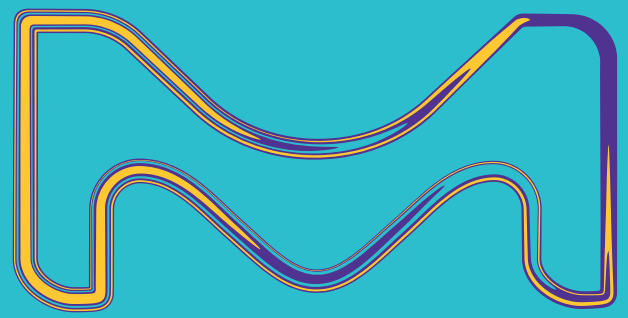
Trends in Manufacturing of Sterile Medicinal Products by Filtration

Michael Payne

Principal Technical Consultant, Merck Millipore

DCVMN Meeting

Hyderabad, May 8, 2018



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Presentation Scope

Common vocabulary – including PUPSIT and redundant filtration

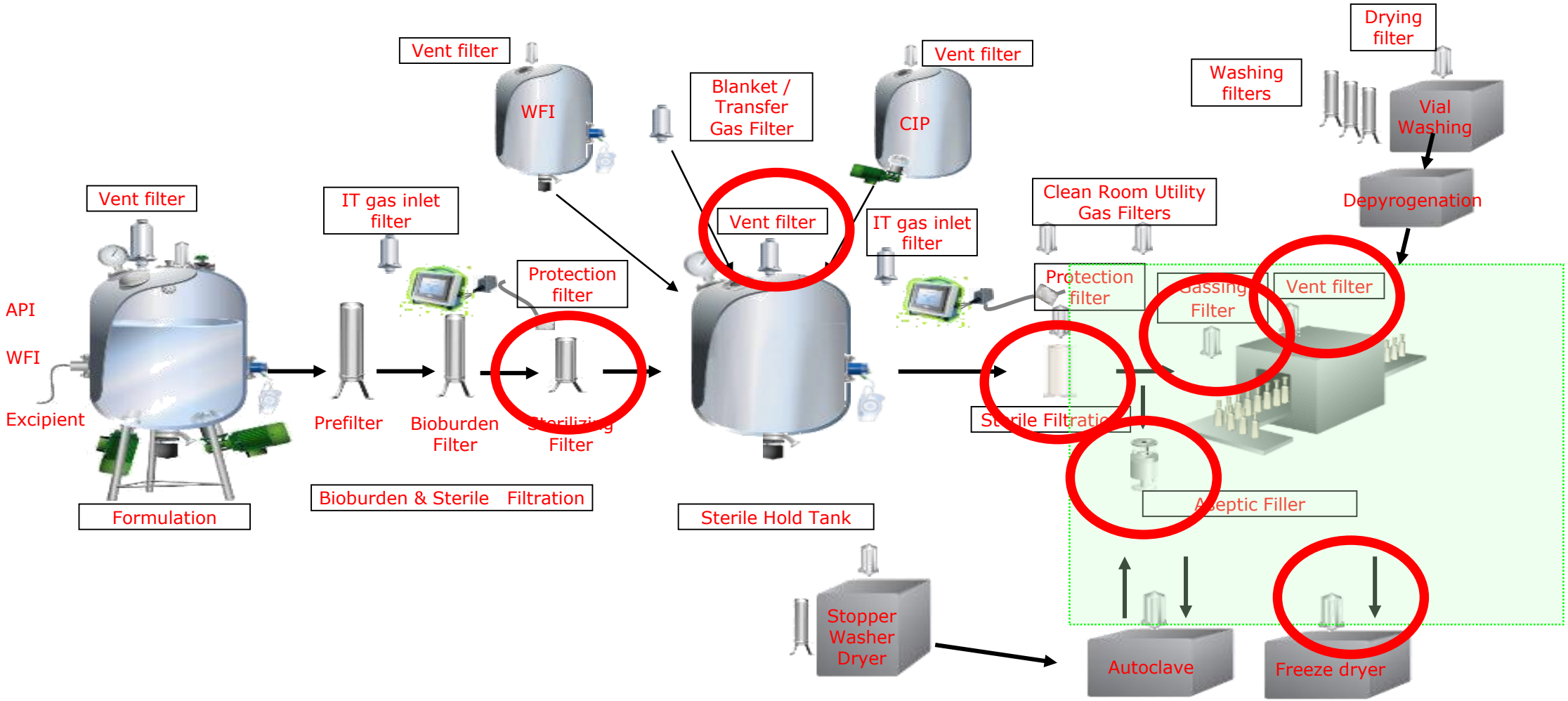
Current sterile medicinal product regulations & guidances

Recent regulatory trends

Future regulatory direction for sterile medicinal products

Scope – Sterile Medicinal Products

Formulation / Filling Suite – Filtration Highlights



Common Vocabulary

What Does “Should” Mean

US FDA

Guidance for Industry Process Validation: General Principles and Practices Jan 2011

"The use of the word should in Agency guidances means that something is suggested or recommended, but not required"

PICS

RECOMMENDATION ON THE VALIDATION OF ASEPTIC PROCESSES, PI 007-6, January 2011

"the term "should" indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality“

Key Definitions Section

“Aseptic filling: Operation whereby the product is sterilised separately, then filled and packaged using sterilised containers and closures in critical processing zones.”

“Bioburden: Total number of viable microorganisms on or in pharmaceutical product prior to sterilisation.”

“Integrity test: Test to determine the functional performance of a filter system.”

“Sterile: Free of any viable organisms. (In practice, no such absolute statement regarding the absence of microorganisms can be proven, see sterilisation.)”

“Sterilisation: Validated process used to render a product free of viable organisms.”

Some Useful Definitions

Validation - **Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.** (PICS PE-009 GMP Guide)

Critical applications - **Where process fluids "are in direct contact with sterile final product or critical surfaces of the associated equipment."** (PDA TR40)

Moderately critical applications - **Are "those where the filtered gas will not be in direct contact with exposed sterile product or surfaces."** (PDA TR40)

Some Useful Definitions

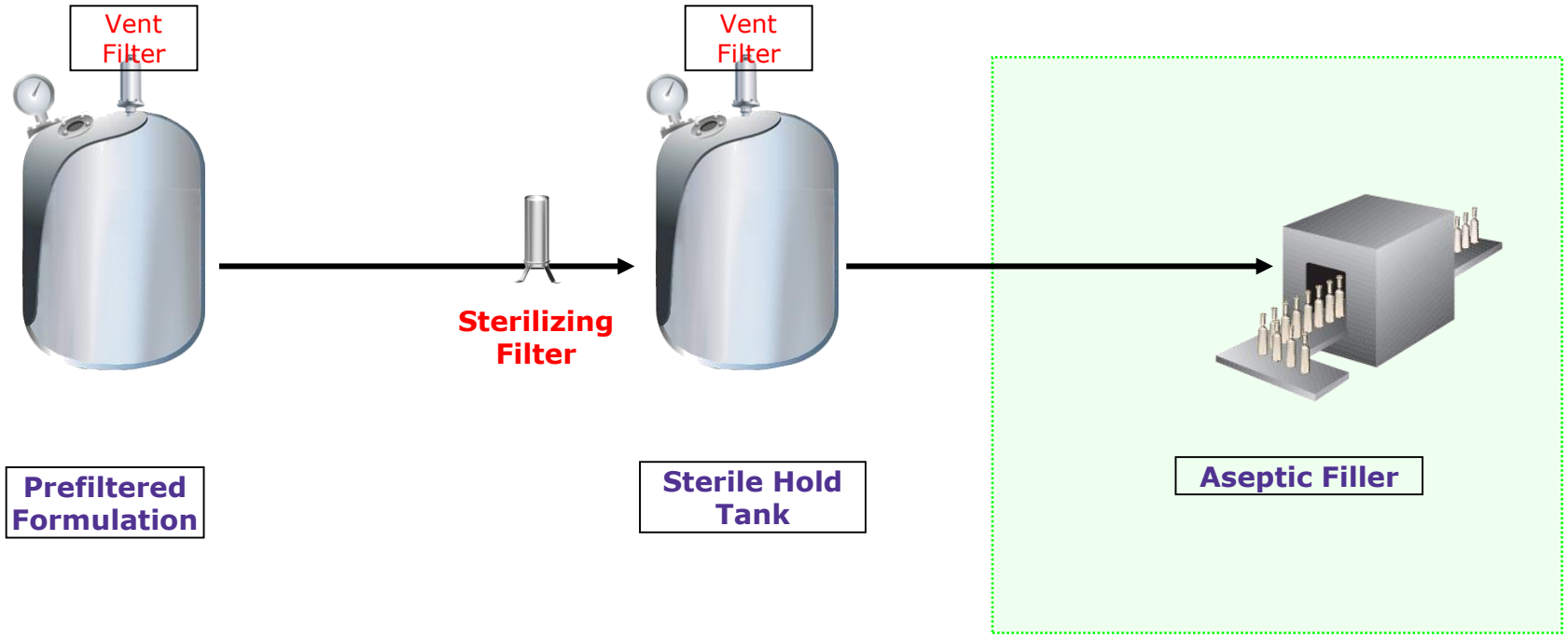
Sterilising Filter - **"a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties"** (PICS PE-009 GMP Guide)
"A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent" (FDA)
"A filter that reproducibly removes all test microorganisms from the process
stream, producing a sterile effluent." (PDA TR26)

