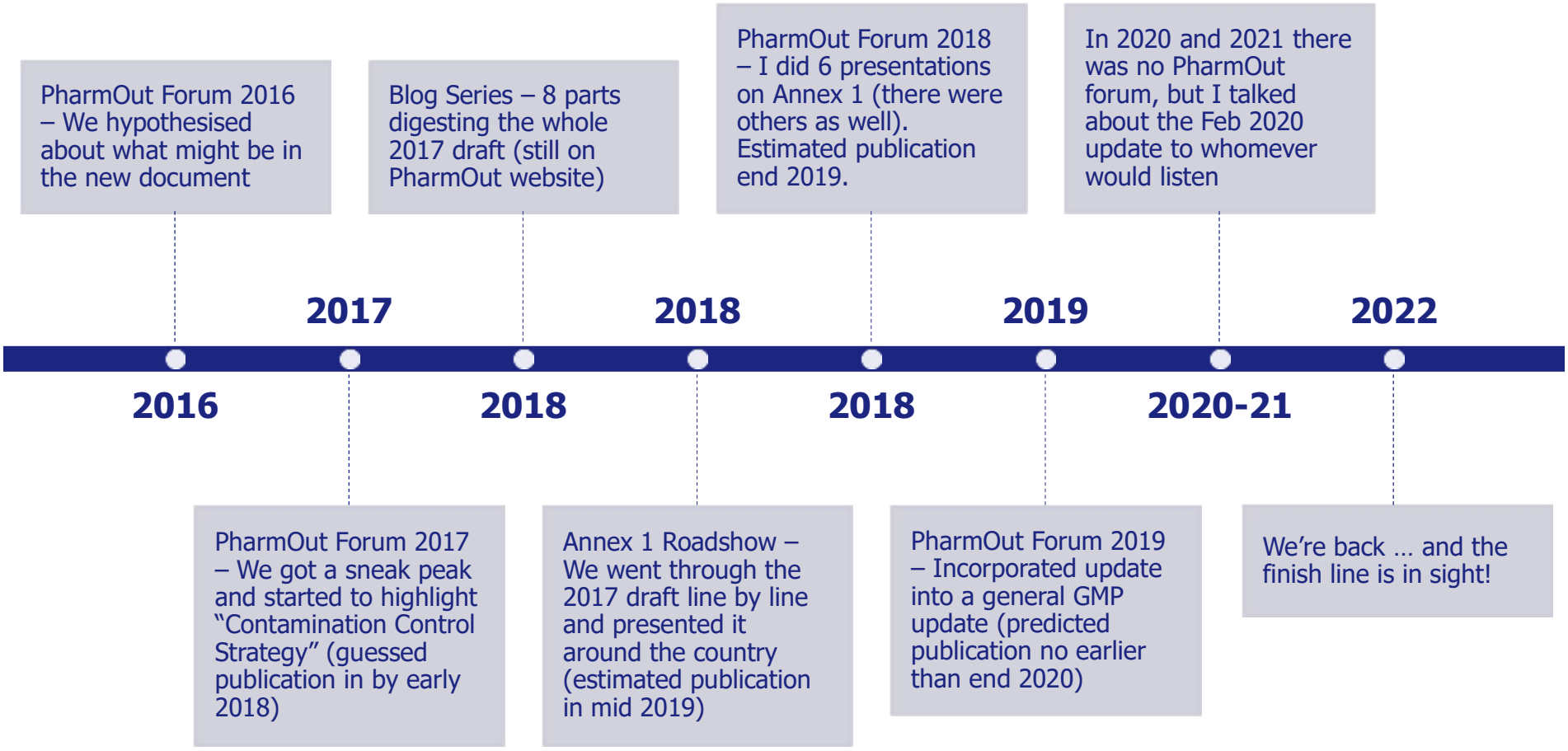
1st public draft issued in December 2017, followed by public consultation

2nd public draft issued in February 2020, followed by targeted consultation

Document is still not published (more later)

