# An Aseptic Processing Update: Industry and Regulatory Trends The Path Forward

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Aseptic Processing and Sterilization
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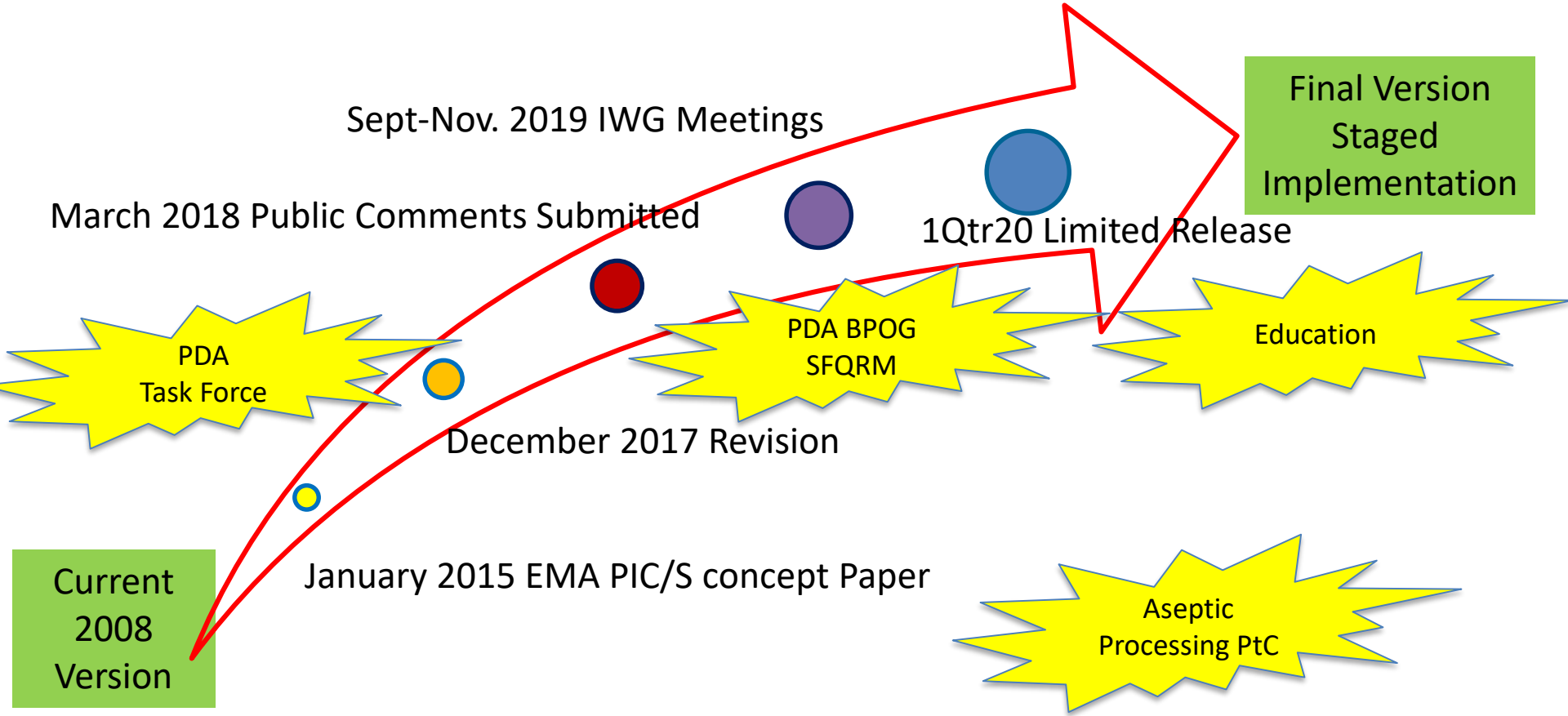
# A Call to Action

There is a need and opportunity for **improvement** in the manufacture of sterile biopharmaceutical products.

1. **Aseptic processing is here to stay**
2. **Traditional process control methods may not be sufficient**
3. **We are not changing fast enough**

# Part 1: Updates

# Update: Annex 1 Manufacture of Sterile Medicinal Products



# Update: Annex 1 revision general highlights

- Improved document, but retains lower value control expectations
- Sets expectation for use of quality risk management principles, but needs to do more for alternative approaches
- Misses opportunity to modernize and harmonize terms

# Update: Annex 1 revision specific highlights

- Sterile filtration: positioning and PUPSIT
- APS acceptance criteria, operator qualification, duration
- Isolator barriers: unidirectional airflow, settling plates, glove IT, sterilization of indirect contact surfaces
- 5 $\mu$ classification and monitoring
- Disinfectant rotation
- Container closure integrity testing
- WFI distribution temperature, steam generation, moist heat sterilization

