Sterility by Design

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Sterility by Design

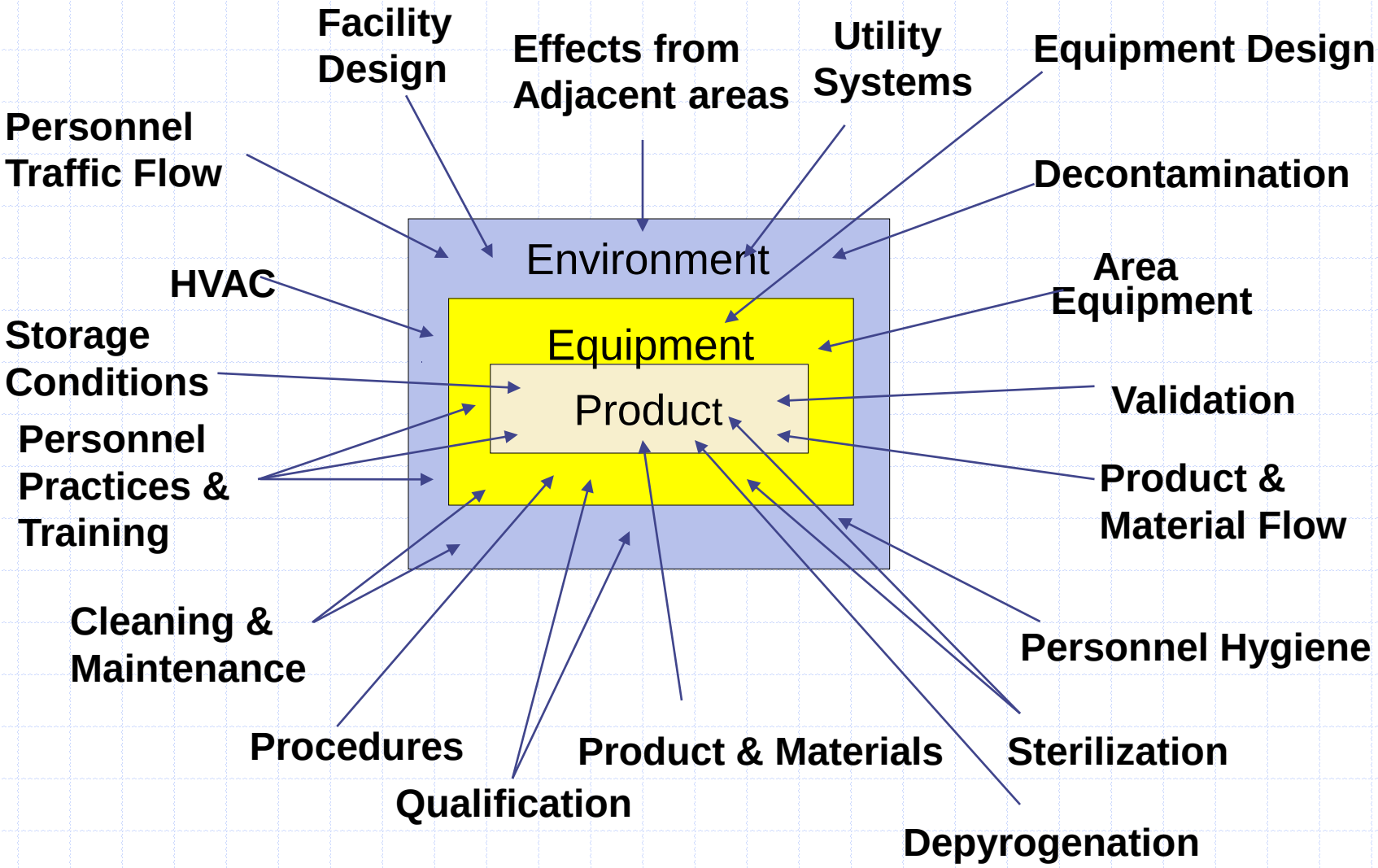
- What is it?
- Where did it come from?
- Why do we need it?
- How do we implement it?
- What's the regulatory reaction?

Definition of Sterility by Design

- The interrelated facility design, processing and operating practices which in combination ensure the microbiological safety of sterile products. It encompasses facilities, equipment, utilities, personnel, materials, components and microbial control procedures such as decontamination, sterilization and depyrogenation. Microbial testing is a supplemental activity that monitors and verifies performance.

What is Sterility by Design?

Influences on Sterile Products



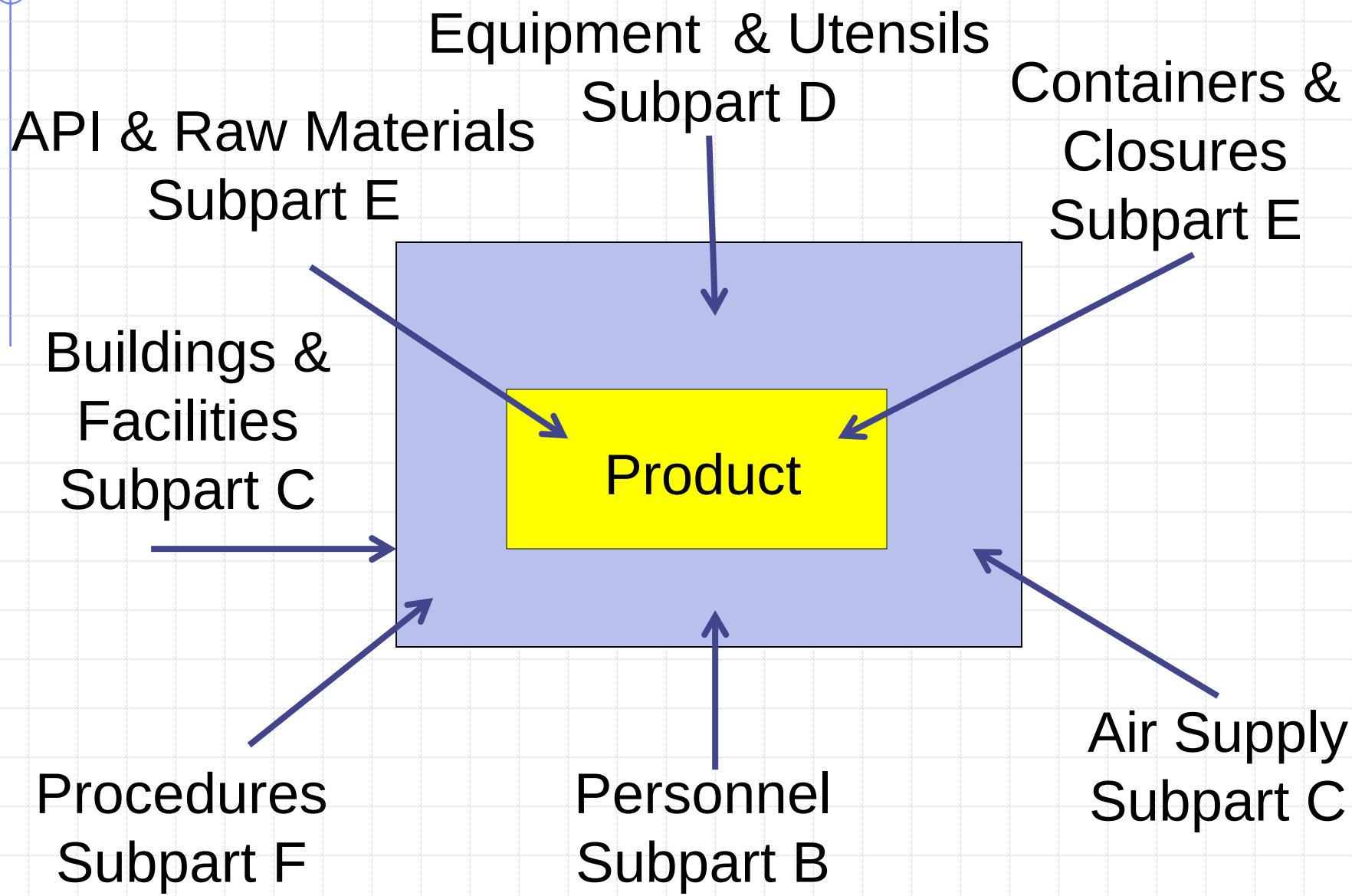
Adapted from Leonard Mestrandrea

Where did Sterility by Design come from?