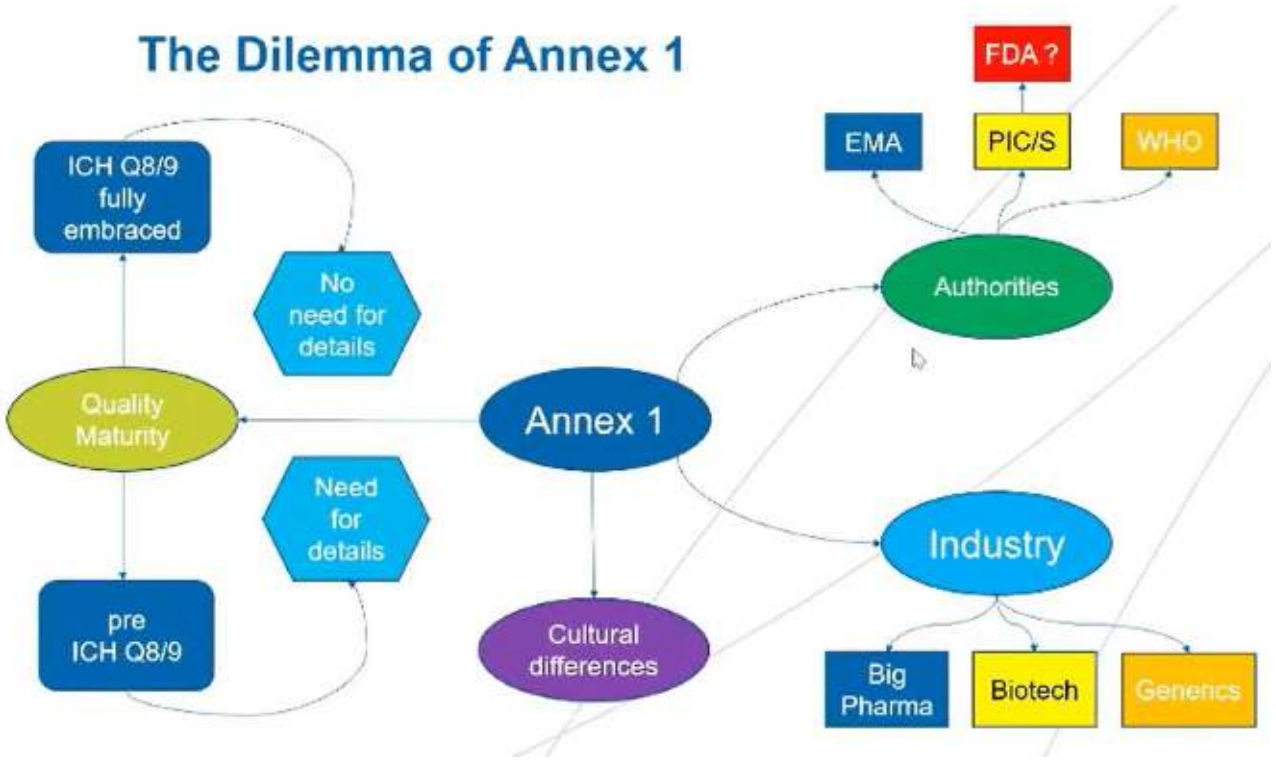
Several key issues (both content and political) have delayed the process

Not Annex 1 Again?