# Why is the Annex  1 Revision Important?

First new discussion on aseptic processing in a while

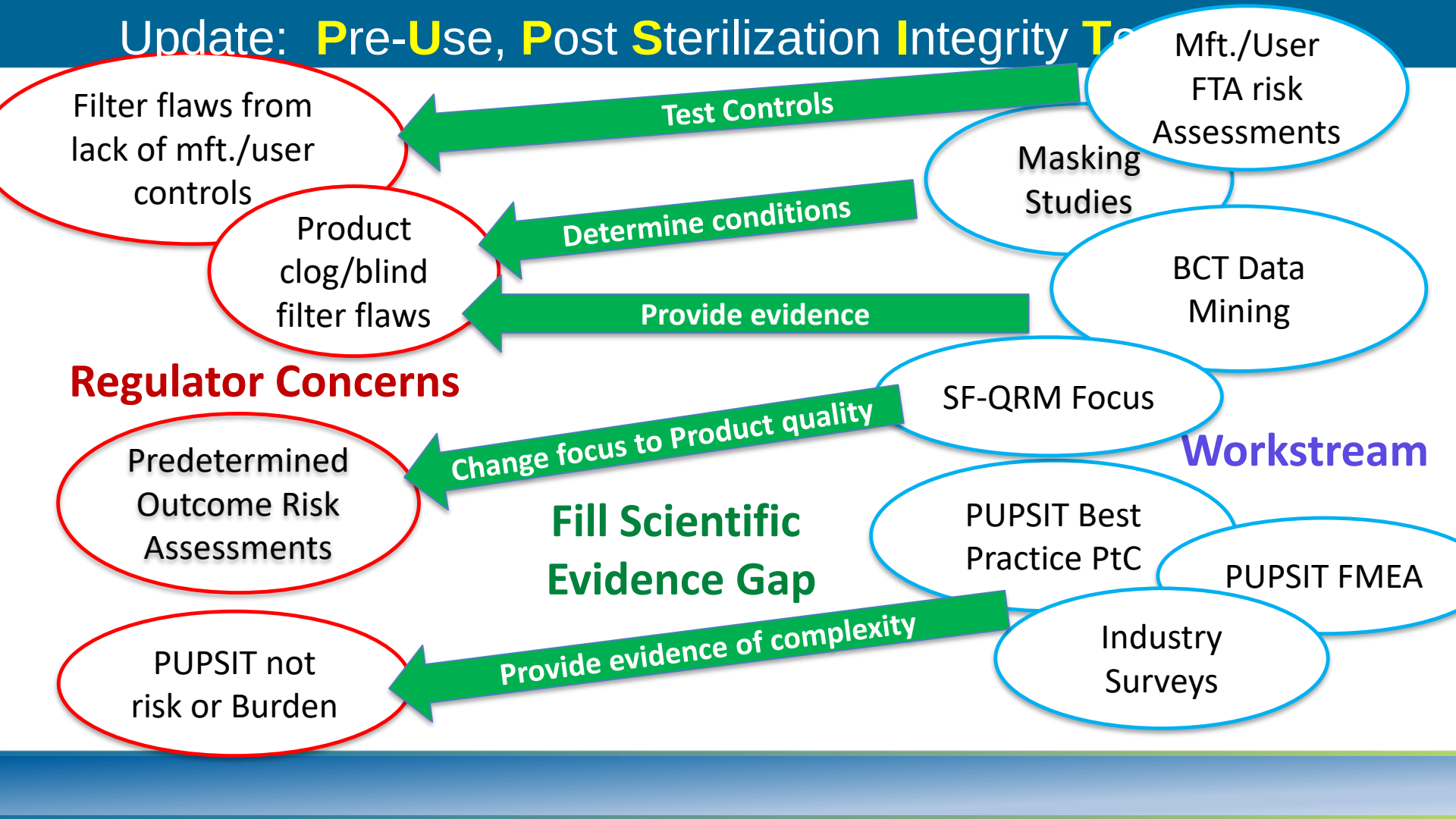
*Proposed revision to EMA Annex 1 contained 43 recommendations for risk-based approaches to sterile product manufacturing and control.*