Origins of Sterility by Design

- It's always been a part of sterile product preparation.
- The design elements and procedural controls have evolved incrementally as sterile production means advanced with technology improvements.
- The concepts of 'sterility by design' are present in 21 CFR 211.

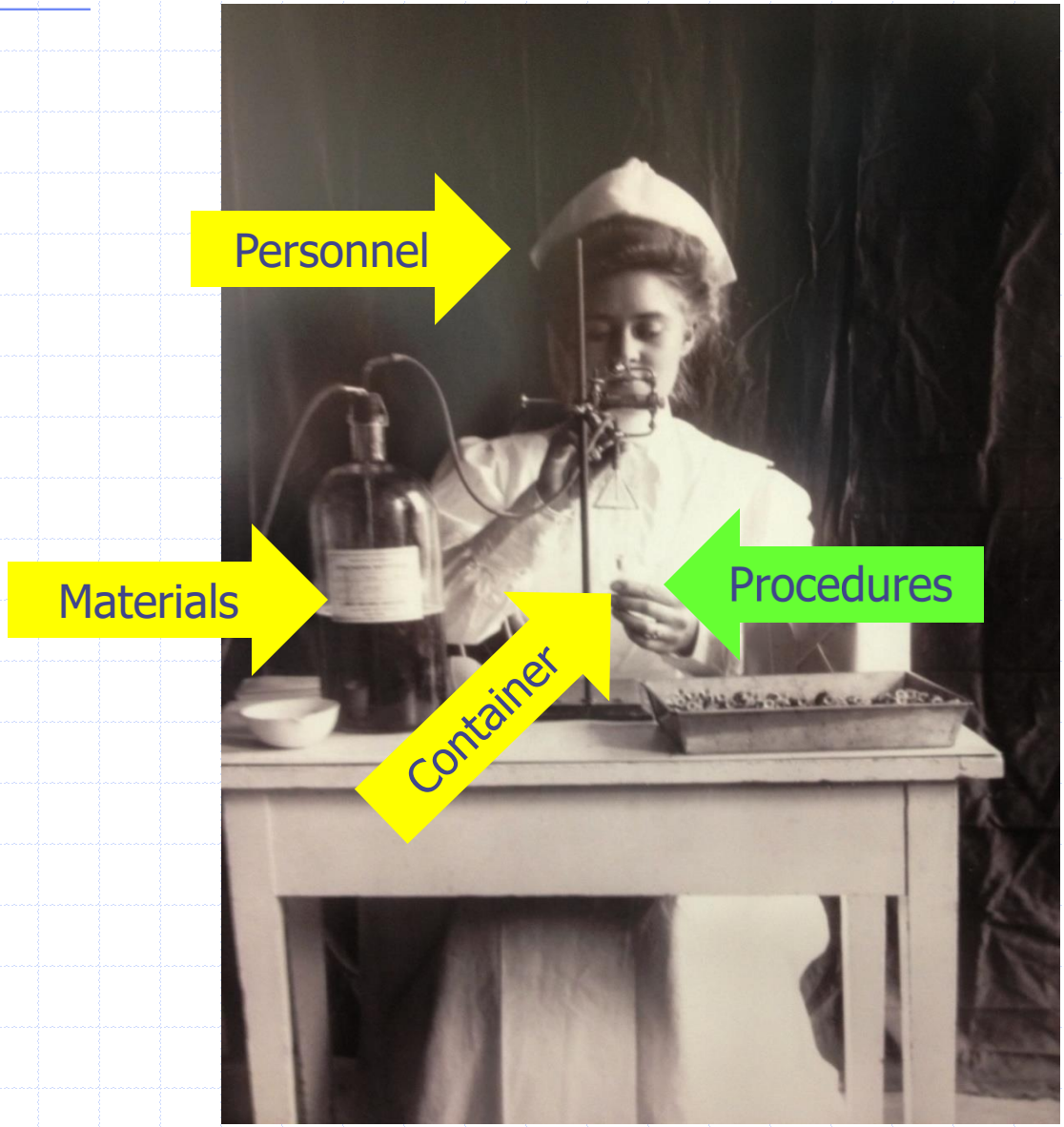
Asepsis & CGMP Regulations



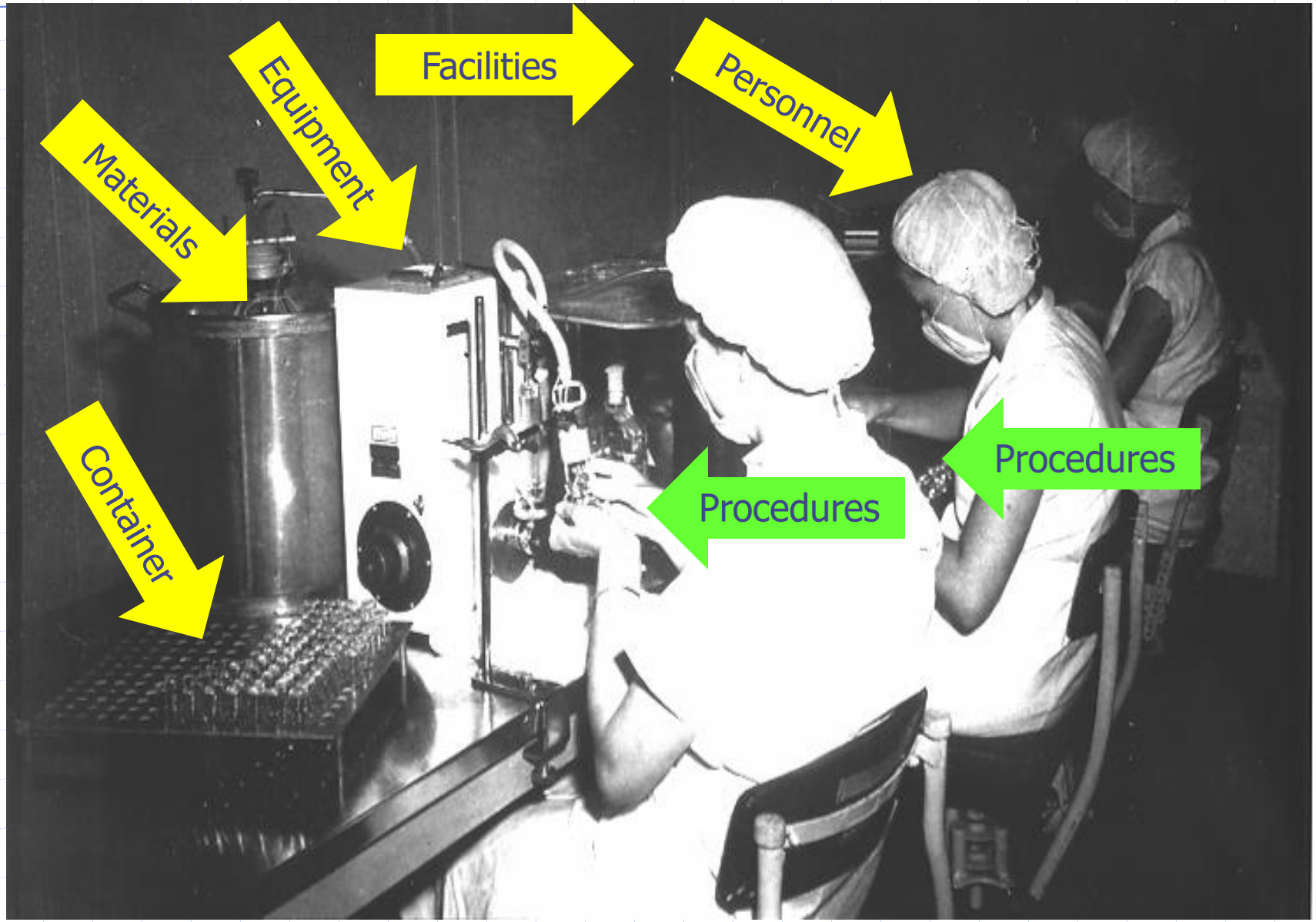
Personnel & Contamination

- "It is useful to assume that the operator is always contaminated while operating in the aseptic area. If the procedures are viewed from this perspective, those practices which are exposing the product to contamination are more easily identified."
- Hank Avallone – 1988