Serial Filtration - **Filtration through two or more filters of the same or decreasing pore size one after the other** (PDA TR26)

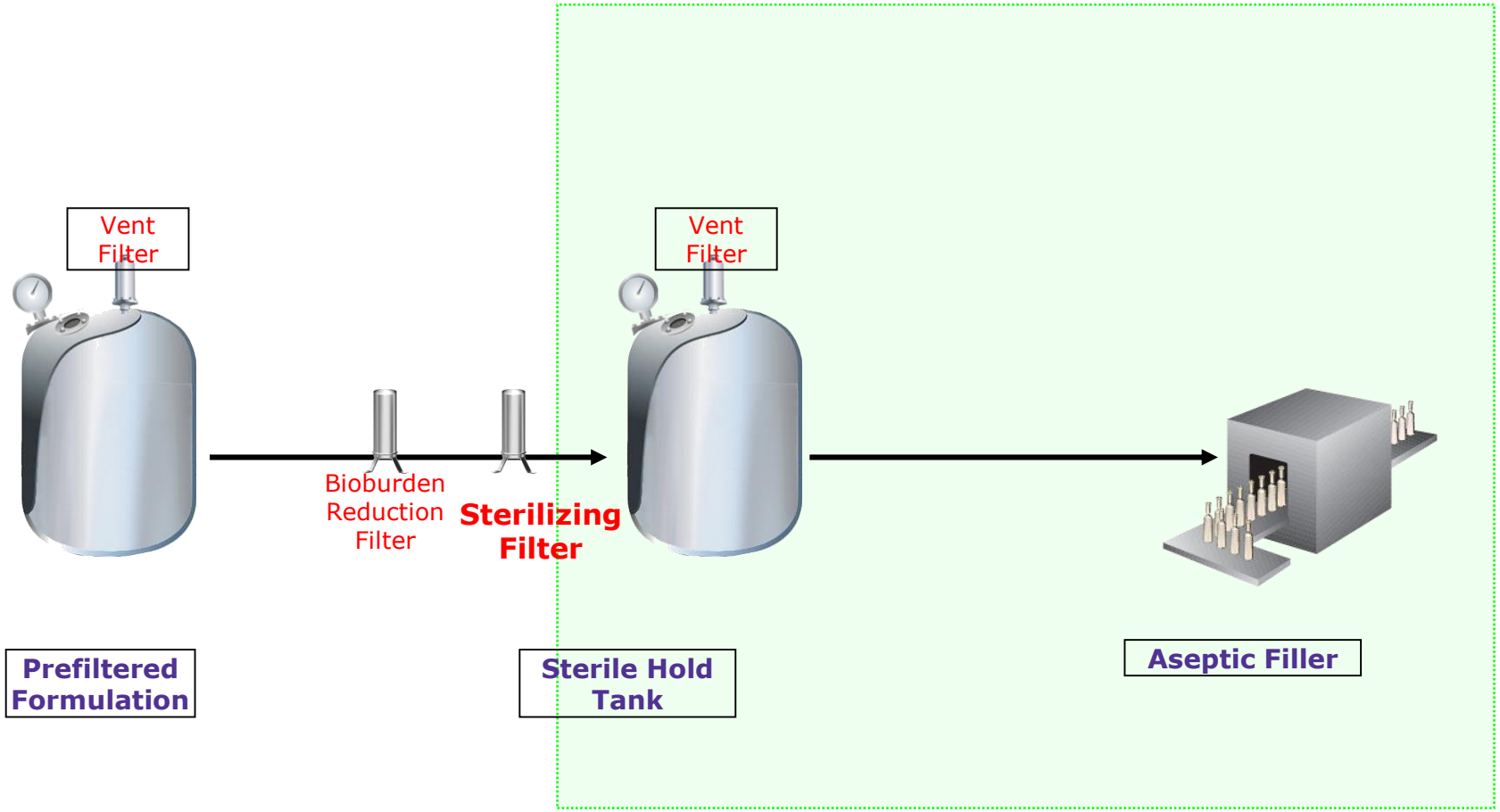
Redundant filtration - **A type of serial filtration where a second sterilizing filter is used as a backup in the event of an integrity failure of the primary sterilizing filter.** (PDA TR26)

cGMP Sterilizing Filtration Systems over the past 20 years

Generic Sterile Formulation / Filling Suite - Traditional style sterile filtration system

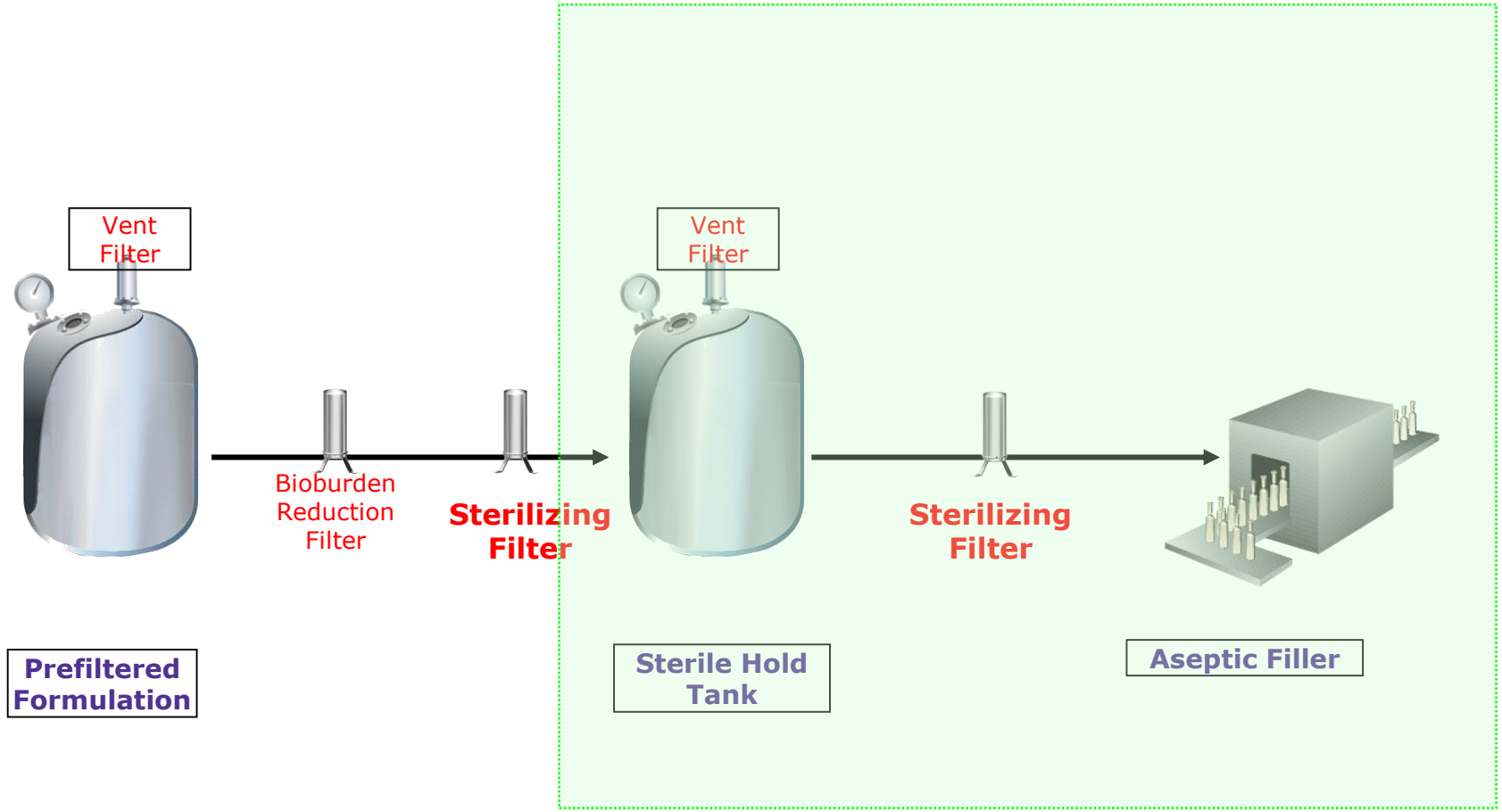


Traditional style sterile filtration system *with bioburden reduction filter*



Monitor bioburden for each batch, state maximum value or if value is >10 CFU/100ml, use a bioburden reduction filter

