Process Validation:

Case Study

Achieving Regulatory Acceptance

For

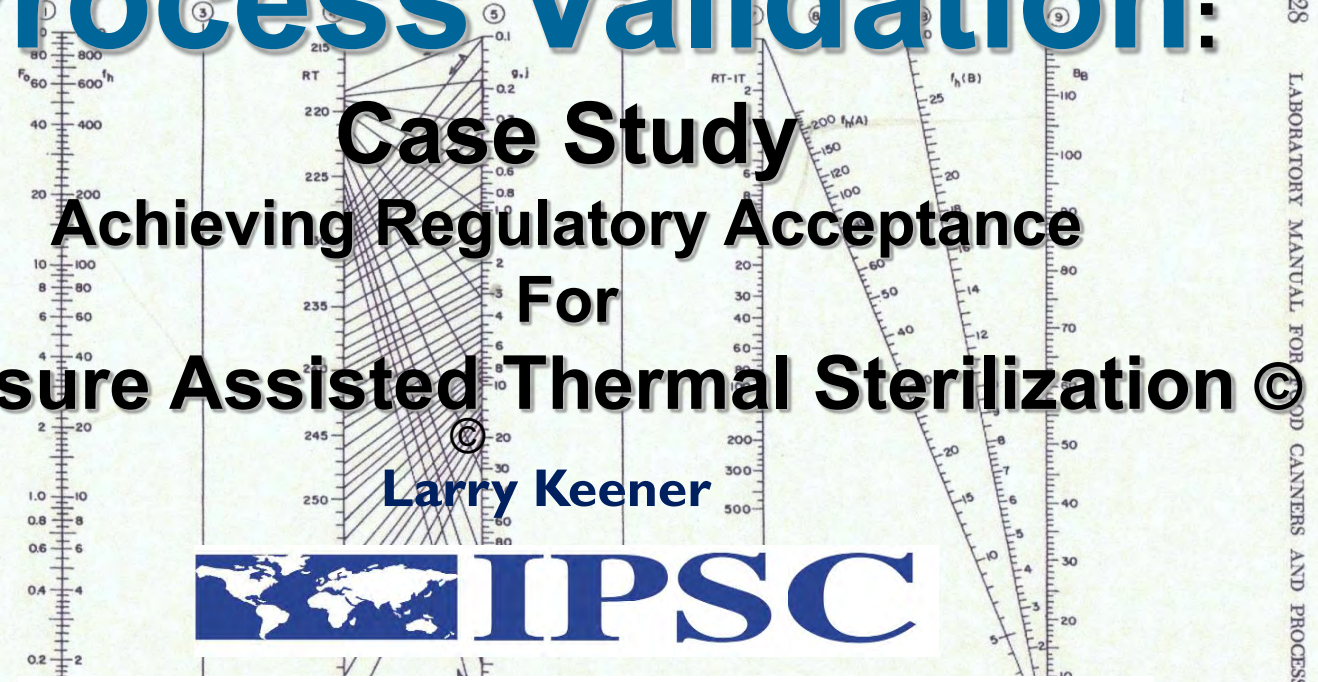
Pressure Assisted Thermal Sterilization ©

Larry Keener

IPSC

International Product Safety Consultants LLC

"*TheFoodSafetyProfessionals*" (since 1996)



Food Safety Summit

Acknowledgements

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U.S. Food and Drug Administration
Washington Farms

Summary

1. Prospective validation is preferred for evaluating novel preservation processes
2. Validating a novel process ***must*** consider; the equipment, the process, process critical monitoring and measurement devices and the product
3. Process validation requires the skills of many…you need an "expert team"
4. Involve external experts and regulatory officials in the development of both the master validation plan and the validation protocols
5. Process validation *is predicated on* objective data that are properly analyzed