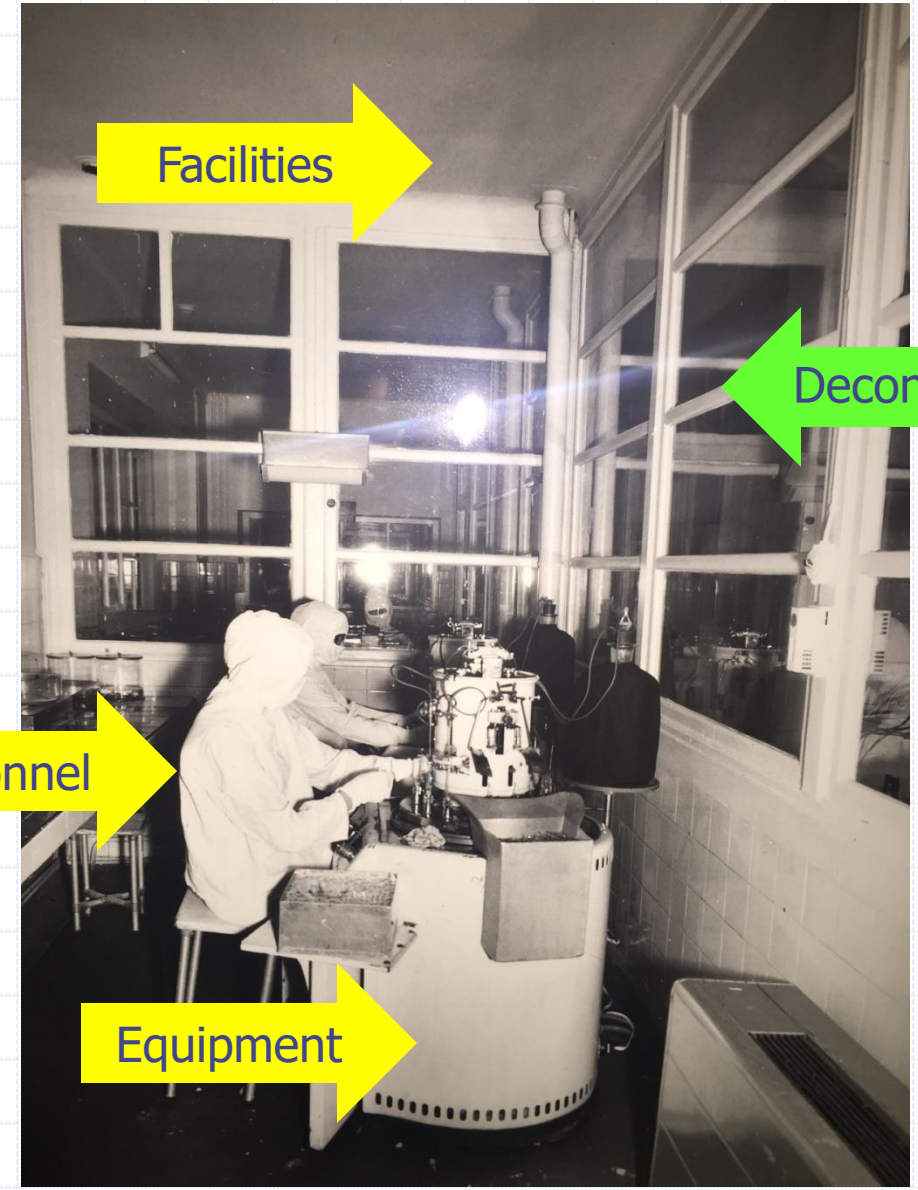
Aseptic Processing – circa 1905?



Aseptic Processing – circa 1930?