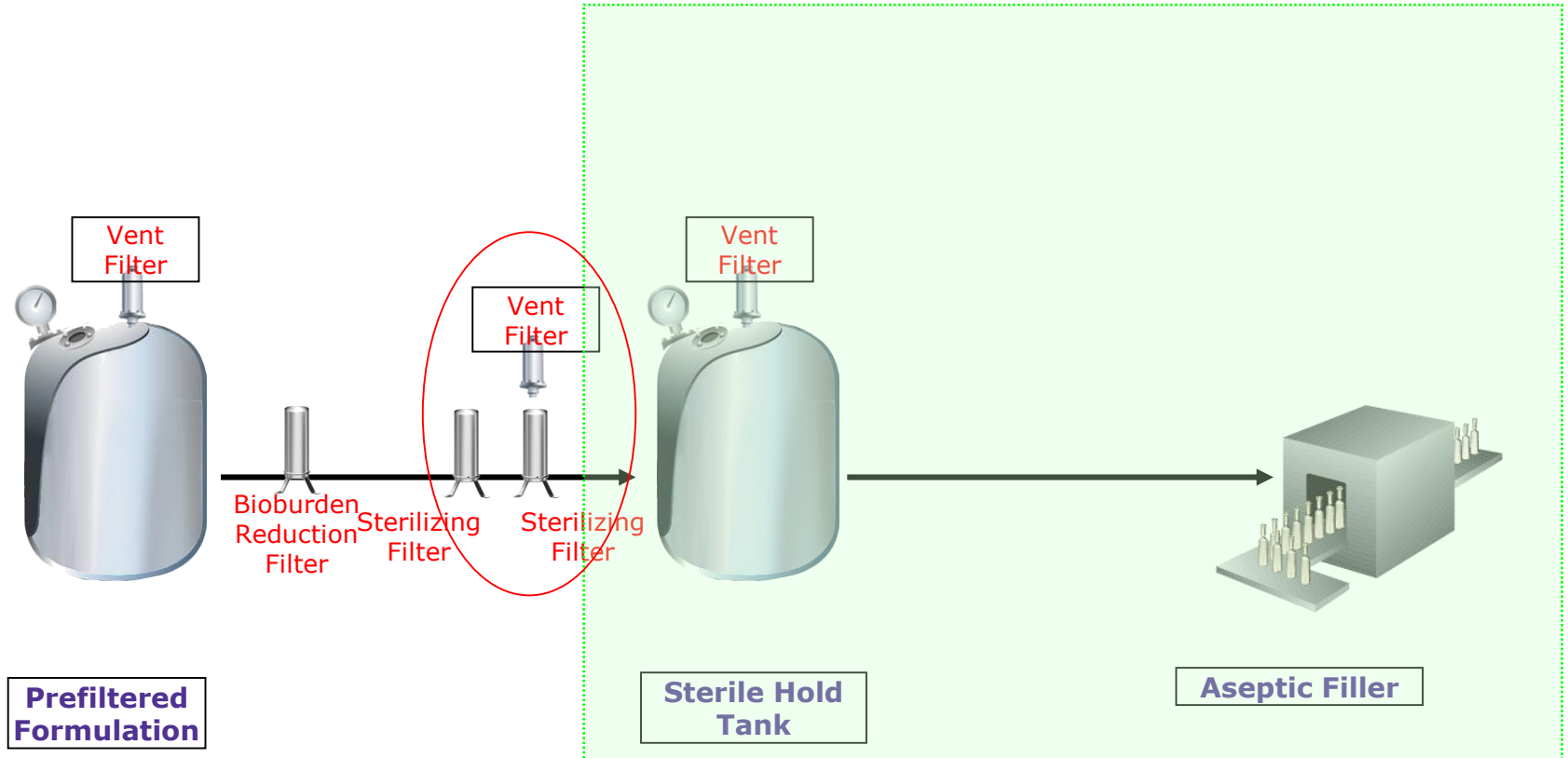
Traditional style sterile filtration system with bioburden reduction filter and EMA compliant



NOT Redundant Filtration

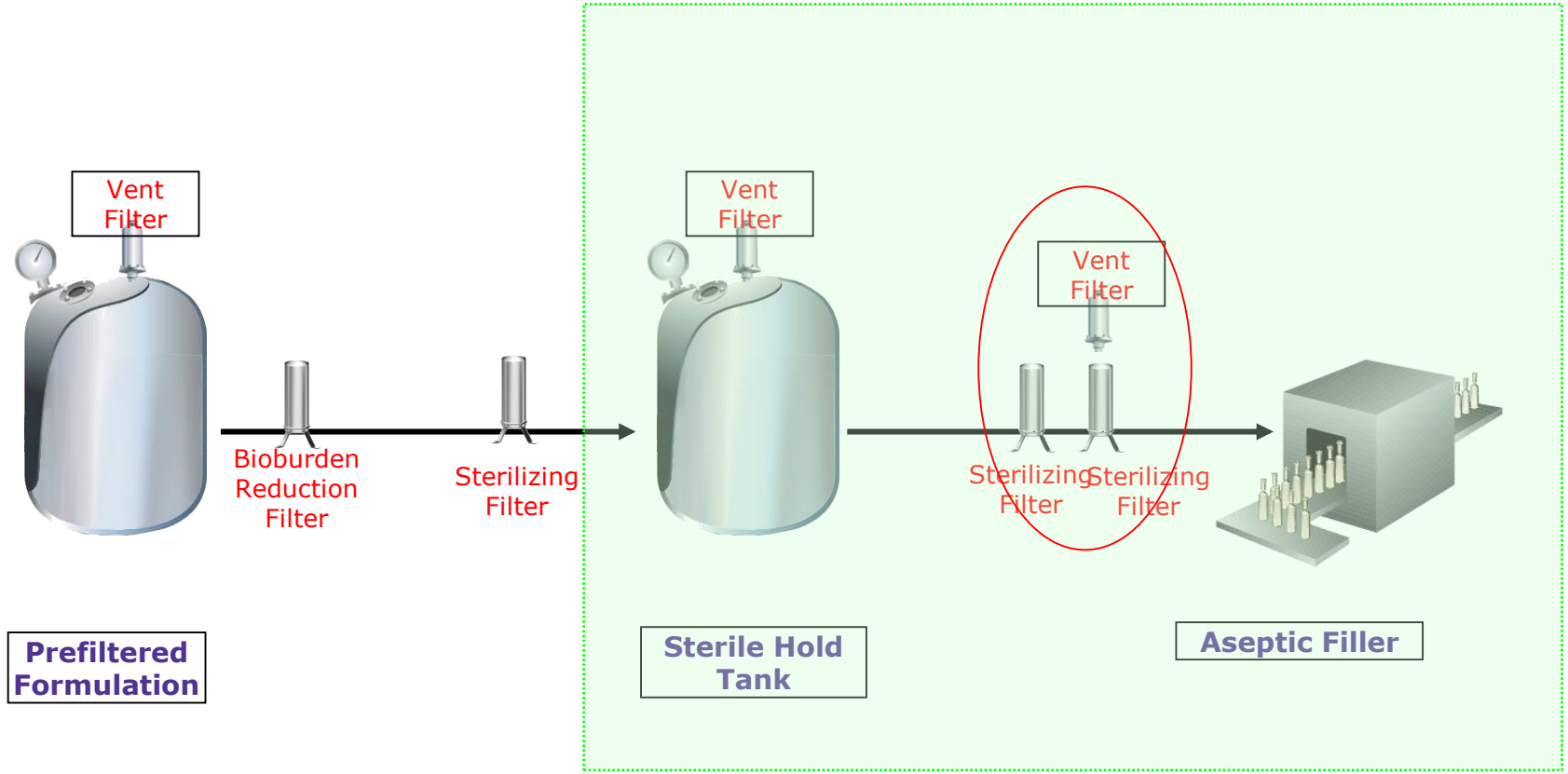
Use a second microorganism retentive filter as close as possible to the final use

Traditional style sterile filtration system with bioburden reduction filter and FDA compliant for "at risk" product (redundant final filtration system)



HOWEVER - justify use of a sterilizing filter and a second sterilizing filter not being as close as possible to the final use and operation of sterilizing filter in Grade C

Traditional style sterile filtration system with bioburden reduction filter
and EMA compliant, and FDA compliant for “at risk” product (redundant final filtration system) at POU



Use a sterilizing filter and a second sterilizing filter as close as possible to the final use

Redundant Filtration

The ONLY Redundant Filtration Regulatory Reference

Guidance for Industry

Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

Filtration is a common method of sterilizing drug product solutions. A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent. Currently, such filters usually have a rated pore size of 0.2 µm or smaller. Use of redundant sterilizing filters should be considered in many cases.