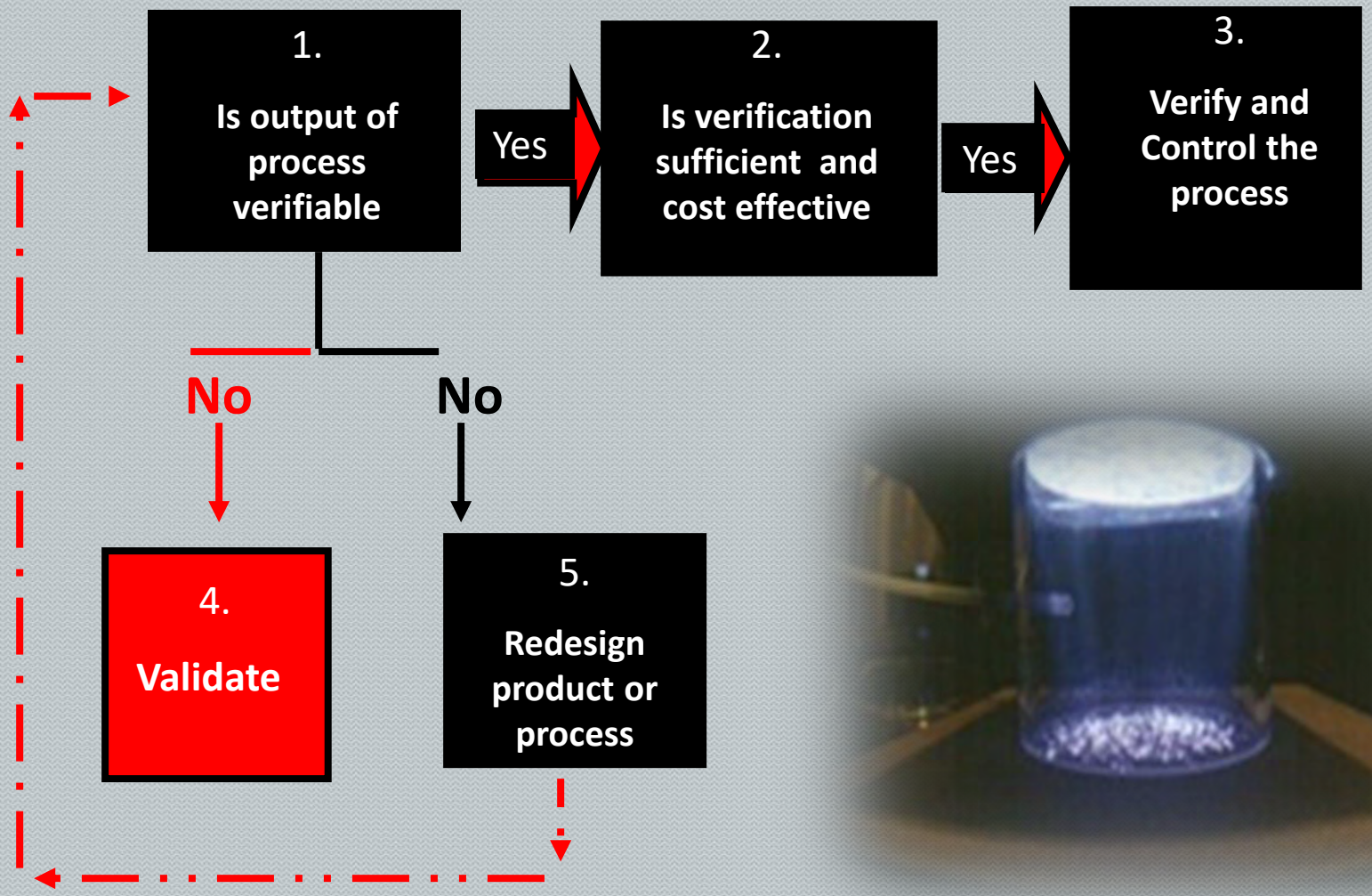
Validation

Validation: Obtaining evidence that a control measure or combination of control measures, if properly implemented, is capable of controlling the hazard to a specified outcome. Codex 2013

Validation **means obtaining and evaluating scientific and technical evidence that a control measure, combination of control measures, or the food safety plan as a whole, when properly implemented, is capable of *effectively* controlling the identified hazards. US FDA 2011**

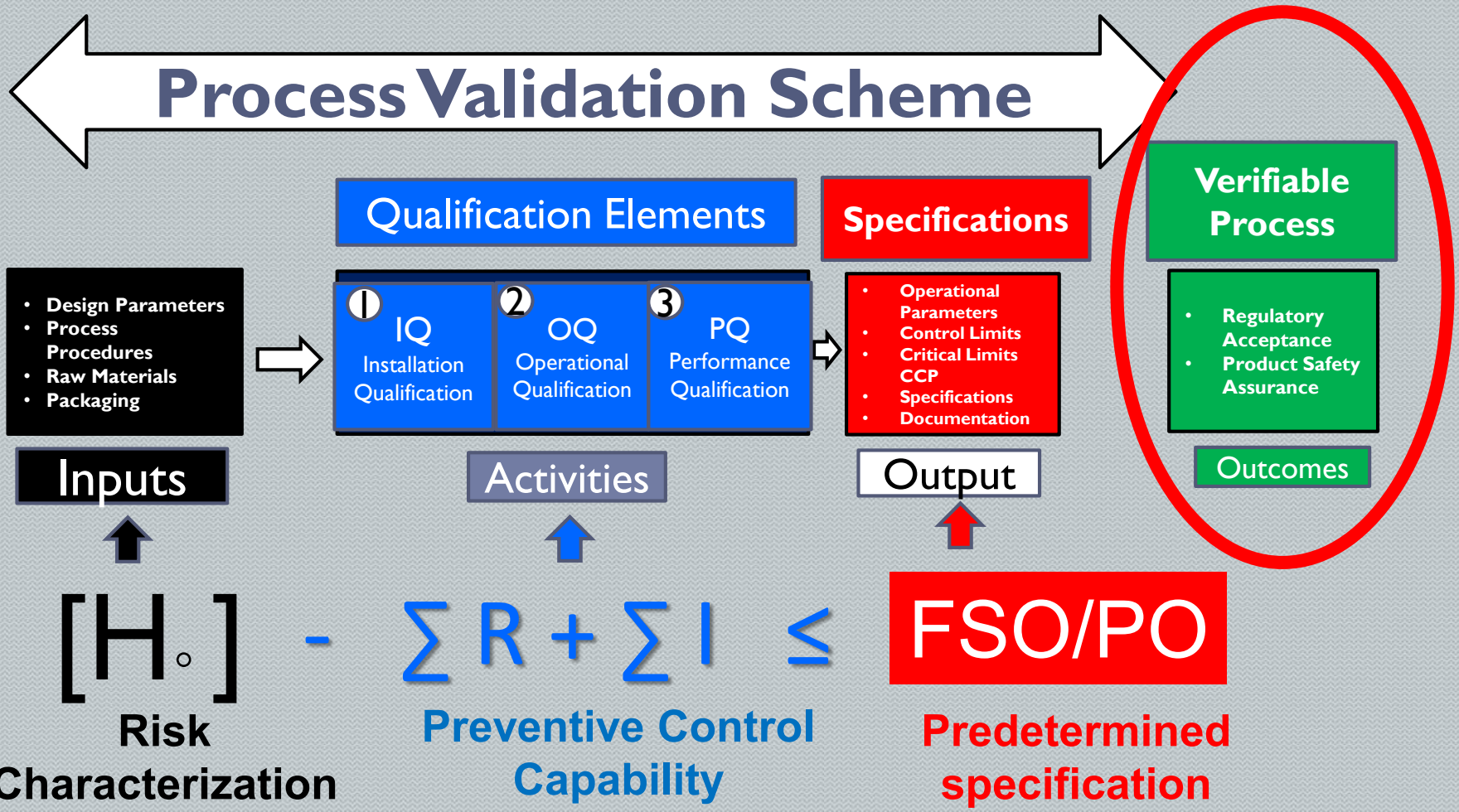
Validation: Establishing *documented evidence* which provides a *high degree of assurance* that *a specific process* will *consistently* produce a product *meeting* its *pre-determined specifications* for quality and [*food]* *safety. US FDA 1987*