K. Waldron, 2017

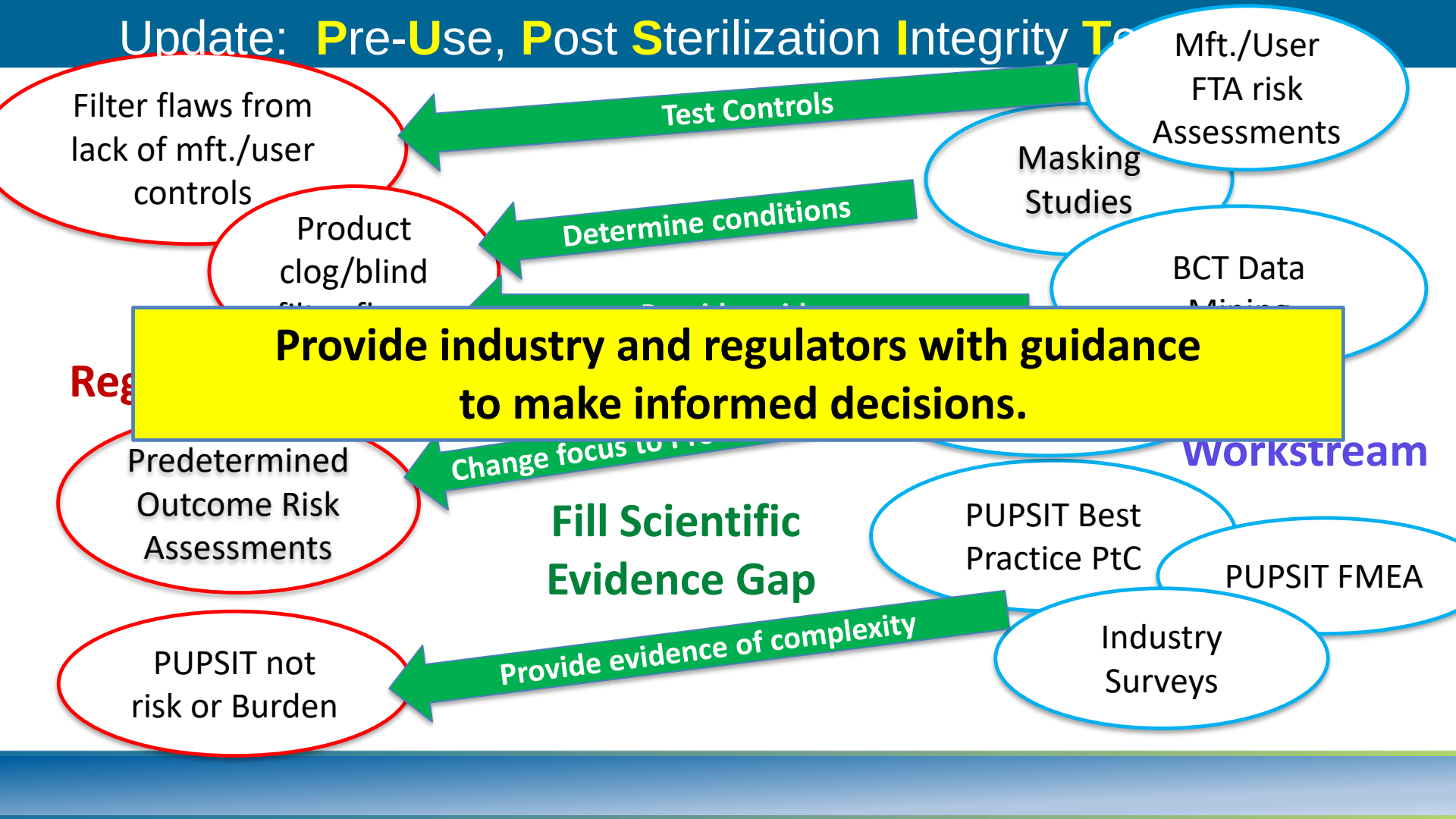
# Why is Annex 1 and QRM important?

*If regulators expect industry to use QRM to justify current approaches … then QRM can be used to justify new approaches.*

# Update: Pre-Use, Post Sterilization Integrity Te



# Update: Pre-Use, Post Sterilization Integrity Te



# Part 2: Moving Forward

# Changing business …

1. New therapies
2. Drug supply and public health
3. Business aspects of quality and manufacturing reliability
4. New technology
5. **Competition for technical talent**