The Dilemma

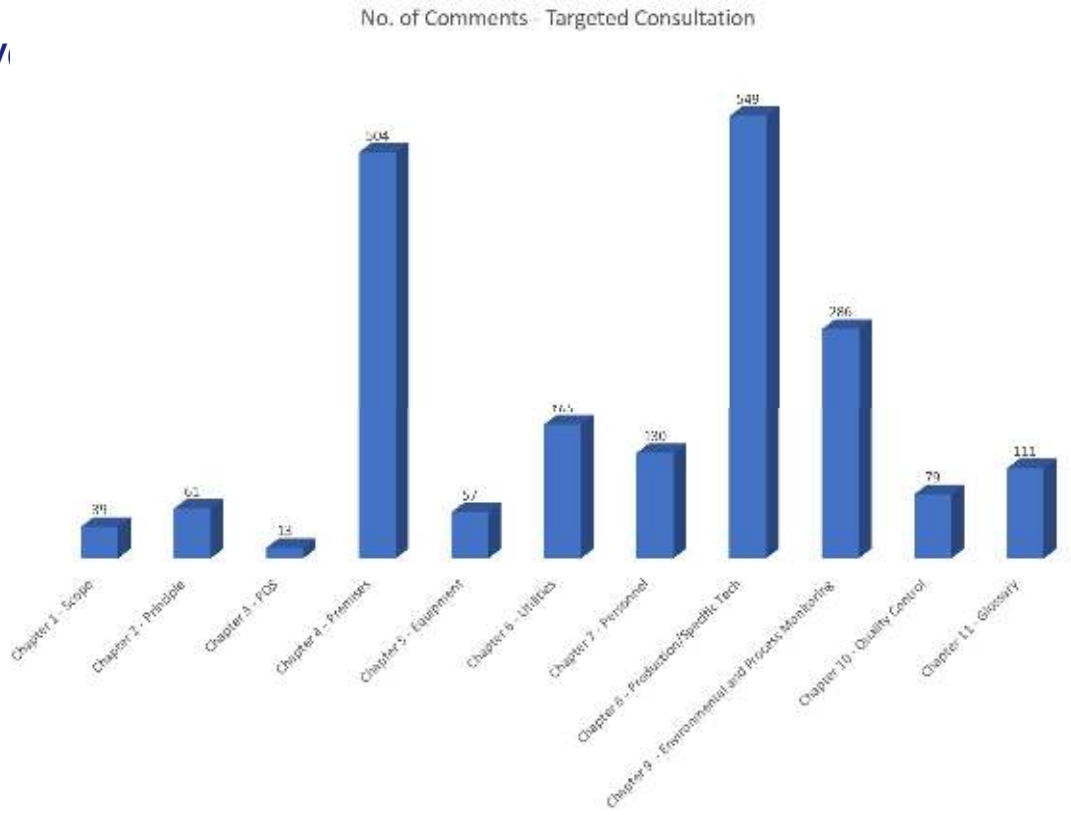
Some of the reason for the delay … agreement has not been easy



Credit: Jörg Zimmermann,
Vetter Pharma-Fertigung GmbH & Co.

Public and Targeted Commentary

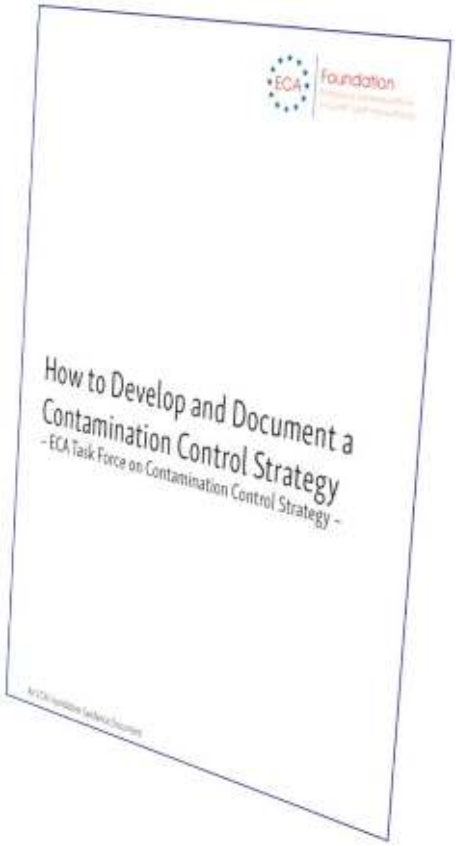
- Public consultation (1st draft) receiv over 4000 comments
- Targeted consultation (2nd draft) received a further 2000 comments



Areas of Significant Impact

Contamination Control Strategy

- A significant shift in the way we are required to present data
- A single source document, providing the full story for contamination control at your site
- Implications for the way in which contamination control is assessed
- Certain to impact the way in which regulatory inspections are performed