Validation Decision Tree



Source: Global Harmonization Task Force 1996

Hypothetical Validation Scheme



L. Keener Oct. 2017

You cannot verify that which has not been validated

Validation Strategies

Prospective validation- Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

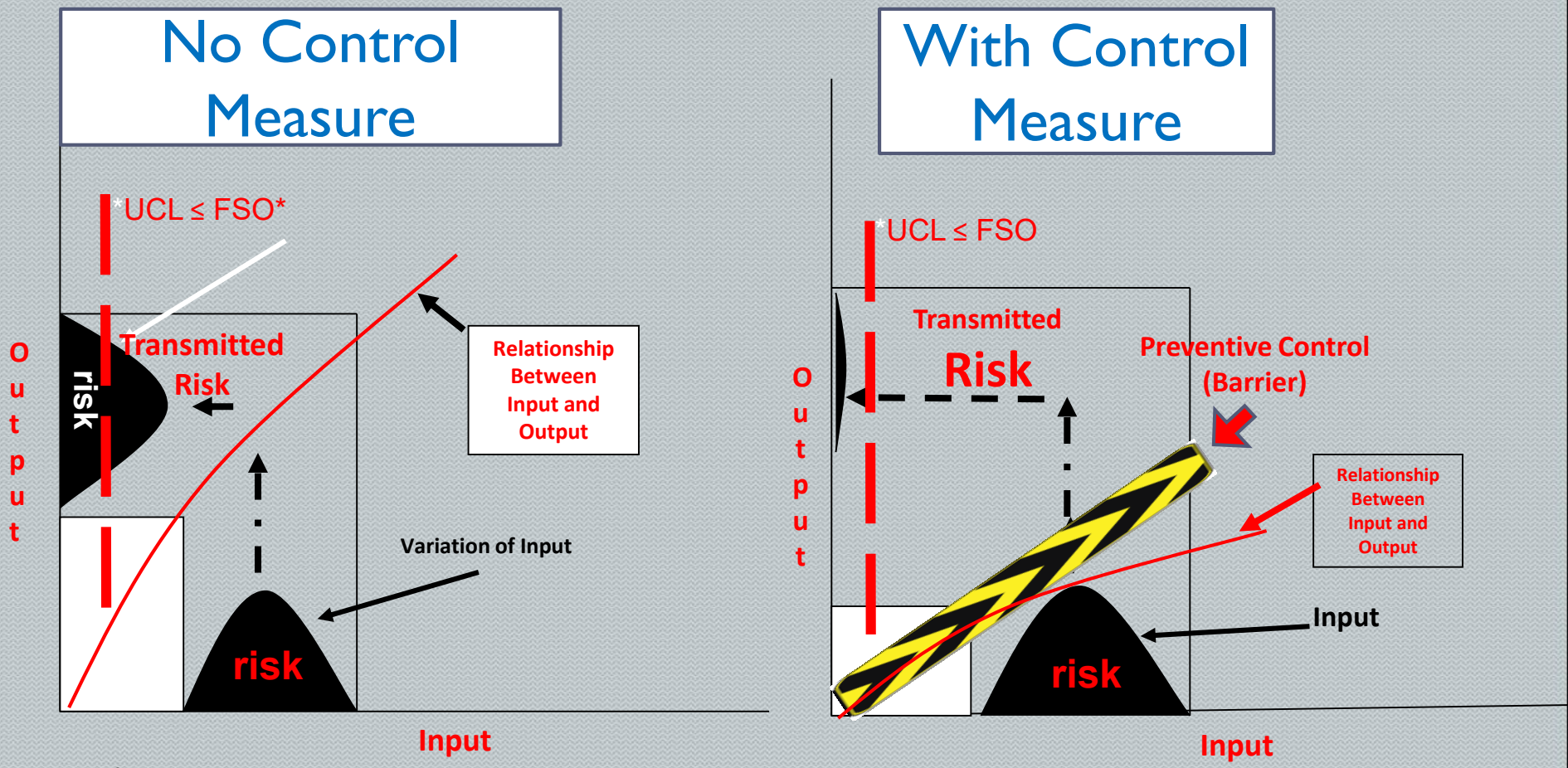
Or

Concurrent validation - Validation conducted concurrent with manufacturing process.

Retrospective validation - Validation of a process for a product already in distribution based upon accumulated production, testing and control data.

Source: USFDA

Transmission of Risk & Preventive Controls



Source: After Global Harmonization Task Force 1996

$$*[H_o] - \sum R + \sum I \leq FSO=UCL$$

Justification and Rationale for Validation

(1)Safety, quality, and effectiveness must be designed and built into the product;

(2) Safety cannot be inspected or tested into the finished product; and

(3) Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all safety, quality and design specifications.

Source: USFDA

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Pressure **A**ssisted **T**hermal **S**terilization

Pressure assisted thermal sterilization (PATS) is the process whereby high pressure (350-800MPa) and heat (80-90°C) are combined to achieve processing temperatures that are customarily used in the preservation of ambient stable, low acid, food products.