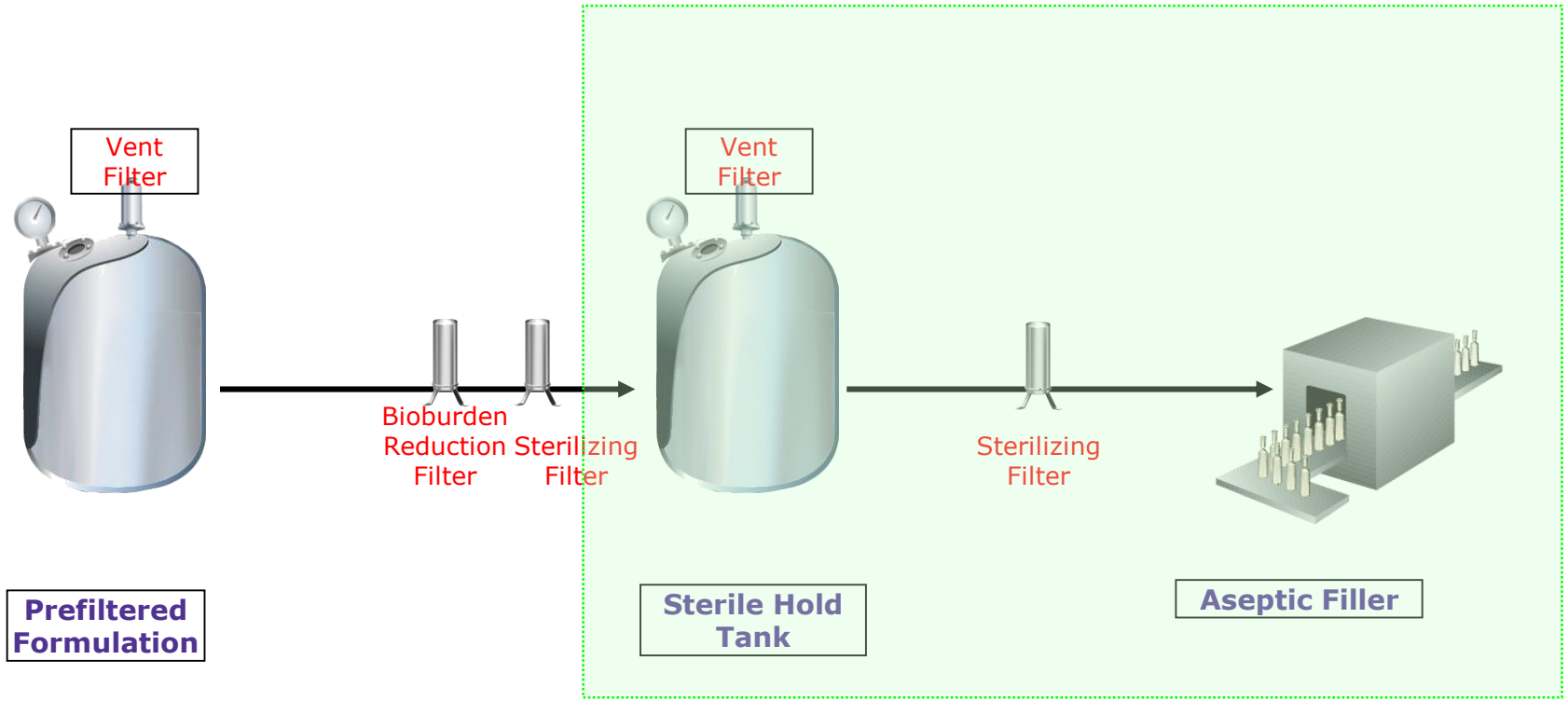
Use of Redundant sterilizing filters should be considered in many cases (No indication from FDA on specific cases – should be chosen based on risk

The manufacturing process controls should be designed to minimize the bioburden of the unfiltered product.

Bioburden of unsterilized bulk solutions should be determined to trend the characteristics of potentially contaminating organisms.

EMA / PICS / WHO Does *not mention* Redundant Filtration

111. Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point."



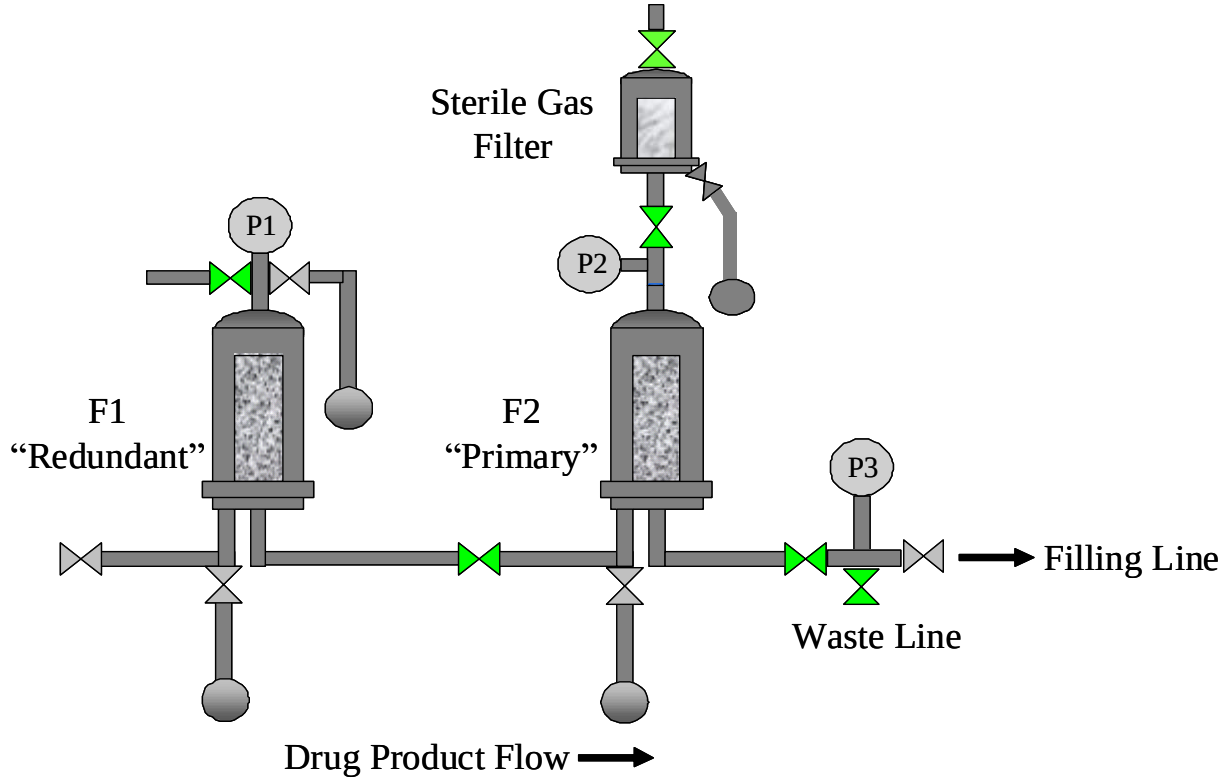
What is Redundant Filtration?
Key Industry Advice - PDA Technical Report 26 rev 2008

Serial Filtration

Filtration through two or more filters of the same or decreasing pore size, one after the other.

Redundant Filtration

A type of serial filtration in which a second sterilizing-grade filter is used as a backup in the event of an integrity failure of the primary sterilizing filter.



Key point for a redundant filtration is that each filter alone is capable of delivering a sterile filtrate and that at least one of them is integral at the end of the process

Key Technical Support Industry Reference - PDA TR 26, Sec. 7.6.3

In the event an additional sterilizing-grade filter is placed in the filter train to ensure against the loss of product due to potential failure of the primary sterilizing filter, the additional filter does not require post-use integrity testing unless the primary sterilizing filter fails.