# Attracting new talent

| | % | % | % | |
|---|---|---|---|---|
| Restaurant industry | 66 | 25 | 8 | +58 |
| Computer industry | 61 | 28 | 11 | +50 |
| Grocery industry | 58 | 27 | 15 | +43 |
| Farming and agriculture | 58 | 24 | 17 | +41 |
| Travel industry | 52 | 35 | 13 | +39 |
| Accounting | 45 | 45 | 9 | +36 |
| Automobile industry | 53 | 29 | 18 | +35 |
| Retail industry | 50 | 28 | 19 | +31 |
| Real estate industry | 49 | 31 | 19 | +30 |
| Banking | 50 | 25 | 25 | +25 |
| Electric and gas utilities | 47 | 28 | 24 | +23 |
| Sports industry | 45 | 29 | 25 | +20 |
| Airline industry | 42 | 32 | 23 | +19 |
| Telephone industry | 42 | 32 | 26 | +16 |
| Publishing industry | 39 | 36 | 24 | +15 |
| Internet industry | 43 | 26 | 30 | +13 |
| Movie industry | 41 | 31 | 28 | +13 |
| Education | 45 | 18 | 35 | +10 |
| Television and radio industry | 40 | 27 | 32 | +8 |
| The legal field | 35 | 34 | 30 | +5 |
| Oil and gas industry | 39 | 25 | 36 | +3 |
| Advertising and public relations industry | 33 | 32 | 34 | -1 |
| Healthcare industry | 38 | 14 | 48 | -10 |
| The federal government | 25 | 23 | 52 | -27 |
| **Pharmaceutical industry** | **27** | **15** | **58** | **-31** |

GALLUP, AUG. 1-14, 2019

# Desired state: What if we were able to …

**continuously manufacture aseptically processed sterile products,**

- without reliance on human intervention, unidirectional airflow, viable environmental monitoring,
- release those products parametrically, in real time, without sterility testing,
- based on …
  - ✓ well engineered process design,
  - ✓ fully automated equipment,
  - ✓ contamination-protected critical zones,
  - ✓ complete process understanding,
  - ✓ indisputable correlation of data and outcome

**Suppose we call it a 100 year project**

# Sterile Biopharmaceutical Manufacturing Today and Tomorrow

| KEY ELEMENTS | YESTERDAY & TODAY | TOMORROW |
|---|---|---|
| **Process** | Batch driven, single shift, intervention laden, personnel dependent, environment constrained | Continuous, small closed environment, automated, data driven and controlled, standardized |
| **Control** | Test, monitor, demonstrate, lagging, excursion and deviation investigation, reactive, corrective | Design driven, line of sight, risk-based, scientific, data, leading, predictive, preventive |
| **Sterility Assurance** | Parameter based, anecdotal, product and process testing, compliance risk, subjective | Quality attribute based, statistical evaluation, trend analysis, science/risk awareness, unbiased, objective |
| **Communication** | Lack of transparency, reluctance to share experience, failures, criteria for success | Exchange of ideas, information, results, failures, remedies, criteria for success |
| **Cooperation** | Conflict relationship between manufacturers, suppliers, and regulators, blurring roles and responsibilities, regulatory risk concern | Partnership of manufacturers, suppliers, and regulators with defined roles and responsibilities |

# Part 3:  Thoughts to consider …

# The manufacturing intelligence revolution is here …

1. Digital clone facilities and modeling
2. Predictive maintenance and machine learning
3. Data linked environmental and process trending
4. Data driven parametric release
5. Virtual reality training
6. Visual SOPs and instructions
7. Mission control centers

# … are we ready?

- Will the increase in data outpace process understanding?
- How will we react to increased data and process awareness?
- How will validation change?

# We need to …. reduce complexity

Smaller, scalable, standardized critical area are less complex, less variable, lower the cost, with less contamination risk