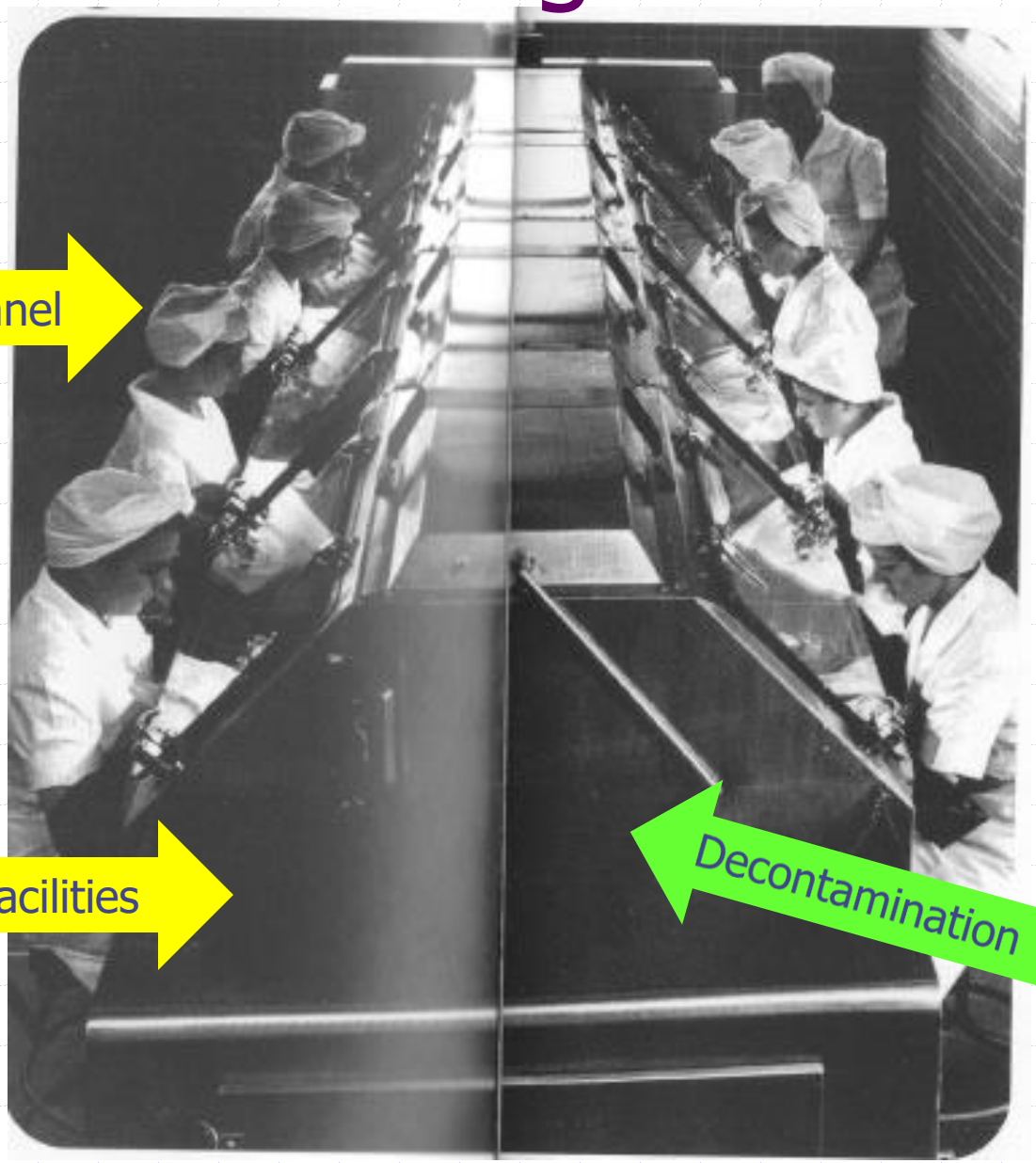


Manual Fill in Uncontrolled Room



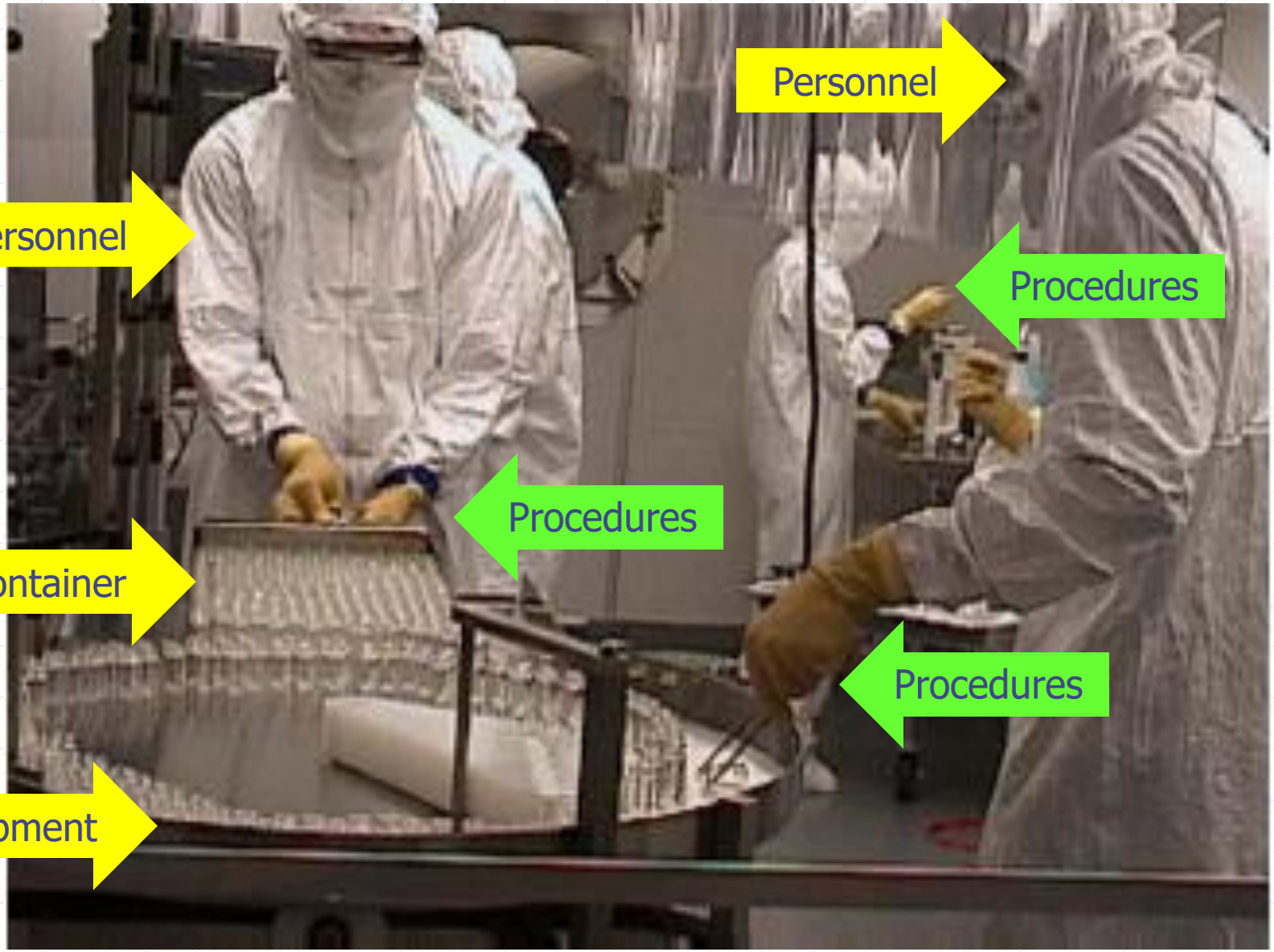
~1950

Manual Processing in Glovebox



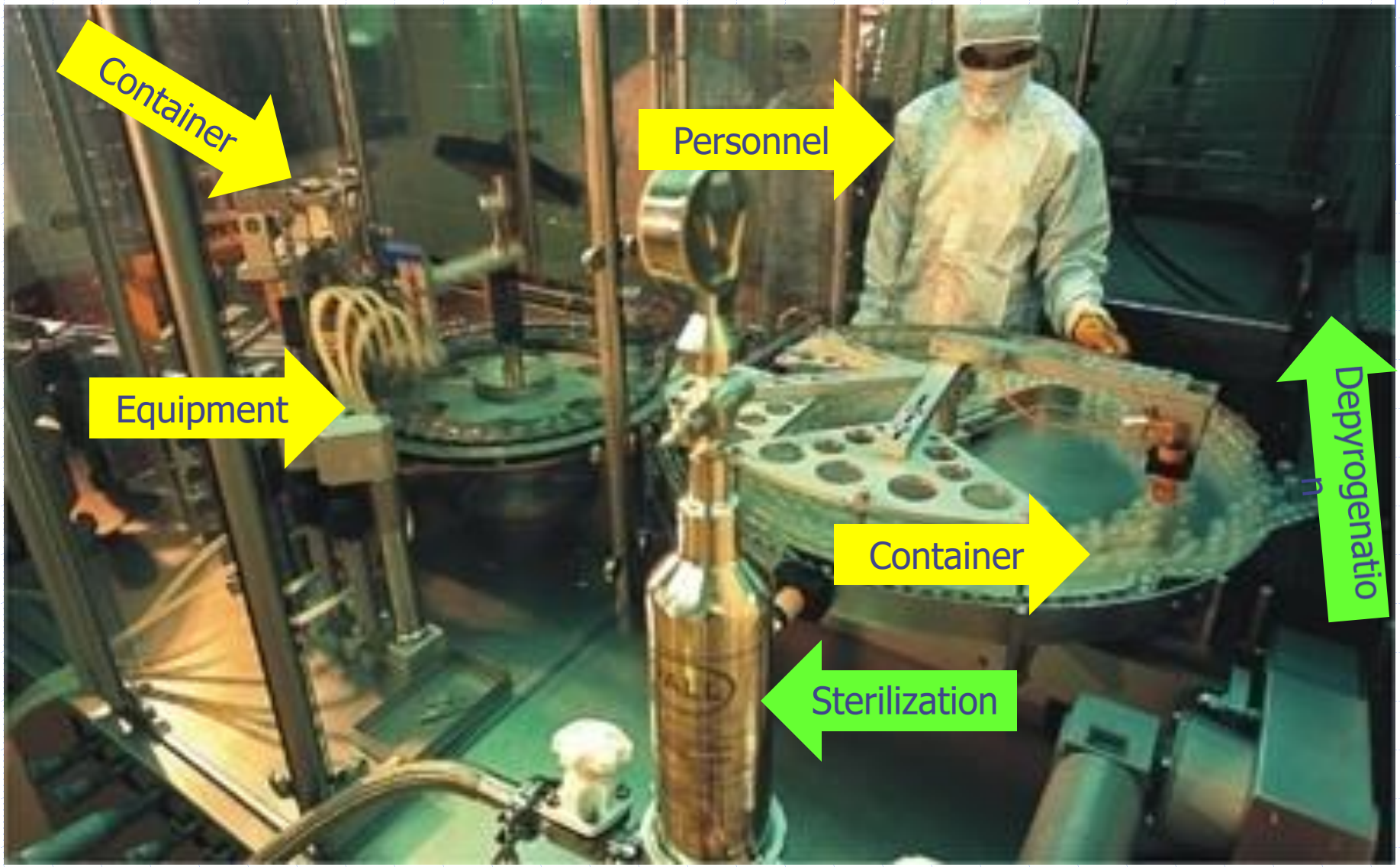
~1950

Cleanroom – 1960-70 Designs