Novel Preservation Method

Project Objectives

1. To demonstrate the efficacy of Pressure Assisted Thermal Sterilization for used in the production of ambient stable, low-acid, food products held in hermetically sealed packaging

2. Comply with existing FDA regulatory requirements as codified at 21CFR108 and 21CFR113 for the registration, manufacturing and process filing of low-acid canned foods

Pre-determined Specification

FSO=Commercial Sterility

NOT

~~12D~~

or Terminal Sterility

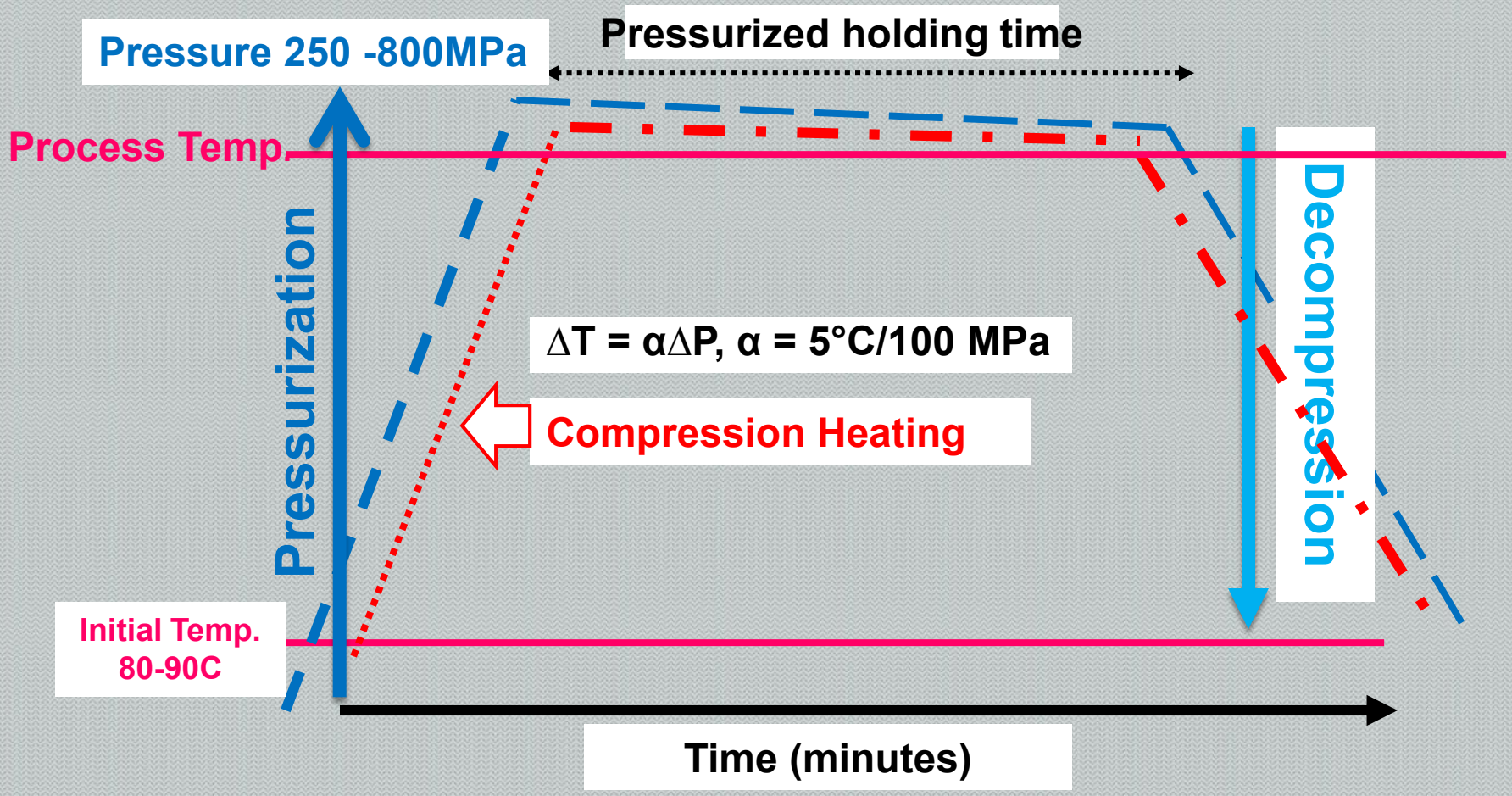
Food Safety Objective

Sterility Assurance – "Commercial Sterility" (CS)

Free from microorganisms capable of reproducing in the food under normal non-refrigerated conditions of storage and distribution; and viable microorganisms (including spores) of public health significance

(Larkin)