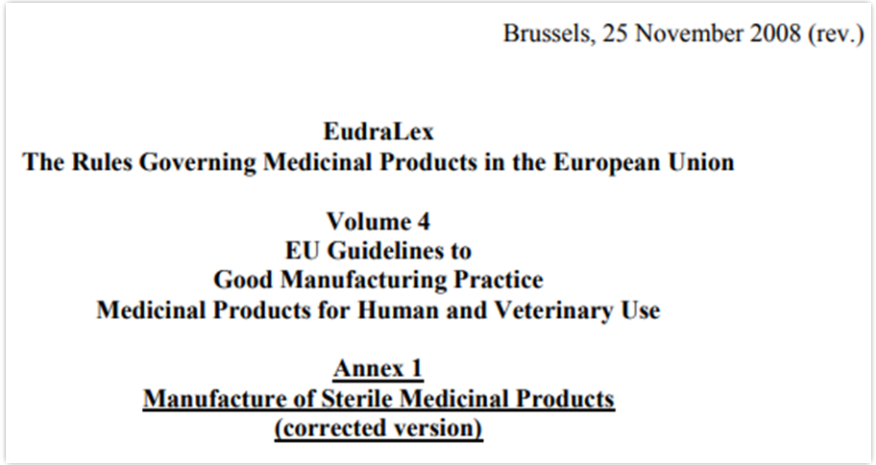
In that case, the second, or redundant filter, must satisfactorily pass post-use integrity testing. (Note: The primary sterilizing filter in the filter train should be the last filter in the series).

For processes requiring in-series integrity testing (e.g., where both filters are sterilized in series), each filter must be tested individually. Precautions should be taken to maintain the sterility of the fluid pathway between the two filters.

Pupsit

Pre-use
Post-sterilization Integrity Testing

Regulatory PUPSIT References



Brussels, 25 November 2008 (rev.)

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products
(corrected version)

Annex 1 to Volume 4 of EU GMP
(only for countries in Europe)

"113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold" test.

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

2017 PICS guidelines
(for PICS member countries OR countries who export to PICS members)

"113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test."

Some Reasons for PUPSIT

Comments from EMA in 2011 - Q&A on GMP

"The filter sterilisation process, may be physically stressful for the filter. For example high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2µm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons filters should be tested both before use but after sterilisation, and again after use."

Economic batch disposition

If the filter fails post-use FIT then the batch is discarded or reprocessed (if practicable)

Other considerations that can affect pre-use filter integrity

Mechanical damage to filter (shipping / handling etc.), recognition of probability of filter failure from manufacturer (zero defect is impossible – note that "out of the box failure" is < ~1:25,000), filter housing maintenance (issues with damage to surface or code 7 base in housing), etc.

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Three Major PUPSIT Misconceptions on the Internet in mid 2017

PUPSIT has not been required until now

Response: PUPSIT has been in the EMA regulations and PICS guidelines since 1997 (or 2007 according to one EMA inspector)

PUPSIT was going to be removed from the regulations

Response: Guidelines are regularly revised. PUPSIT was not one of the items that EMA was going to change

Customers have no choice and MUST do PUPSIT

Response: Customers can either perform PUPSIT or provide a written risk assessment document to show that the risk of doing PUPSIT is greater than the current risk of not doing PUPSIT

Current Inspectional Trends

Analysis of 483s issued 2013 - 2017

		2013	2014	2015	2016	2017
Total 483s for 'Drugs'		690	645	678	691	694
211.192	Production record review, investigations of discrepancies	239	209	250	227	203
211.42(c)	Requirement for adequate facilities to prevent contamination..	94	125	235	227	115
211.22(d)	Quality unit responsibilities should be in writing and followed	168	148	165	153	189
211.160(b)	Development of scientifically sound specifications	199	165	246	133	198
211.166(a)	Expiration dating should be supported by appropriate studies	104	82	126	124	109
211.113(b)	Validation of aseptic processes including sterilization	119	109	157	118	92
211.100(a)	Written procedures describe production & controls	135	107	123	110	116
211.67(b)	Cleaning and maintenance of equipment	83	80	91	102	91
211.188	Batch production records	114	74	110	100	120
211.25(a)	Staff shall have training, education & experience	132	115	119	99	113

None of these should be strange or uncommon or unusual in GMP manufacturers

Data Integrity – US FDA Comments

Douglas Stearn, Director of Office of Enforcement and Import Operations in the Office of Regulatory Affairs

Data integrity is considered good manufacturing practice

If evidence of falsification, manipulation or concealment of test result, batch processing or operational data found, the agency can determine that products are adulterated

Two reference sources highlighted:

21 CFR Part 11 requirements such as;

- "backup data are exact and complete,"
- data is "secure from alteration, inadvertent erasures, or loss"
- activities are "documented at the time of performance"
- company maintain "complete records of all tests".

FDA's 2016 draft guidance, "Data Integrity and Compliance With CGMP".

"Everything else that we do is based on the integrity of the data. When you've got this problem, you've got a very big problem."

Notable Recent Example of 483 for India - February 2018

Failure to close ten CAPAs within the allowable timeframe and did not request an extension of the deadlines.

Did not establish quality agreements with some of its starting materials suppliers, including a supplier that provided ingredients used to manufacture product for the U.S. market.

Failed to follow complaint handling procedures related to API materials.

Did not maintain buildings used in manufacturing, processing and packing of API finished materials

Deficiencies in having separate or defined areas to prevent contamination for quarantine storage of finished materials.

Failure to properly maintain equipment used for manufacturing

Common regulatory Threads and Direction in 2017

Quality Risk Management
QbD principles & Global compliance

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Example of Revised EMA / PICS Documentation

Guideline on process validation for finished products – Nov 2016 - information and data to be provided in regulatory submissions

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Example of Revised EMA / PICS Documentation

Guideline on manufacture of the finished dosage form – Jan 2018

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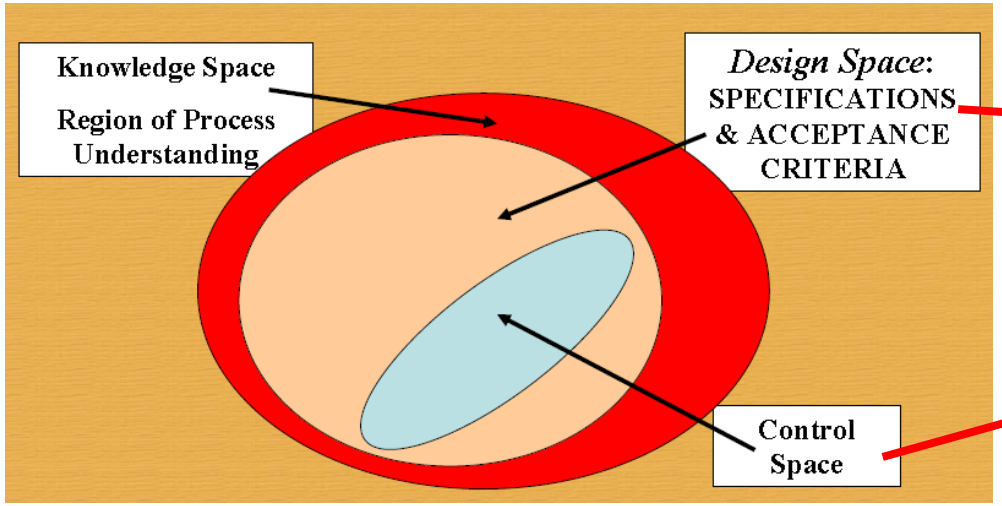
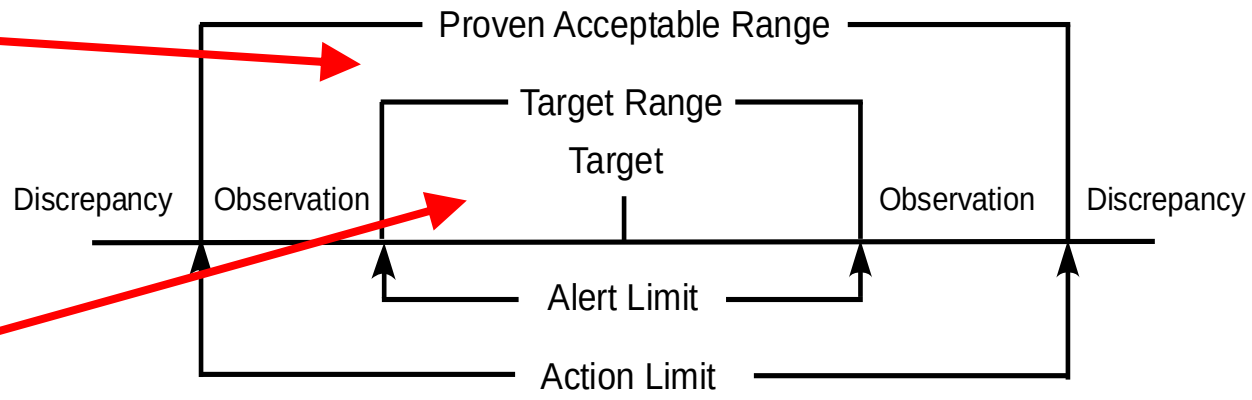
QbD Concept - Design Space (ICH Q8)