Areas of Significant Impact

Microbiological monitoring

- Aseptic Process Simulations
  - Target Zero (instead of acceptable failure rates)
  - Significant expansion of guidance, especially around interventions and routine inclusions
  - Greater emphasis on program design and therefore less excuse for inadequate/minimalist programs.
- Identification
  - Required to species level for Grade A and B isolates
  - In Grades C and D, consideration for identification (extent not stated) should be given in certain circumstances (e.g. alert/action limits exceeded, potential objectionable organisms identified)
- Rationale for environmental monitoring plans for both total and viable particles
  - Considerably more emphasis is placed on implementing a QRM approach to establish the extent of environmental monitoring plans

Areas of Contention

Sterilisation of indirect contact parts

- The VHP "fragility" faction appear to have won the day
- VHP/fumigation will not be considered an acceptable "sterilisation" method
- Steam sterilisation may be impractical for some components
- The argument against fumigation is weak for components located permanently inside isolators

Areas of Contention

Airflow qualification (1)

- 2020 draft requires measurement of uni-directional flow velocity "at the working position" as the default (it does allow for justification of alternatives
  - This expectation is not consistent with other regulatory guidance (e.g. FDA Aseptic Processing Guide)
  - The validity of the expectation as a means of determining uni-directional flow has been widely debunked (the 90fpm value was arbitrarily selected by nuclear engineers in the early days of HEPA filtration)
  - Blind application of the expectation may actually result in turbulent conditions in the working zone

Areas of Contention

Airflow qualification (2)

- 2020 draft contains requirement (4.15) which strongly implies that visualisation studies for non-unidirectional areas are expected.
  - This expectation has highly questionable value in most instances, due to modern understanding of airflow dynamics, other monitoring techniques and the limitations of airflow visualisation studies in turbulent air.

There has been no indication from the IWG as to the likely outcome for these airflow issues.

Areas of Contention

Leak testing of barrier systems

- Clause 4.23 of the 2020 draft conflates leak testing requirements for RABS and isolators. It requires that leak testing methods for gloves and isolators are "demonstrated to be suitable for the task and criticality". This raises several concerns
- Many existing isolator systems may not be able to meet this standard for lack of integrated testing systems
- It is unclear if expectations for RABS and isolator glove systems are the same or different.
- The IWG have offered no guidance or reference for what may be deemed acceptable and different inspectorates are likely have to very different interpretations of this.

Again, we have no indication from IWG regarding updates to these clauses.

Areas of Contention – One more time!

PUPSIT

- It is still in!
- Inter Association Group (IAG) put forward survey information and test data to provide a scientific perspective of the relative risks of PUPSIT and non-PUPSIT
- IWG response was "not enough data"
- Alternative methodology supported by RA may be included, but the expectations of different regulators will affect how these are interpreted.
- Nuclear medicines/radiopharmacies will be exempt.

Expected/Desired Changes from Feb 2020 Draft

- General clarity improvements
- Harmonisation of language and terminology across sections
- Greater acknowledgement of management of existing/legacy systems as an acceptable alternative to full compliance with future expectations
- A greater emphasis of effective QRM, and less rigidity in the way requirements are phrased
- Possible separation of barrier systems section within section 8
- Additional clarity expected for integrity testing of fusion sealed containers

And When Will it be Published?

"The target date is to have a revision in mid-2022"

Paul Gustafson, Chair of PIC/S, March 14, 2022.

And When Will it be Published?

If the target date (June-July) is achieved, it is possible for PIC/S to issue a new Annex 1 as part of PE009 version 17, as early as July, but probably September 2022.