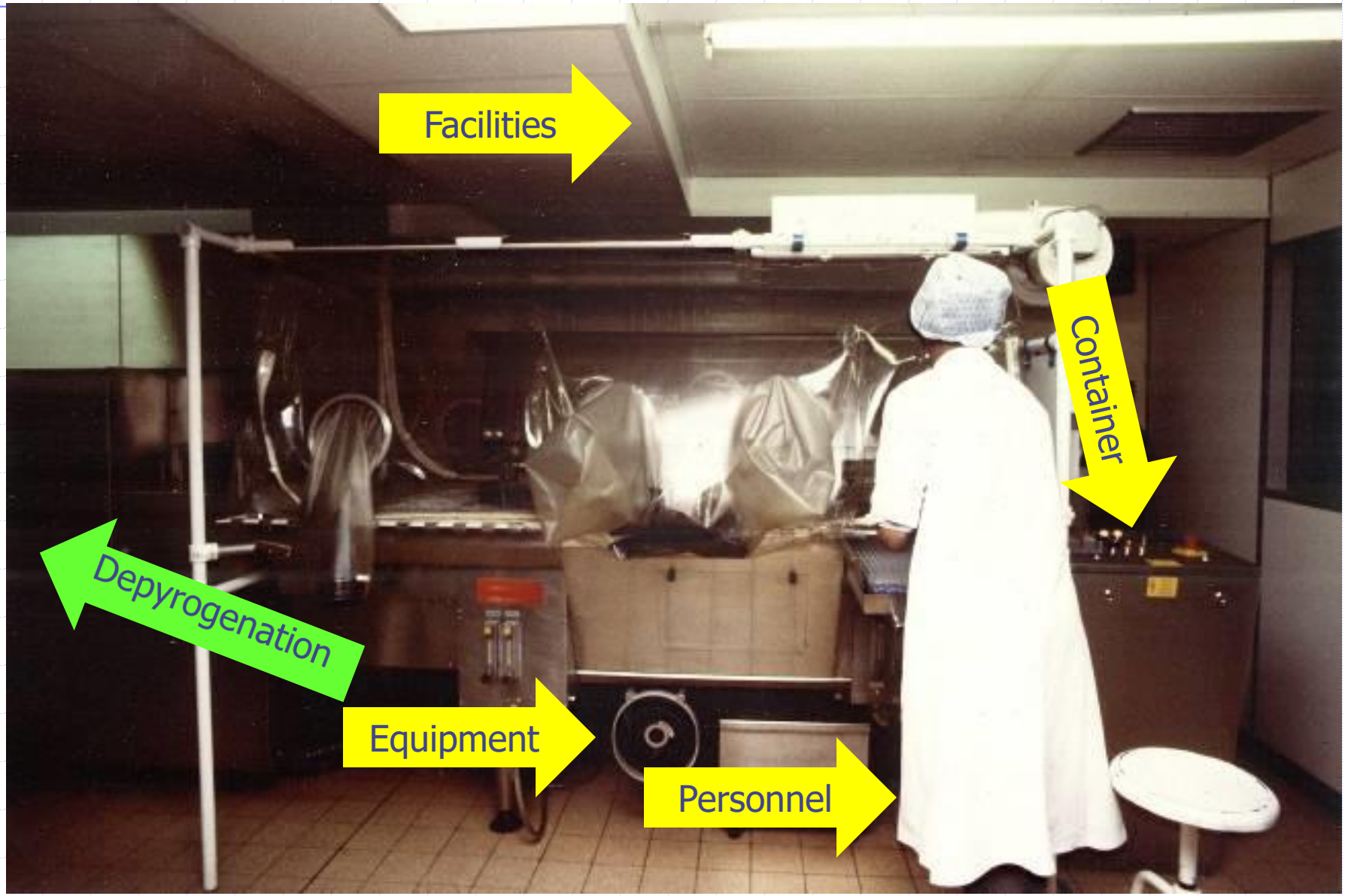


Barrier Around Filler Only

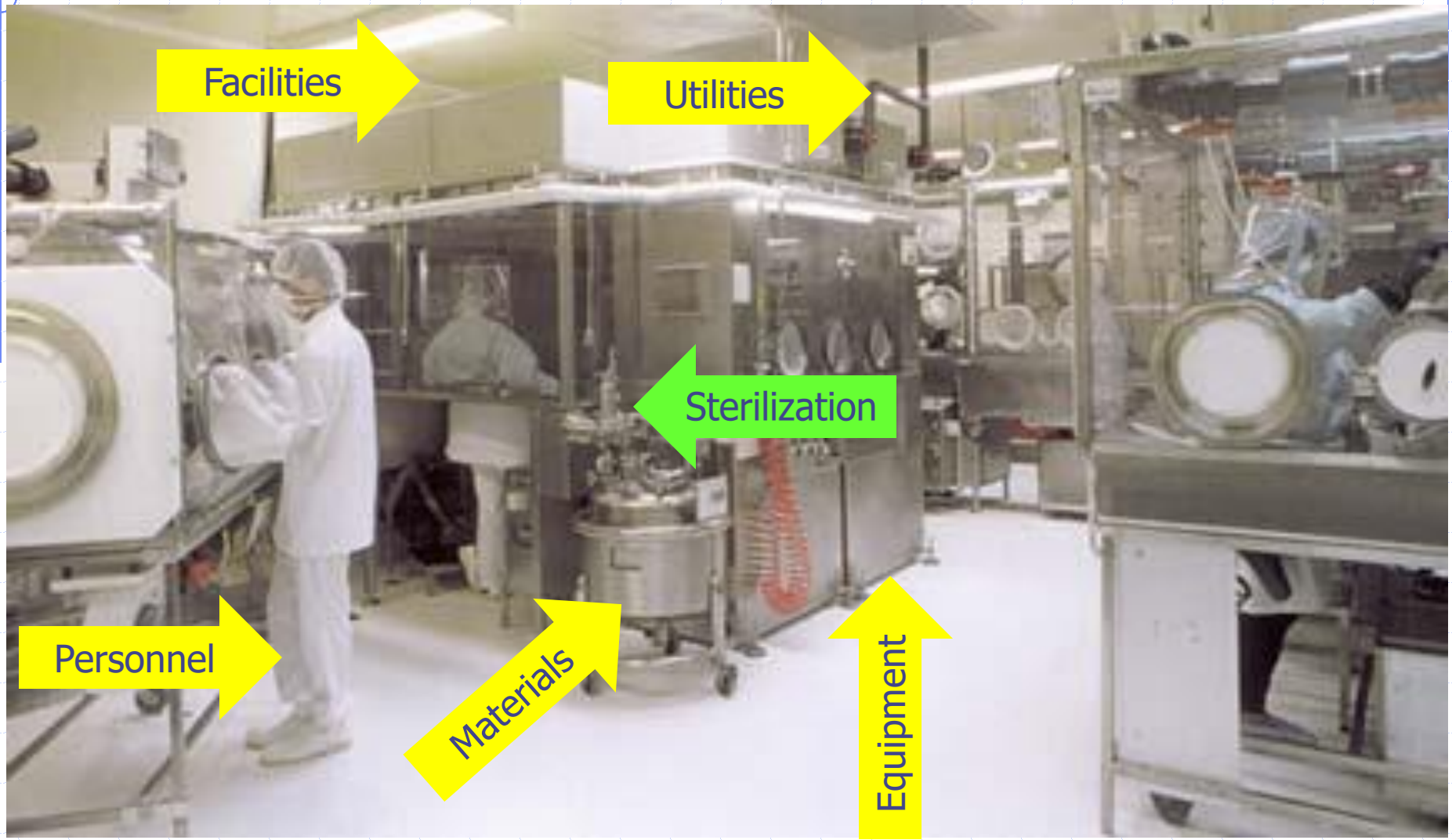
~1980



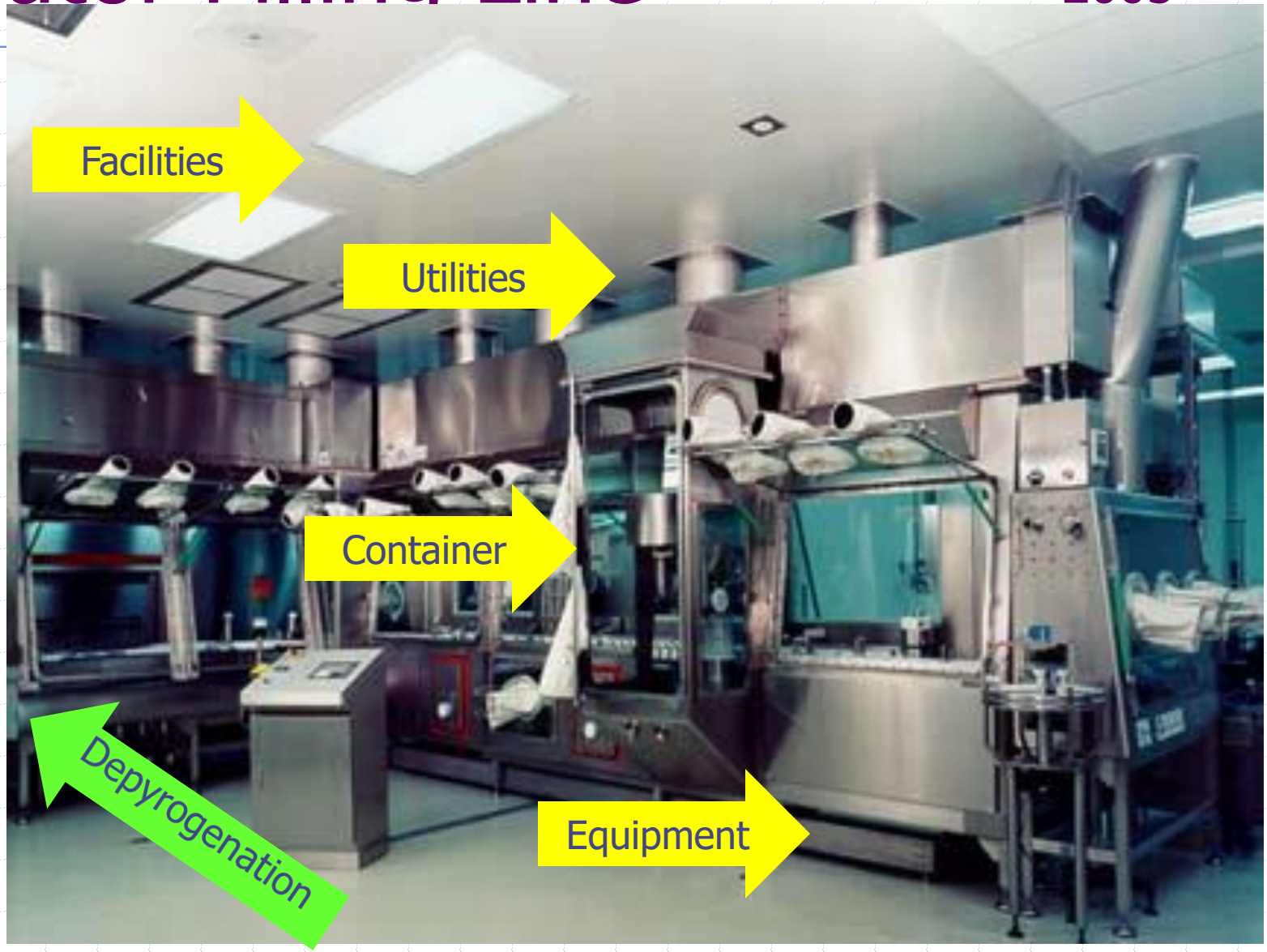
A very early Filling Isolator ~1980



Isolator Filling Line ~1988