- knowledge space (information of the process / activity outside our company)
- design space (information on the product, process, activity inside our company)
- control space (how we control the product, process, activity inside our company)

Design space

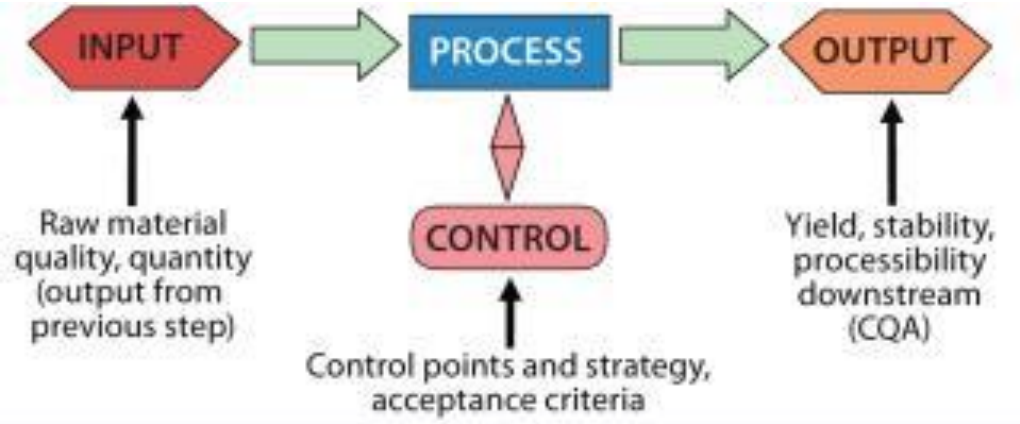
– Demonstrated range of all process parameters where process meets the product's Critical Quality Attributes CQAs





Product Safety, Quality by Design & State of Control

	Systematic Approach
Predefined objectives	▪ Define Quality Target Product Profile (QTPP) ▪ Identify Critical Quality Attributes (CQA)
Product and process understanding	▪ Identify critical material attributes (CMA*) and critical process parameters (CPP) ▪ Establish the functional relationships that link CMA/CPP to CQA
Process control	▪ Develop appropriate Control Strategy, including justifications
Sound science	▪ Science-driven development (scientific literature, prior knowledge, DOEs etc.)
Quality risk management	▪ Risk-based development (ICH Q9)



Peter H. Calcott , Bioprocess International, November, 2011

Link material attributes & process parameters to product's Critical Quality Attributes (CQA)

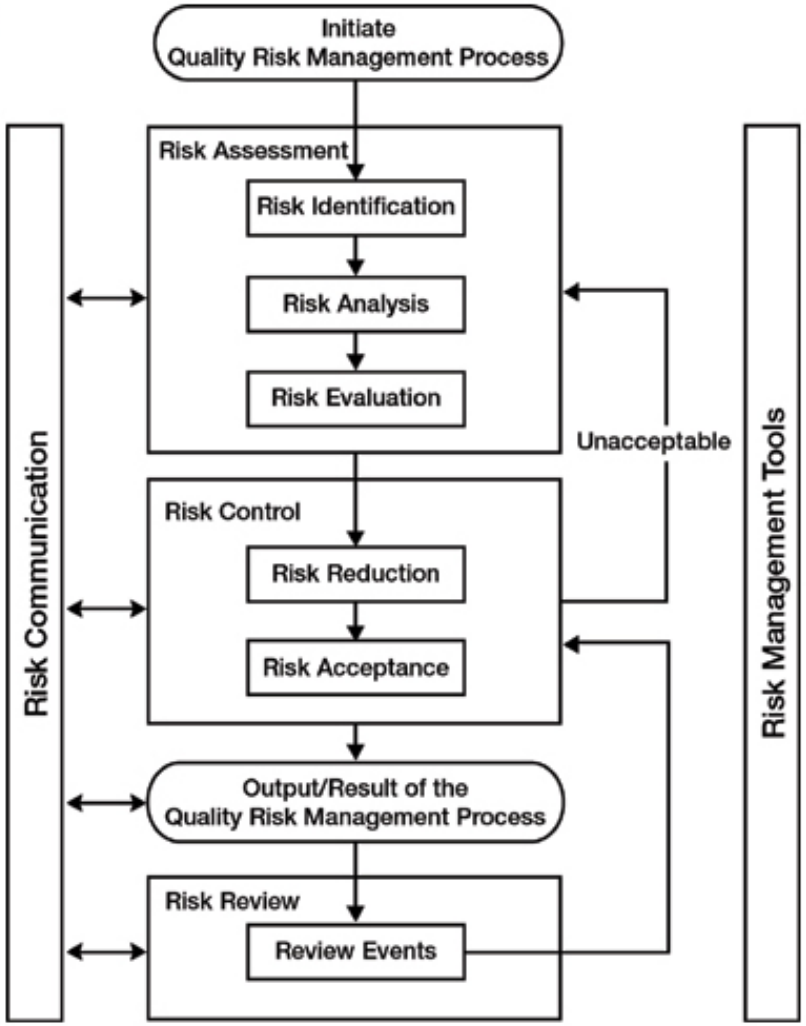
CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

Quality Target Product Profile (QTPP)

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy.

Provides an understanding of what will ensure the quality, safety, and efficacy of a specific product for the patient

Quality Risk Management – ICH Q9



Step 1 - Risk Assessment

What can go wrong?
How likely is it to go wrong
What are the consequences if it does go wrong?

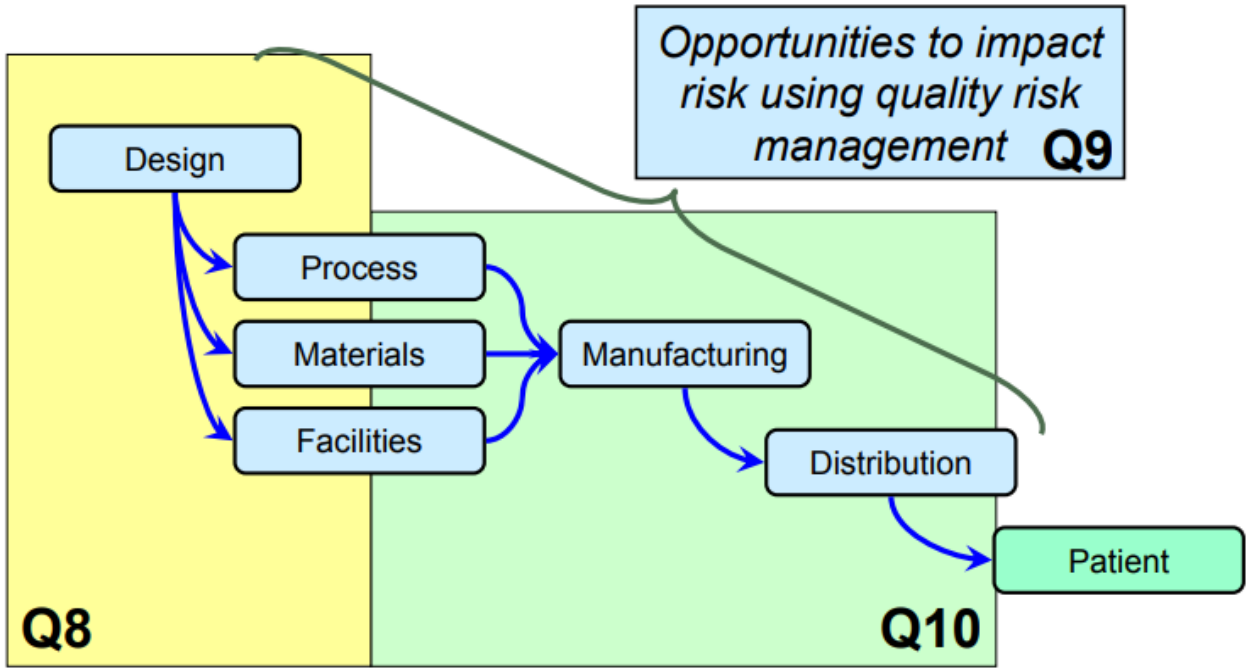
Step 2 – Risk Control

Is the risk level acceptable?
What can we do to reduce or eliminate risks?
What is the right balance between risks, benefits, and resources?
Do the risk control efforts introduce new risks?