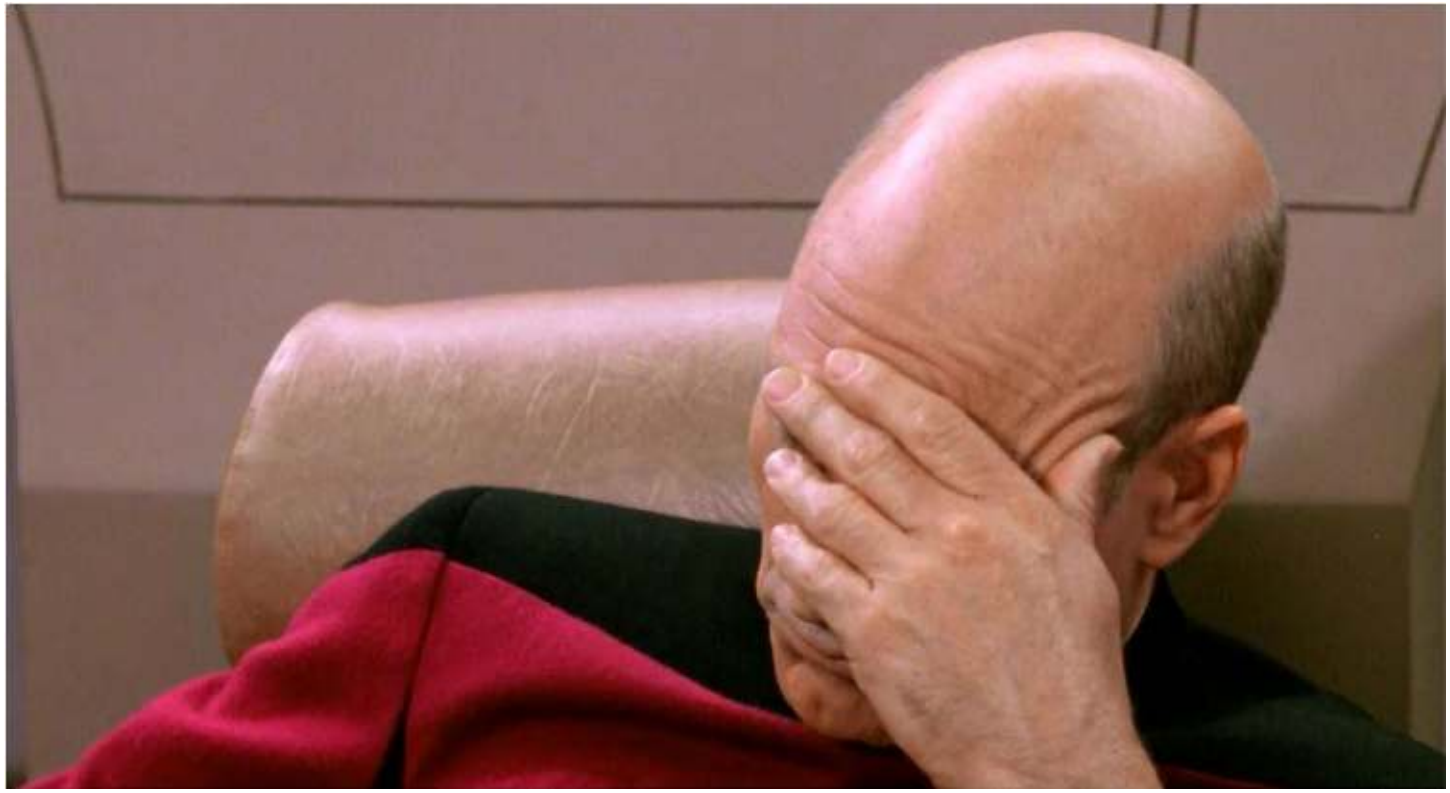
It would then be possible for TGA to adopt the new version as "early" as January 1, 2023

(they completed the transition to version 13 in a similar timeframe)

A 12 month implementation period should be expected

And When Will it be Published?

Or it's possible a new argument has broken out in the last 8 weeks, and we will be guessing again at the next conference



What should you be doing in the meantime?

Feb 2020 is still a great starting point

A gap assessment against this document will likely address virtually all issues expected to be gaps against the final document

Consider if your QRM activities are adequate in relation to legacy systems and processes

- May require new assessments and documented justifications
- May require modifications to facilities, equipment or processes

If you haven't already, get cracking on CCS (TGA are already expecting it)

Thank you