PATS Process Profile



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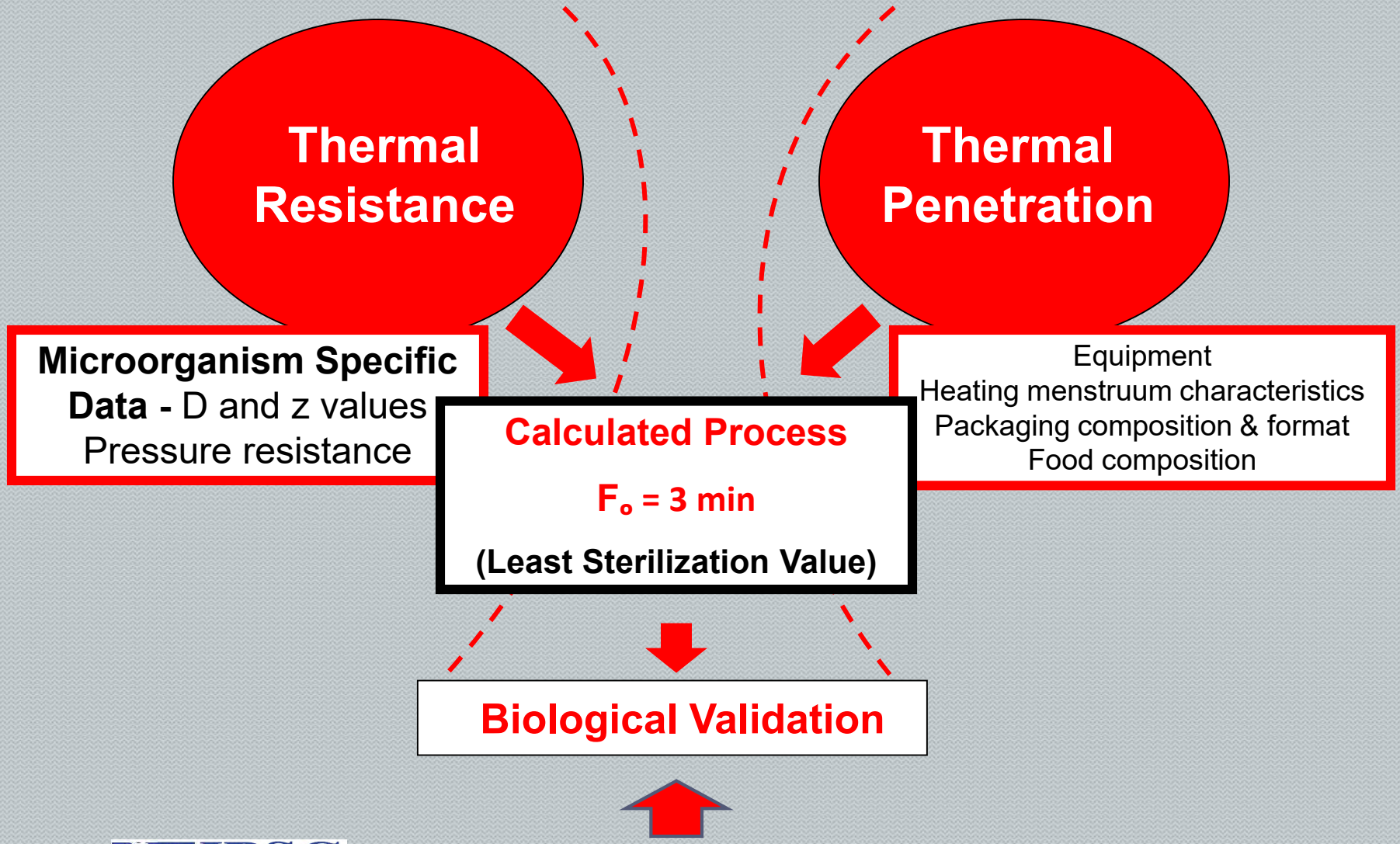
Establishing a PATS Process & LACF Filing