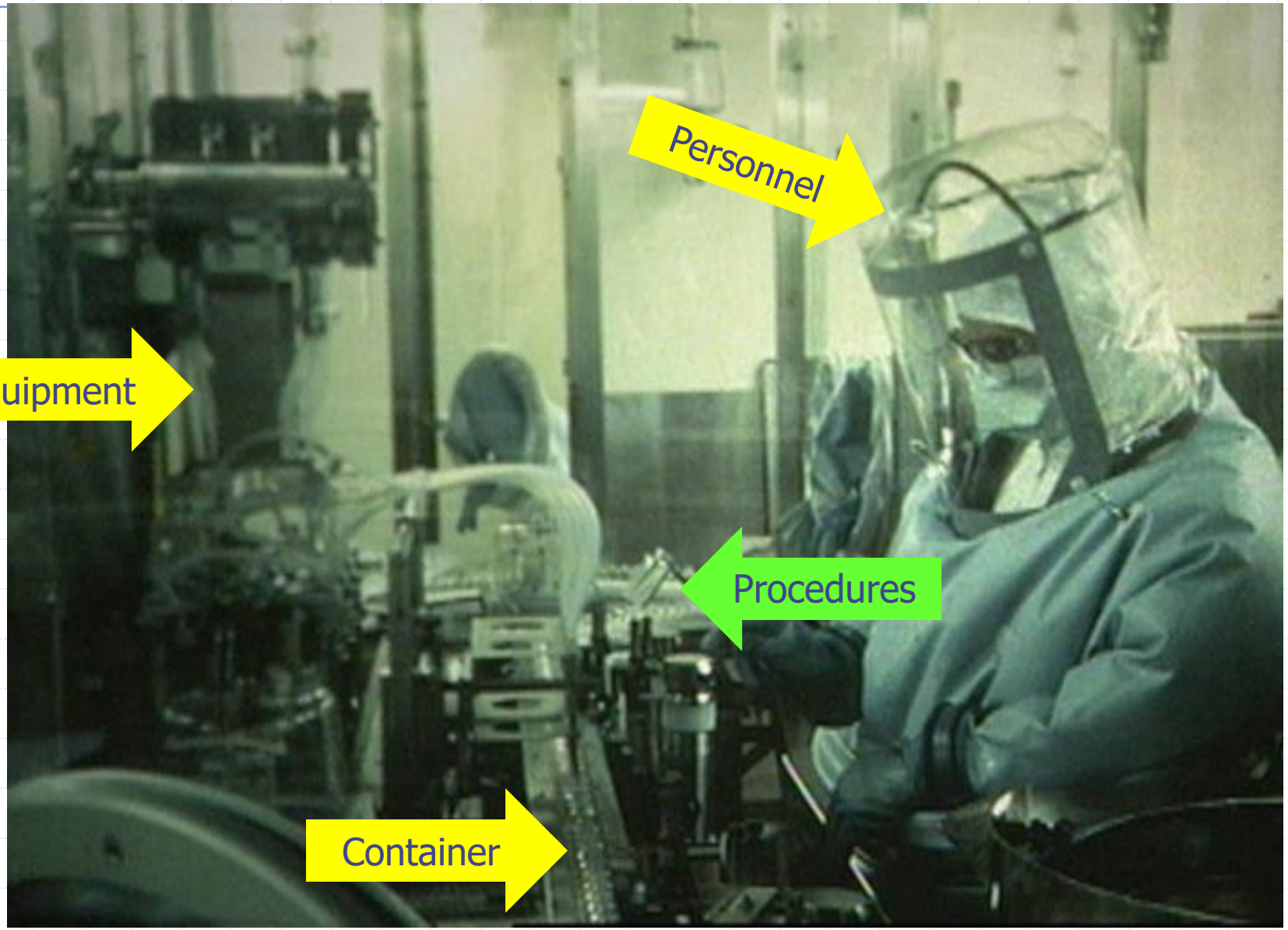


Isolator Filling Line – ~2005



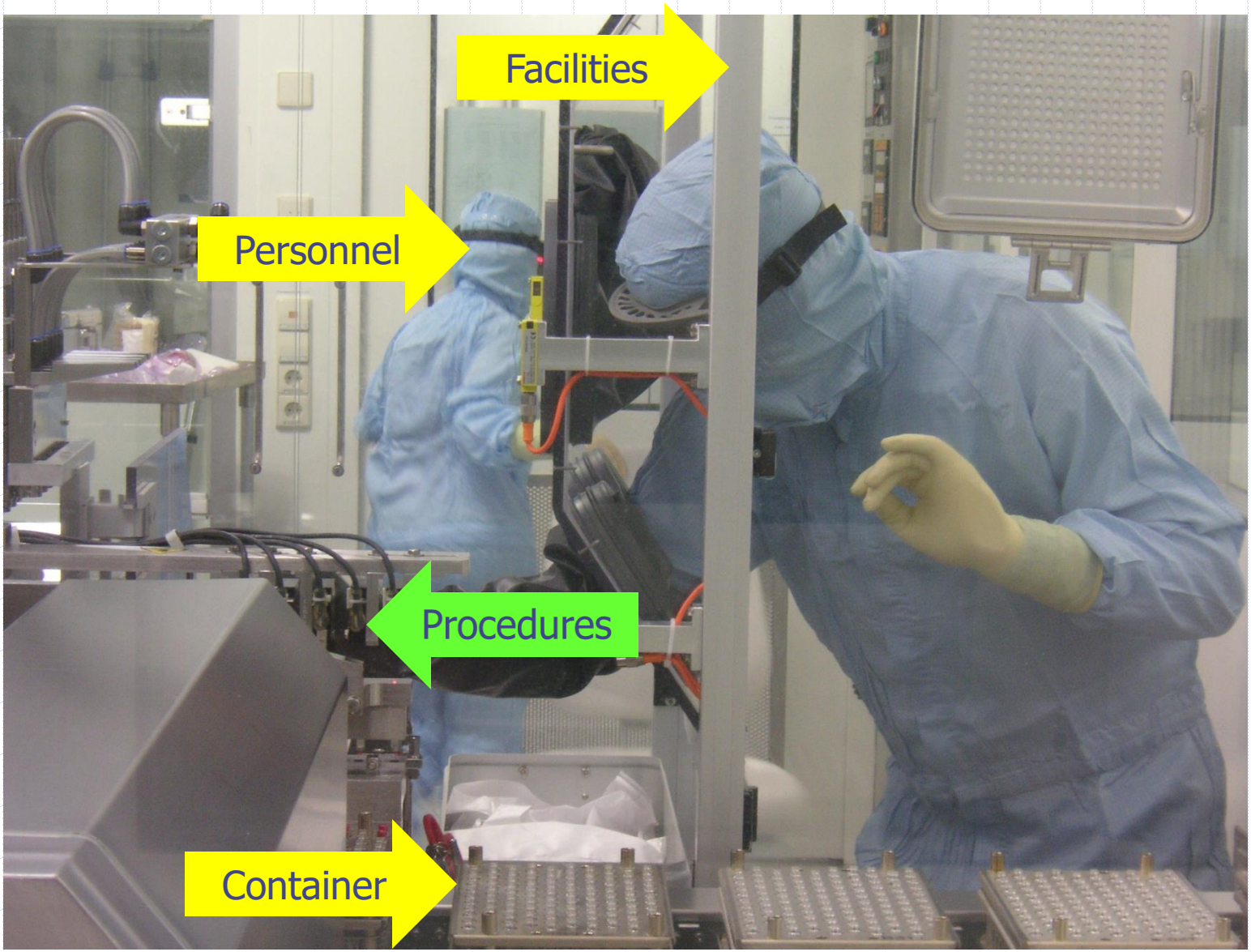
Early RABS installation

~2000



Another RABs –

~2002



Why do we need Sterility by Design?