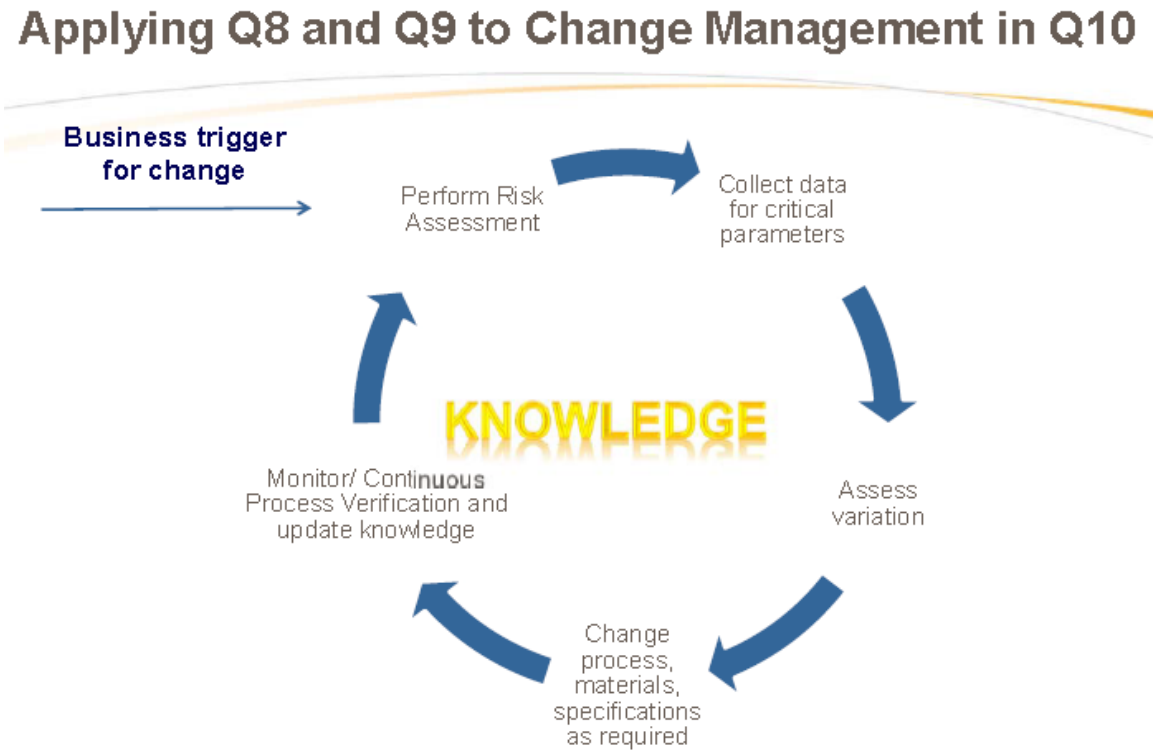
Step 3 – Risk Review

Integrated in quality management system
Can use product review, process review or change control review as inputs / triggers

Linking Pharmaceutical Development (ICH Q8), Risk Management (ICH Q9) and Quality Systems (ICH Q10)

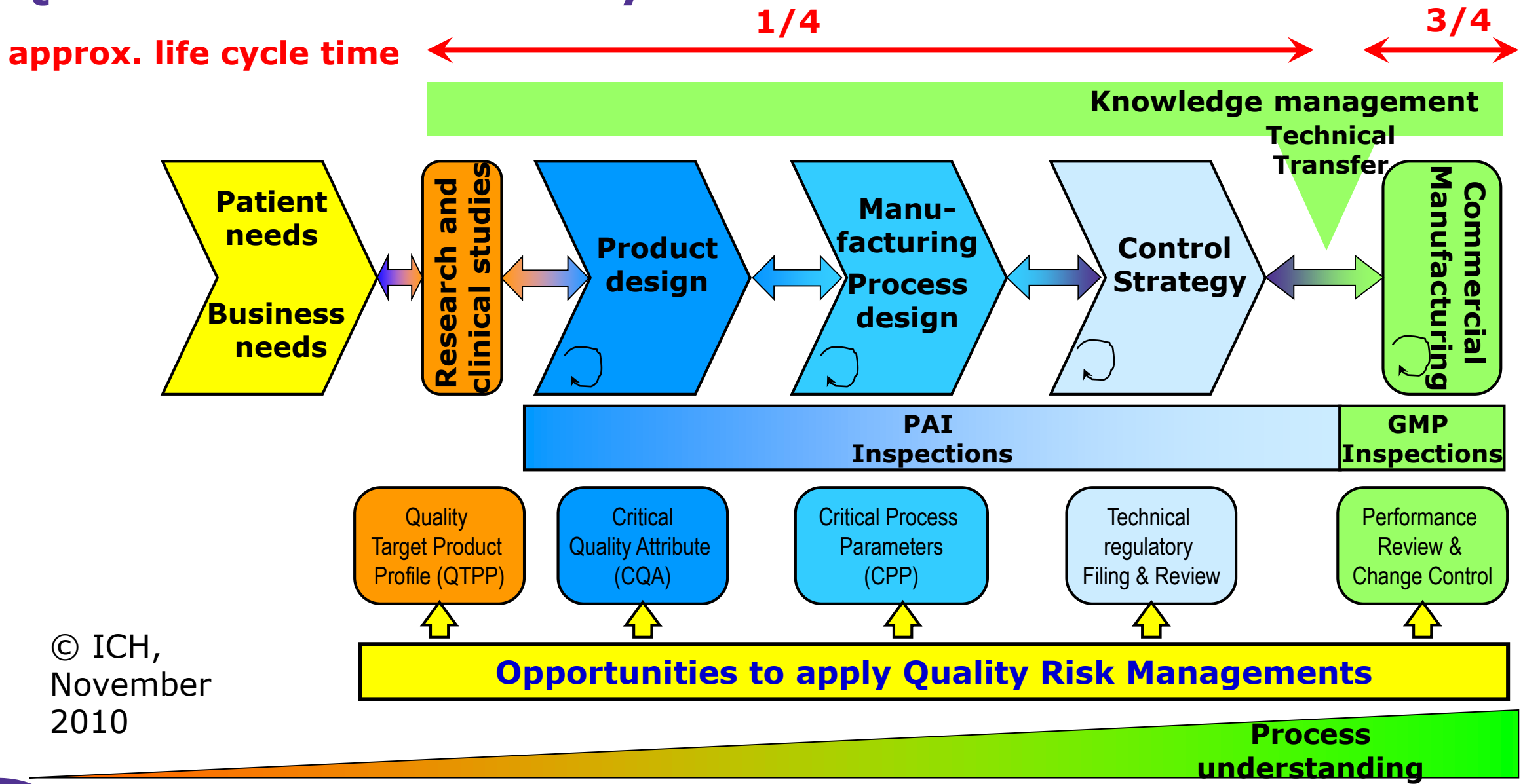


Joseph C. Famulare, "Workshop on Implementation of ICH Q8/Q9/Q10 and Other Quality Guidelines" Beijing, China, 3-5 December 2008



ICH Q10 and Change Management: Enabling Quality Improvement Dr. Bernadette Doyle, GlaxoSmithKline

QRM in the Product Life Cycle



Regulations, Guidances - Current & Future

Some Current Key Guidances & Regulations

FDA guidance for industry sterile drug products produced by aseptic processing - current good manufacturing practice
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

WHO annex 6 good manufacturing practices for sterile pharmaceutical products
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex6.pdf

EU GMP guide to good manufacturing practice for medicinal products annex 1
http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf

PICS Validation of Aseptic Processes

http://picscheme.org/layout/document.php?id=153

PICS Technical Interpretation to Revised Annex 1 of PICS GMP Guide

http://picscheme.org/layout/document.php?id=159

ICH Q9 Quality Risk Management
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50000287 3.pdf

ICH Q10 Pharmaceutical Quality System
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50000287 1.pdf

NB FDA, EMA / PICS, WHO regulations are supported and supplemented with guidance documents

Draft Regulations – Revision of Annex 1 of EU GMP Guide Guidelines to Good Manufacturing Practice for Medicinal Products – manufacture of sterile medicinal products

"The revised Annex 1 has been prepared in co-operation with the EMA, World Health Organization (WHO), and PIC/S in order to maintain global alignment of standards, and provide assurance of product quality.