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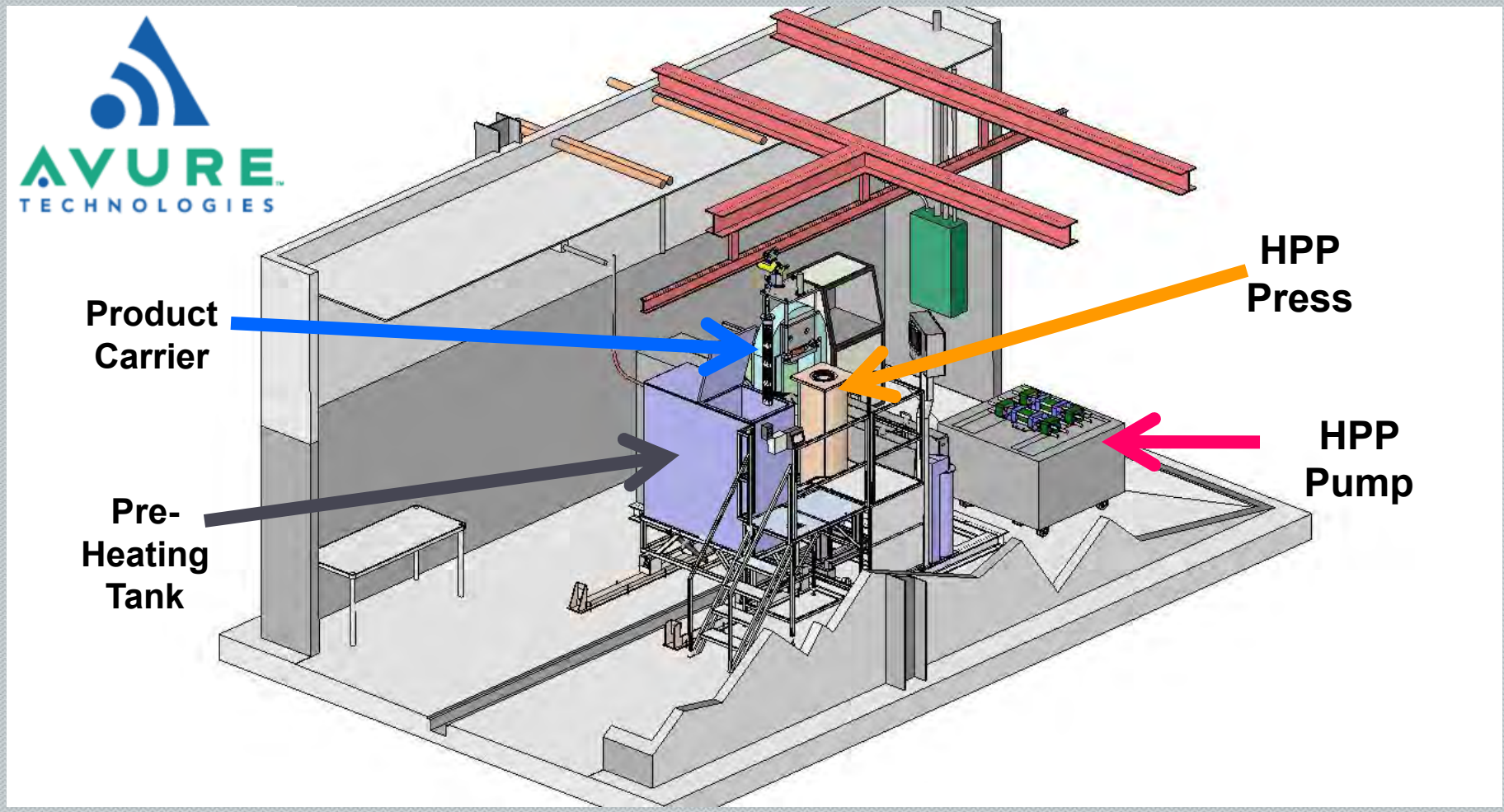
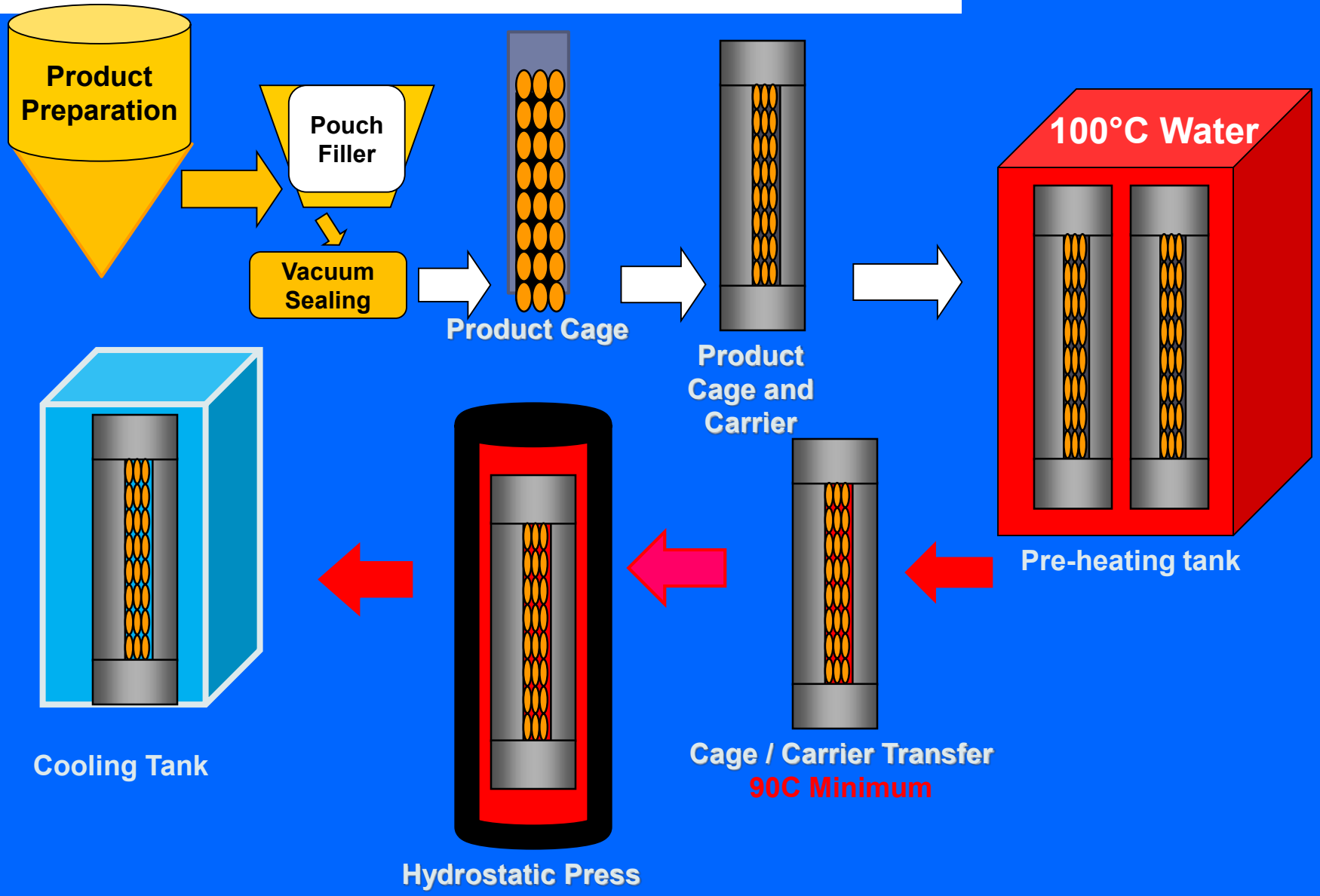
Equipment Layout for PATS Process