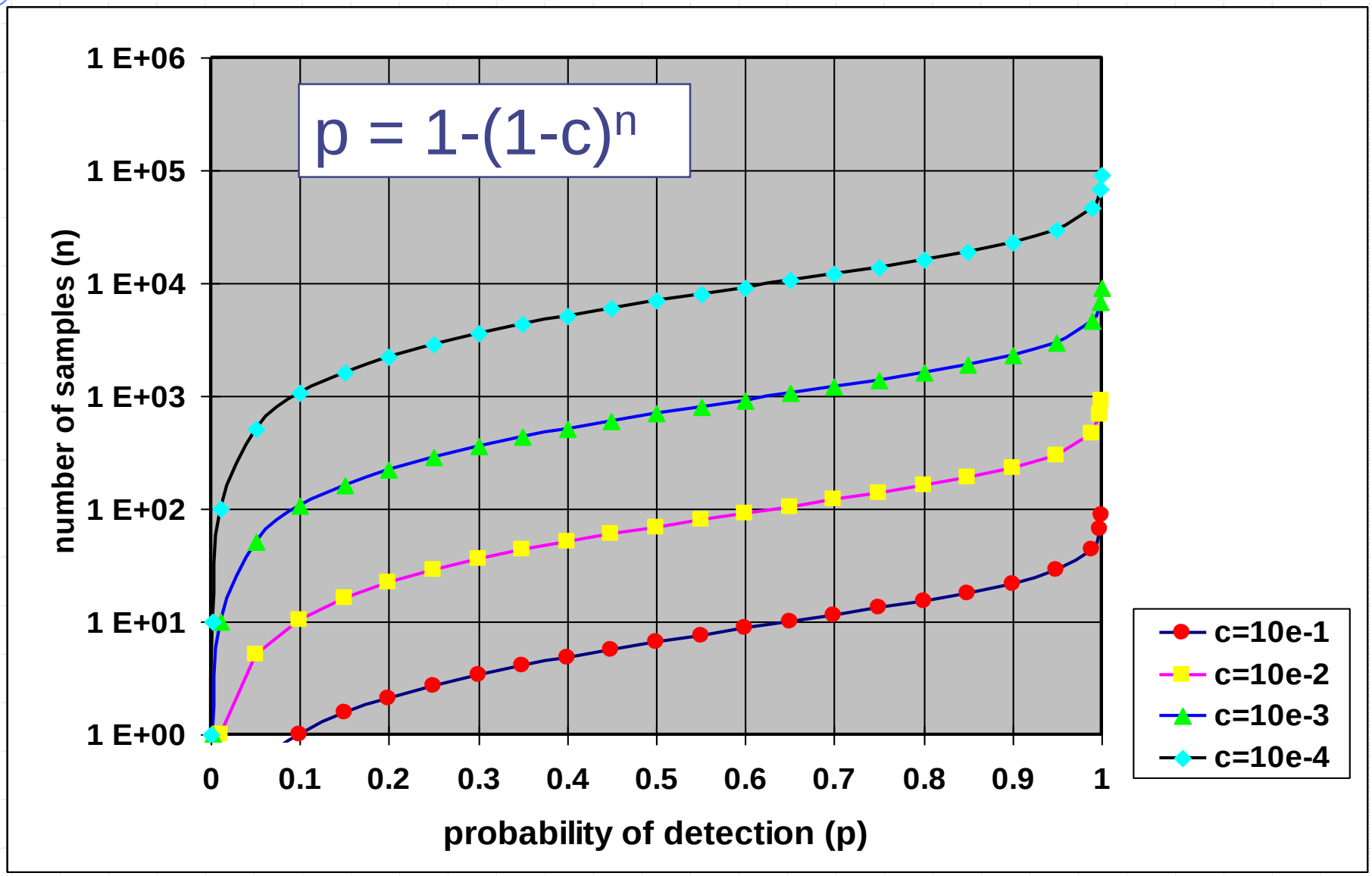
Sterility & Sterility Assurance - 1

- Sterility is an absolute concept, and cannot be directly measured.
- Sterility assurance is easier to define, but no easier to quantify:
  - In sterilization, it is estimated using a PNSU (or SAL) for each process. Sterilization process performance is much better than the minimum expectation of $1x10^{-6}$.
  - In aseptic processing, process simulation demonstrates a maximum contamination rate from a point-in-time evaluation. SAL does not apply and is indeterminate.
- Neither sterility nor sterility assurance can be quantified for aseptic processes.

Sterility Testing

- Sterility testing is so severely limited statistically it could be renamed "the test for gross microbial contamination".
- The sterility test was introduced in the 1930's when lot sizes were smaller, processing was manual and contamination rates were considerably higher. Advances in process capability have made it more of a ceremonial regulatory exercise, than a means of establishing process control or patient safety.

Limitations of Sterility Testing



Environmental Monitoring

- Viable monitoring is not an ‘in-process sterility test’.
- Absence of evidence is not evidence of absence; nor is evidence of presence indicative of process inadequacy.
- Microbial monitoring can never recover all of the microorganisms present.
- Aseptic processing does not require a ‘sterile’ environment, but even if it did, we can’t prove the environment was actually ‘sterile’.
- It’s also subject to both false ‘positives’ and false ‘negatives’.

Environmental Monitoring Realities

- Aseptic environments (including isolators) aren't and can't be proven 'sterile'.
- Detection of low numbers of microorganisms in manned cleanrooms should be considered a rare, but not unusual event.
- Investigations into recoveries of low numbers of human related microorganisms in manned cleanrooms is a make work exercise. There's few sustainable corrective actions that can be taken when it does occur.
- Significant excursions (>1 log higher) from the routine microbial prolife should be investigated.

Media Fill Criteria – PDA Survey Results

Criteria	1980	1986	1992	1996	2001	2017
0						25%
<0.05%		11.5%	13.2%	7.5%	12.5%	
0.05-0.09%		7.7%	9.4%	22.6%	18.8%	
1/5000*						73%
0.10%	25.0%	73.1%	67.9%	92.6%	68.8%	2%
0.11-0.20%	25.0%	3.8%	1.9%			
0.21-0.30%	18.8%	3.8%	9.4%			
>0.30%	31.2%					

* - Follow criteria in FDA aseptic guidance

Advanced Microbial Methods - 1

- Rapid microbiology gives the same uncertain results as any other test albeit sooner.
- The limitations of sample size, intensity, frequency and recovery efficiency are all unchanged.
- Fluorescence or other real-time RNA/DNA tests may confirm the presence of microorganisms, we should already understand are present. That knowledge doesn’t change anything, though it can cause greater anxiety.

Advanced Microbial Methods - 2

- The 'holy grail' for sterility testing would be a non-destructive and 100% effective method suitable for use at high speeds across the full range of products, containers and microorganisms. Nothing like that exists.
- There's questions on how to use a test like that even if it did exist:
  - Viable, but non-culturable microorganisms
  - Population threshold to create actual infections
  - Correspondence to current controls
  - ??