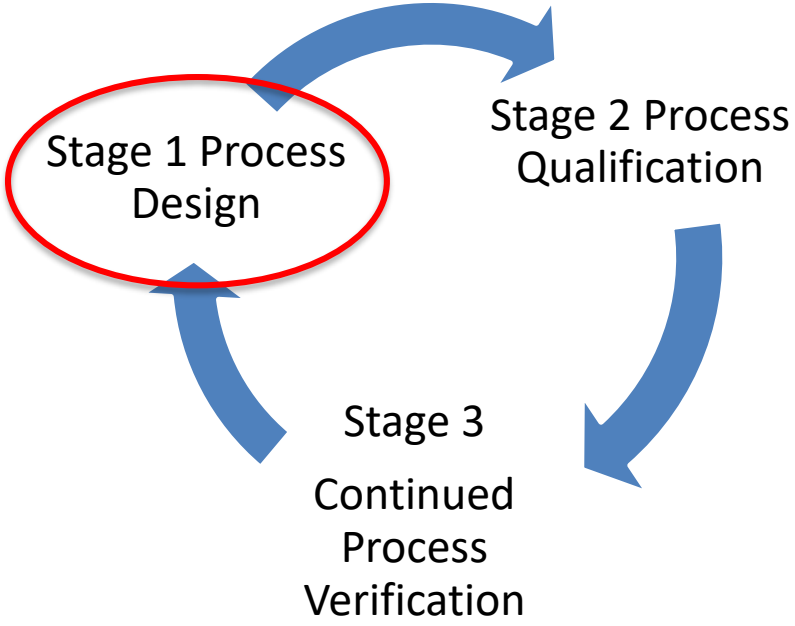
# … design better isolator processes

1. Aseptic technique and practice remain important

2. Re-define decontamination

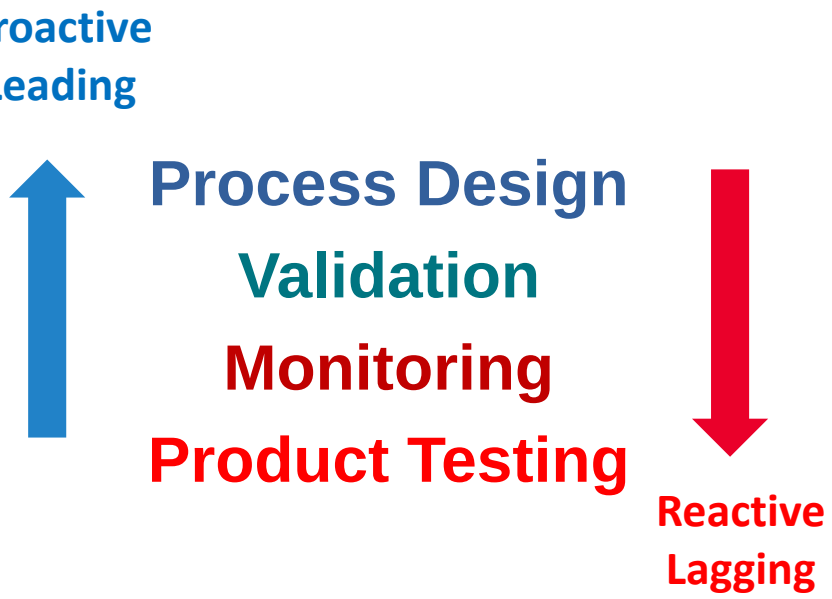
3. Establish operations based design and control criteria

# … change emphasis of validation



# … challenge testing as a contamination control strategy

- Excursions have different risks
- Evaluation of the trend more useful than detecting excursions
- Understand capability and limitations of control strategies
- Improper reaction can de-sensitize or distract



# … think critically about aseptic process validation

Does the aseptic process simulation _____ ?

- X Judge if process effective
- X Qualify personnel or demonstrate proficiency
- X Validate interventions
- X Establish holding times, filling durations or conditions
- X Simulate effect of fatigue on performance
- X Allow for disruptions
- X Verify decontamination process
- X Confirm filling system acceptability
- ✓ Uncover weakness in the process

# … search for the science

- Why are doing this? Validate the aseptic process
- What is the objective? Sterility assurance
- How does it accomplish the objective?
- Is it scientifically valid and useful?
- What is the harm?
- Is there a better way?

Efforts of no value divert resources from efforts of value.

# … ponder APS questions

- Are interventions included at production frequency?
- Does APS establish production duration?
- Do media fills qualify filler parts?
- Should intervention rejects be incubated?
- Must personnel qualification involve APS participation?

- Why?
- Objective?
- Accomplished?
- Good science?
- Harm?
- Better way?

# … put critical thinking to practice

Traditional approach

- Personnel and interventions qualified with APS

Alternate approach

- Separate out personnel and process qualification

# … focus on “value of quality” rather than “cost of quality”

Quality and profit are not mutually exclusive, conflicting objectives

# … embrace le grand partenariat

Technology and innovation based improvement cannot be realized without a partnership of manufacturers, regulators, and suppliers

- Each must accept its unique role
  - **Manufacturers** identify needs
  - **Suppliers** provide solution to need
  - **Regulators** judge acceptability of solution
  - Patients benefit

# Update: PDA Related Efforts

**Annex 1 Revision**

Aseptic Process PtC Part 1 & 2 (3?)
Isolator PtC and revisions to TR 13, 22, 34
QRM Standard for Aseptic Processing

December 2019 QRM Workshops
Second round of Annex 1 commenting
Interpretation of Annex 1 revision education

PDA/BPOG SFQRM collaboration

**Aseptic Processing Future State**

MSOP initiatives in RT release, manufacturing intelligence, and standardization

TRI C&GT education

# Challenge the status quo.  Ask WHY and WHY NOT?

*If everyone is thinking the same way, then not everyone is thinking…*