Key changes from the earlier PIC/S Annex are:

introduction of new sections: scope, utilities, environmental and process monitoring sections and glossary

introduction of the principles of Quality Risk Management (QRM) to allow for the inclusion of new technologies and innovative processes

restructuring to give more logical flow

addition of detail to provide further clarity."

First major revision of Annex 1 in 10 years

Current Annex 1 is 16 pages long. Draft Annex 1 revision is 50 pages long

Overview of Draft Annex 1 Revision

Scope Additional areas (other than sterile medicinal products) where the general principles of the annex can be applied.

Principle General principles as applied to the manufacture of medicinal products.

Pharmaceutical Quality System (PQS) Highlights the specific requirements of the PQS when applied to sterile medicinal products.

Personnel Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.

Premises General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of barrier technology.

Equipment General guidance on the design and operation of equipment.

Utilities Guidance with regards to the special requirements of utilities such as water, air and vacuum.

Overview of Draft Annex 1 Revision

Production and specific technologies Discusses the approaches to be taken with regards to aseptic and terminal sterilisation processes. Also discusses different technologies such as lyophilization and Blow Fill Seal (BFS) where specific requirements may be required. Discusses approaches to sterilization of products, equipment and packaging components.

Viable and non-viable environmental and process monitoring This section differs from guidance given in section 5 in that the guidance here applies to ongoing routine monitoring with regards to the setting of alert limits and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulation.

Quality control (QC) Gives guidance on some of the specific Quality Control requirements relating to sterile medicinal products.

Glossary Explanation of specific terminology.

Example of Additional Recommendations in Draft Annex 1 Revision

8.15 Aseptic manipulations (including non-intrinsic aseptic connections) should be minimized using engineering solutions such as the use of preassembled and sterilized equipment.
Whenever feasible, product contact piping and equipment should be pre-assembled, then cleaned and sterilized in place.
The final sterile filtration should be carried out as close as possible to the filling point and downstream of aseptic connections wherever possible

Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1

8.16 The duration for each aspect of the aseptic manufacturing process should be limited to a defined and validated maximum, including:

Time between equipment, component, and container cleaning, drying and sterilization.

Holding time for sterilized equipment, components, and containers prior to and during filling/assembly.

The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

Aseptic assembly.

Holding sterile product prior to filling.

Filling.

Maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.

Examples of Key Differences in Draft Annex 1 Revision - Filter Integrity Testing

8.84 The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test.

It is recognised that for small batch sizes, this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved.

There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated.

Examples of Key Differences in Draft Annex 1 Revision - Serial and Redundant Filtration

8.87 Where serial filtration (one filtration is followed by a subsequent filtration) is a process requirement the filter train is considered to be a sterilizing unit and all sterilizing-grade filters within it should satisfactorily pass integrity testing both before use, in case of damage during processing, and after use

8.88 Where a redundant sterilizing filter is used, the additional filter does not require post-integrity testing unless the primary sterilizing filter fails, in which case the redundant filter must then satisfactorily pass post-use integrity testing.
Bioburden samples should be taken prior to the first filter and the sterilizing filter, systems for taking samples should be designed so as not to introduce contamination.

8.89 Liquid sterilizing filters should be discarded after the processing of a single lot. The same filter should not be used for more than one working day unless such use has been validated

Key References to Single-use Systems in Draft Annex 1 Revision

8.119 The compatibility of materials used for product contact surfaces with the products should be ensured under the process conditions by evaluating e.g. adsorption and reactivity to the product.

8.120 Extractable profile data obtained from the supplier of the components of SUS may be useful to ensure that extractables and leachables from the SUS do not alter the quality of the product.

A risk assessment should be conducted for each component to evaluate the applicability of the extractable profile data.
For components considered to be at high risk to leachables, including those taking up leachables extensively or those stored for longer periods, an assessment of leachable profile studies, including safety concerns, and should be taken into consideration, as necessary.

If applying simulated processing conditions these should accurately reflect the actual processing conditions and be based on a scientific rationale.

Summary & Conclusion

- ✓ Quality risk management approach is recommended in regulations
- ✓ Quality by design principles are referenced in new guidances
- ✓ Global regulatory harmonisation has taken more steps to realisation
- ✓ New documentation will be more specific and wider ranging
- ✓ Inspection approaches continues to focus on typical issues HOWEVER inow includes more citations aimed at drug lifecycle management
- ✓ Knowledge and awareness of global trends is critical to achieving and maintaining regulatory and inspectional compliance
- ✓ The use of external consultants has become a common part of 483s
- ✓ Good Manufacturing Practice approach should be replaced by Current GMP

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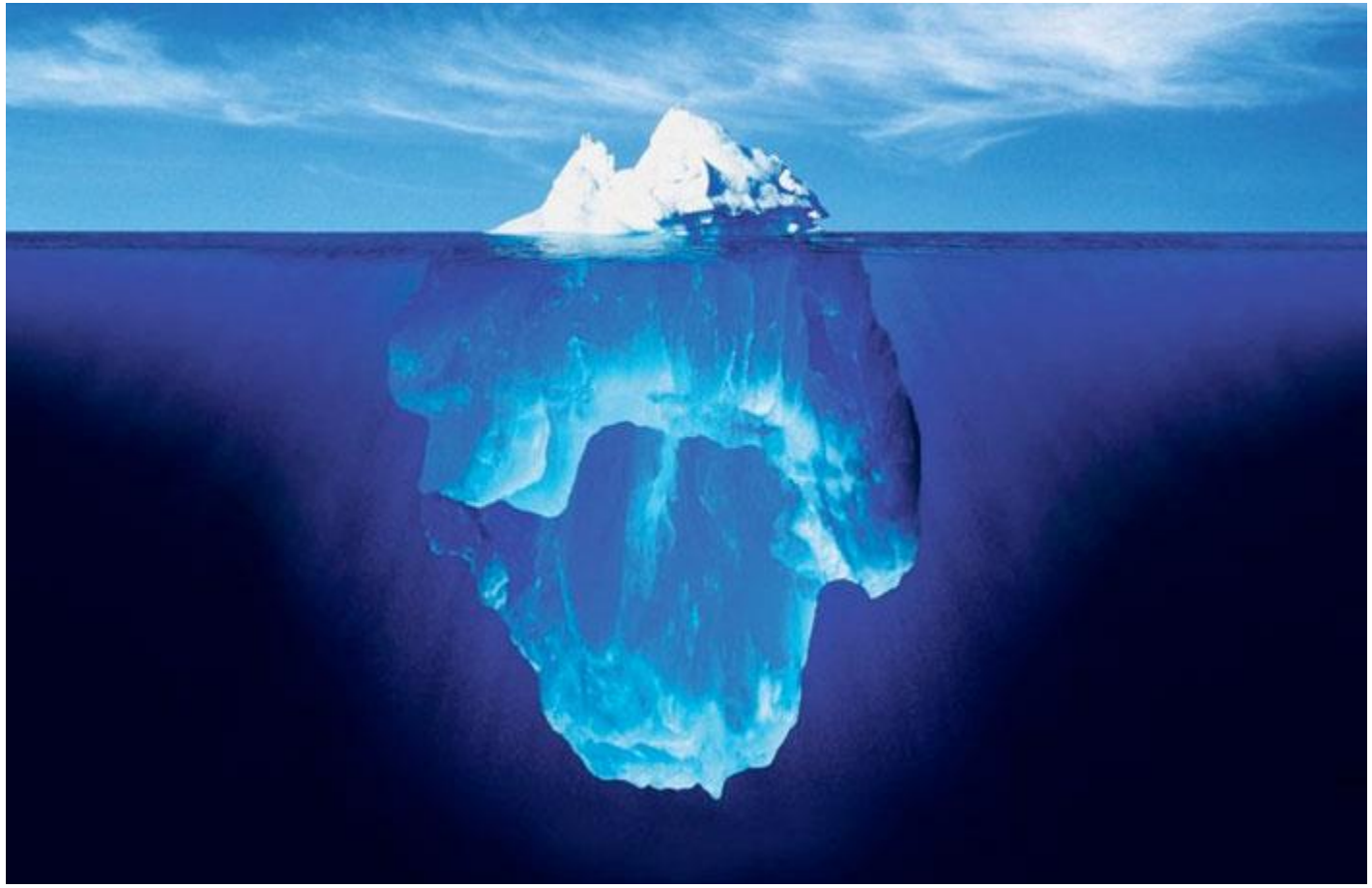
Thank You for your Attention!

May we be of Further Assistance?



michael.payne@merckgroup.com