Sterility & Sterility Assurance - 2

- There are no direct means to measure sterility assurance in aseptic processing.
  - Sterility testing is severely limited by both sample size and microbial recovery.
  - Environmental monitoring suffers from inadequate recovery and limited sample size. In addition, presence of microorganisms may not have any impact on production materials.
  - Process simulation demonstrates maximum contamination rates in an infrequent exercise.
- They essentially 'test sterility into the product'! They are unacceptable as 'proof' of anything, let alone something as important as patient safety.

"Many of the things you can count, don't count. Many of the things you can't count, really count."

Sign in Albert Einstein's office

How do we Implement Sterility by Design?

How do we Implement it?

- Actually, we already did!
- We have been since the inception of sterile product manufacturing. The continuing advances in technology have brought forth substantial improvements in our production capability
- The addition of new technologies are the means for improving the reliability of the process and contribute to enhancing the sterility assurance of materials.

So what's the Big Deal?

- The established means for process capability assessment are no longer useful. Sterile process capabilities routinely exceed the monitoring tools we have relied on.
- We cannot test our way to improved patient safety.
- Monitoring can actually make the processes less safe by adding unnecessary interventions and greater complexity.
- How do we improve further?

So What Does That Mean?

- Microbial monitoring practices are no longer of much value. They can only detect gross failures which are less and less common with increased automation and greater reliability of today's processes.
- Since we can be much safer and (at less expense) with newer technologies we should be implementing them rapidly and reconsider the practices for the most vulnerable products.

What Else Does it Mean?

- Regulatory agencies have to be willing to permit the application of new technologies based upon their design alone.
- Tests relying on microbial recovery designed for less capable processing systems are no longer adequate or useful.
- You can't win the Tour de France with training wheels or judge a fish by its ability to climb a tree.

- **Technology improvement has always been the means for improved patient safety and that won't change.**

Sterility & Sterility Assurance - 3

- It's not the monitoring that assures the 'sterility' of an aseptically produced products.
- Monitoring does not provide control over aseptic processing outcomes.
- The individual elements must be defined and optimized to reduce human involvement and minimize their impact in order to provide the highest confidence in the aseptic process.

Where are the Future Problems?

- 503A Compounding Pharmacies
  - Simple processes, low volumes
- Combination Products
  - Diverse processes, moderate volumes
- Personalized Medicine
  - Numerous diverse, complex & lengthy processes, very low volumes
- Development and Early Clinical
  - Simple processes, modest volumes
- ???

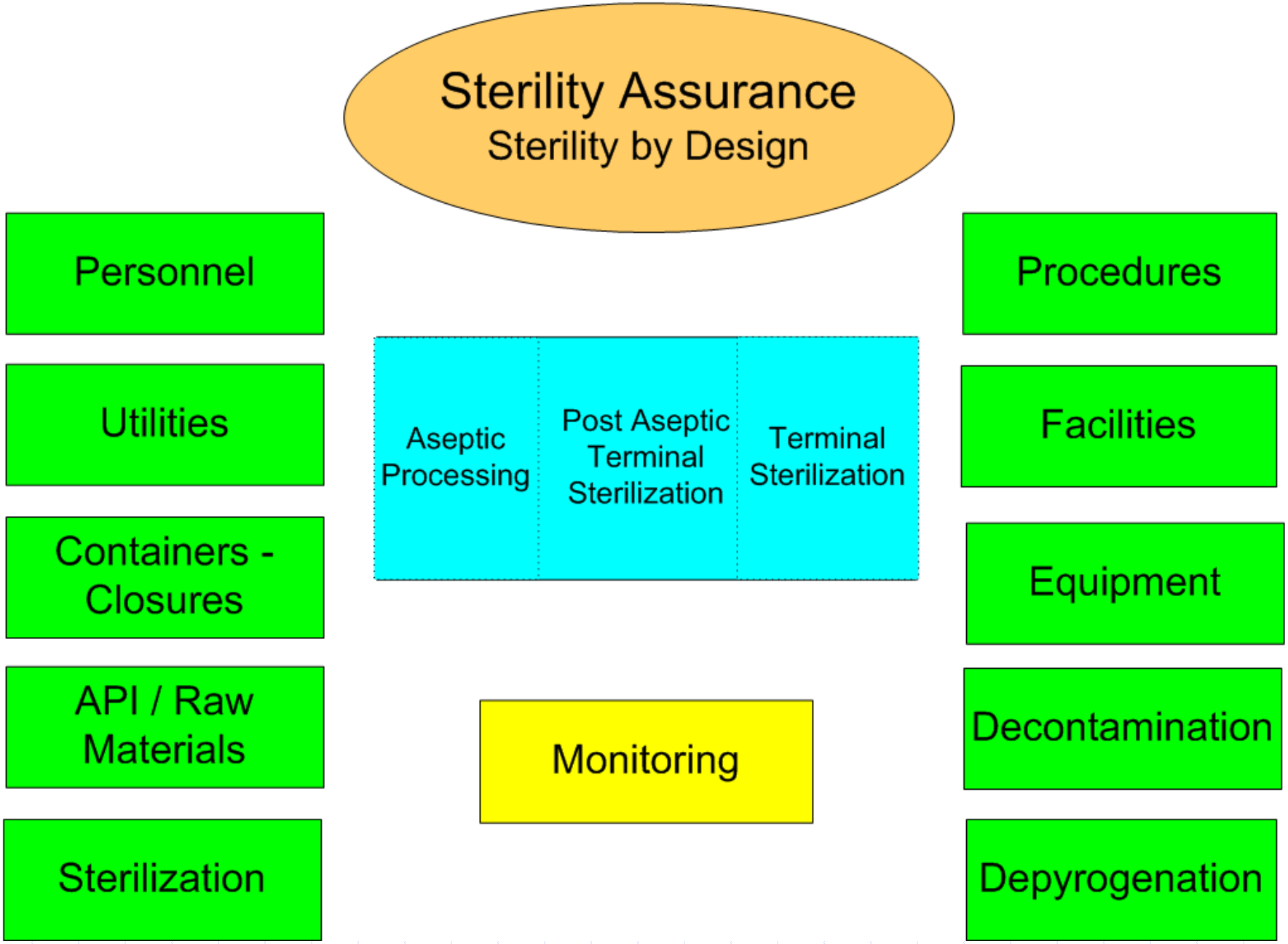
What are the Solutions?

- Currently available (alone and combined)
  - Conventional isolators
  - Closed vial filling
  - Single use disposable fill sets
  - Automation / Robotics
- Future capabilities (alone and combined)
  - Closed system filling
  - Single use disposable processing sets
  - Automation / robotics
  - Low time-temp / low dose terminal sterilization
  - ???

What's the likely Regulatory Reaction?

Who's on Board?

- USP Sterility Assurance <1211> introduced 'Sterility by Design' as the future of sterile manufacturing on all scales. Tries to alter the paradigm.
  - Official March 1, 2019
  - Incorporated comments from many firms
  - FDA HQ staff participated in development
- Growing acknowledgement
  - A&E and consulting firms
  - Major manufacturers
  - Equipment & component suppliers
  - ???


Sterility Assurance
Sterility by Design
Personnel
Utilities
Containers - Closures
API / Raw Materials
Sterilization
Aseptic Processing
Post Aseptic Terminal Sterilization
Terminal Sterilization
Monitoring
Procedures
Facilities
Equipment
Decontamination
Depyrogenation

Who are we Waiting for?

- EMA
- MHRA
- TGA
- FDA ORA – field inspectors
- ???
- The most dangerous phrase in the English language - **We've always done it this way!**
- Clearly there's a considerable amount of work to be done.

Sterility by Design

- The phrase may be new; the thinking isn't.
- Informal risk mitigation brought forth the technology advances seen over the history of aseptic processing.
- Confidence in aseptic processing is not derived from monitoring or testing; it is the result of attention to detail throughout the aseptic process.
- With newer technologies, the emphasis shifts further from monitoring & testing.

PostScript

- The challenge in aseptic processing is always personnel:
  - As the major source of contamination.
  - By slowing the implementation of advanced aseptic processing technologies.
  - By over-emphasizing testing over aseptic process design.

Walter Kelly, 1971

References

- Agalloco, J., Akers, J., "The Myth Called Sterility", *Pharmaceutical Technology*, Vol. 34, No. 3, Supplement, pp. S44-45, 2010 and continued online.
- http://pharmtech.findpharma.com/pharmtech/Analytics/The-Myth-Called Sterility/ArticleStandard/Article/detail/660544
- USP 41, Supplement 2, *Sterility Assurance* <1211>, 2018.