Generalized PATS Process



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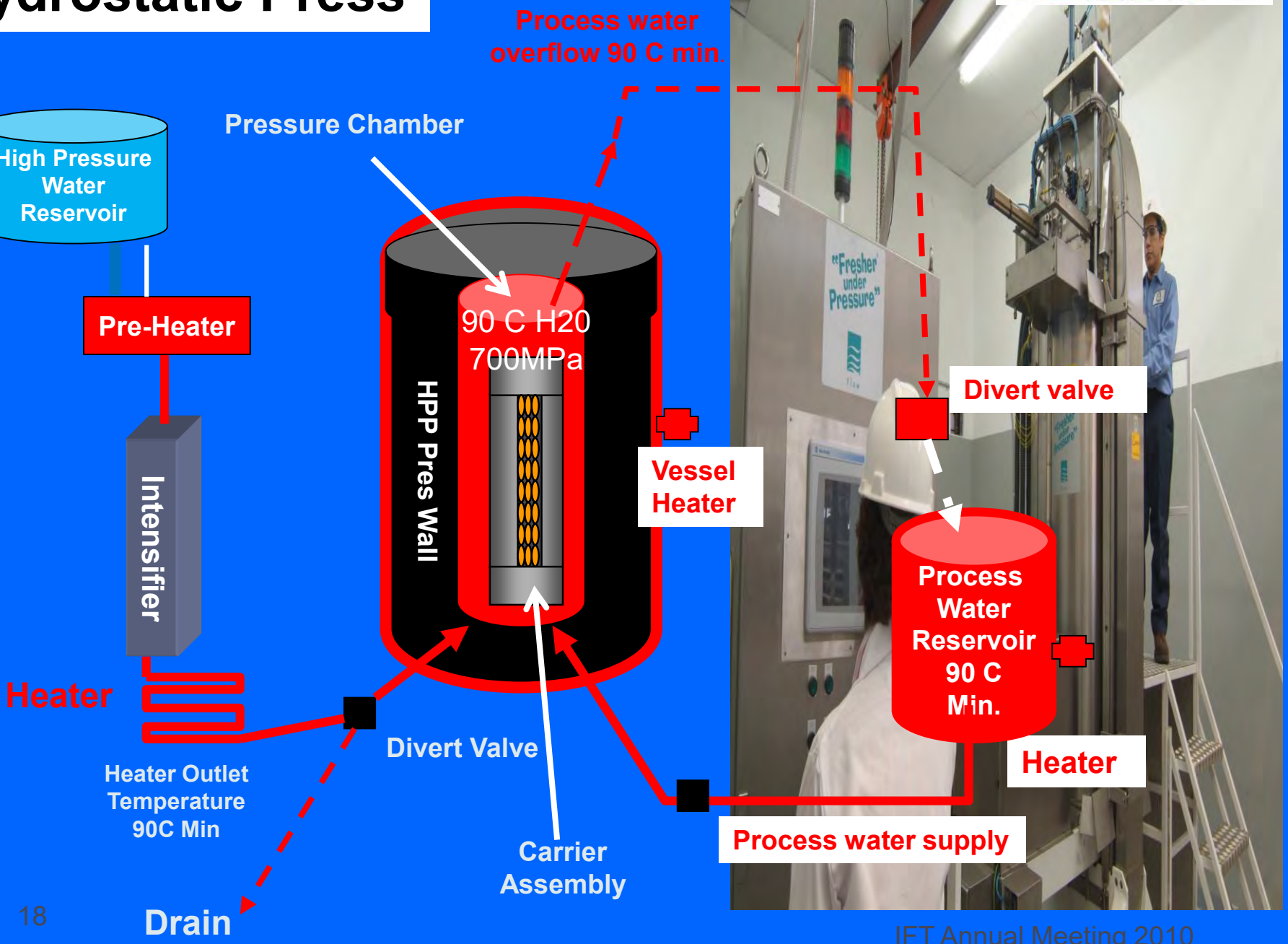
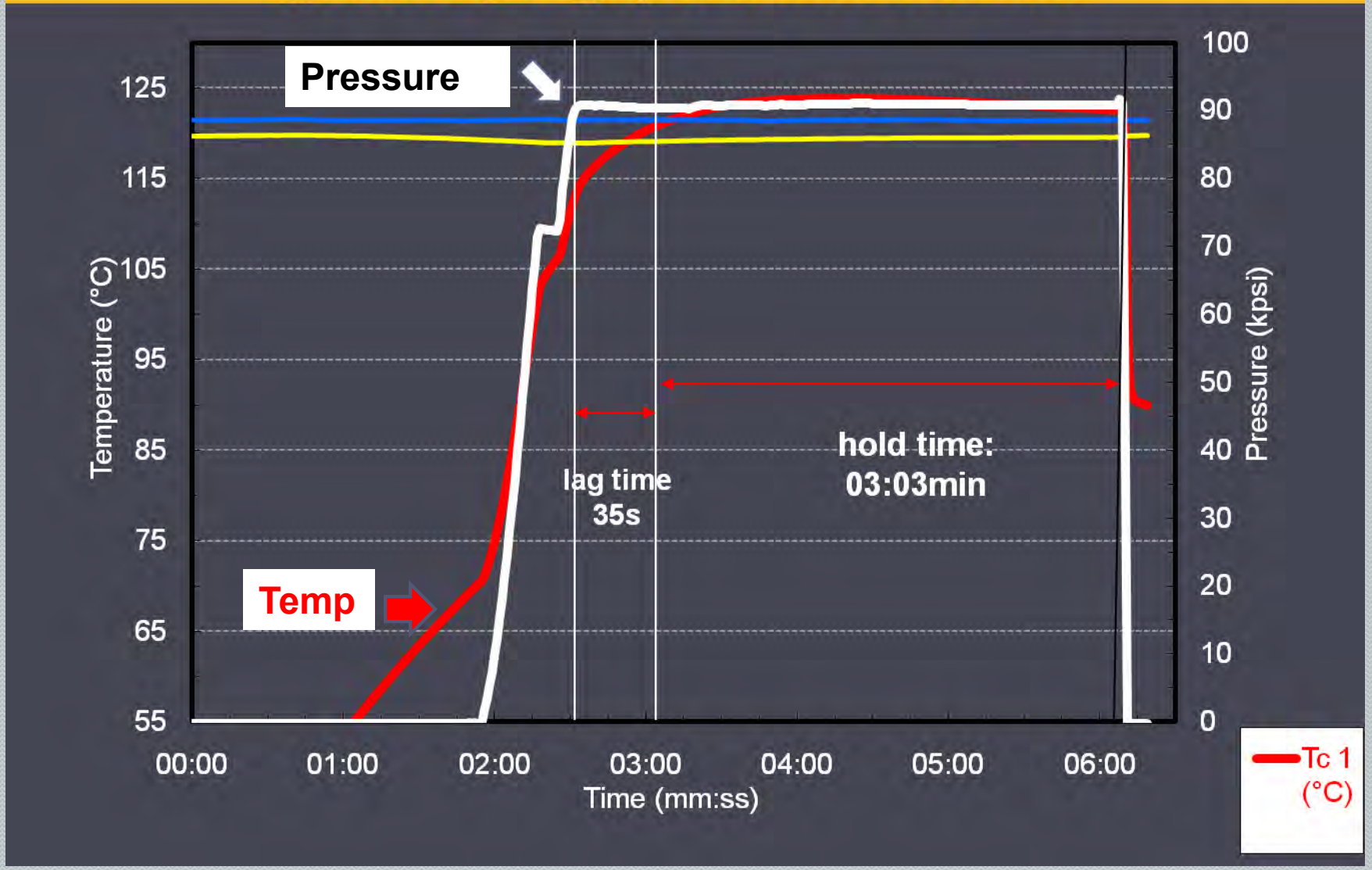
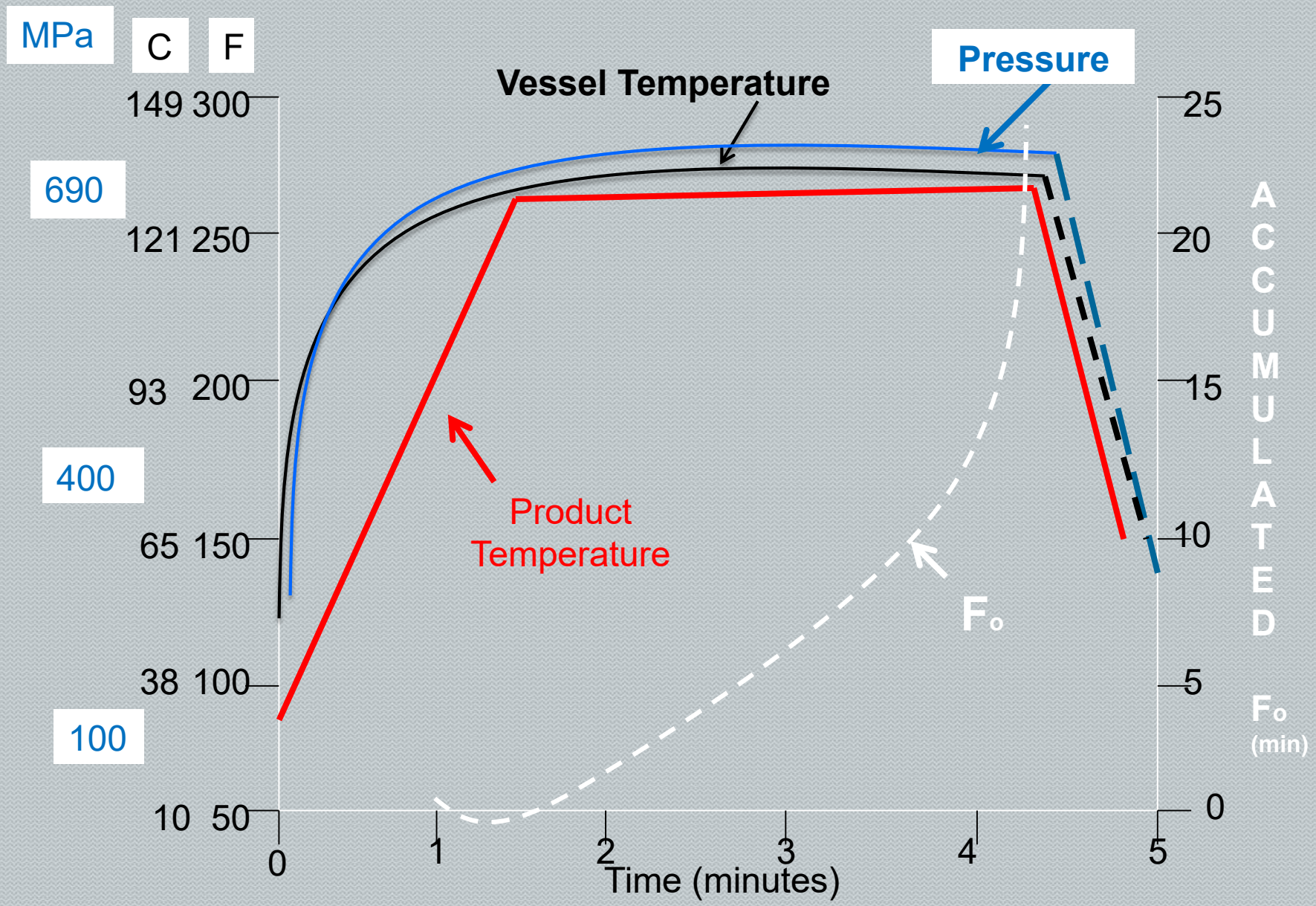
Hydrostatic Press



Preliminary graph developed for process temperature (121C), pressure (90 kpsi) & 3.0 min hold time



Idealized PATS Process with F_o Estimates



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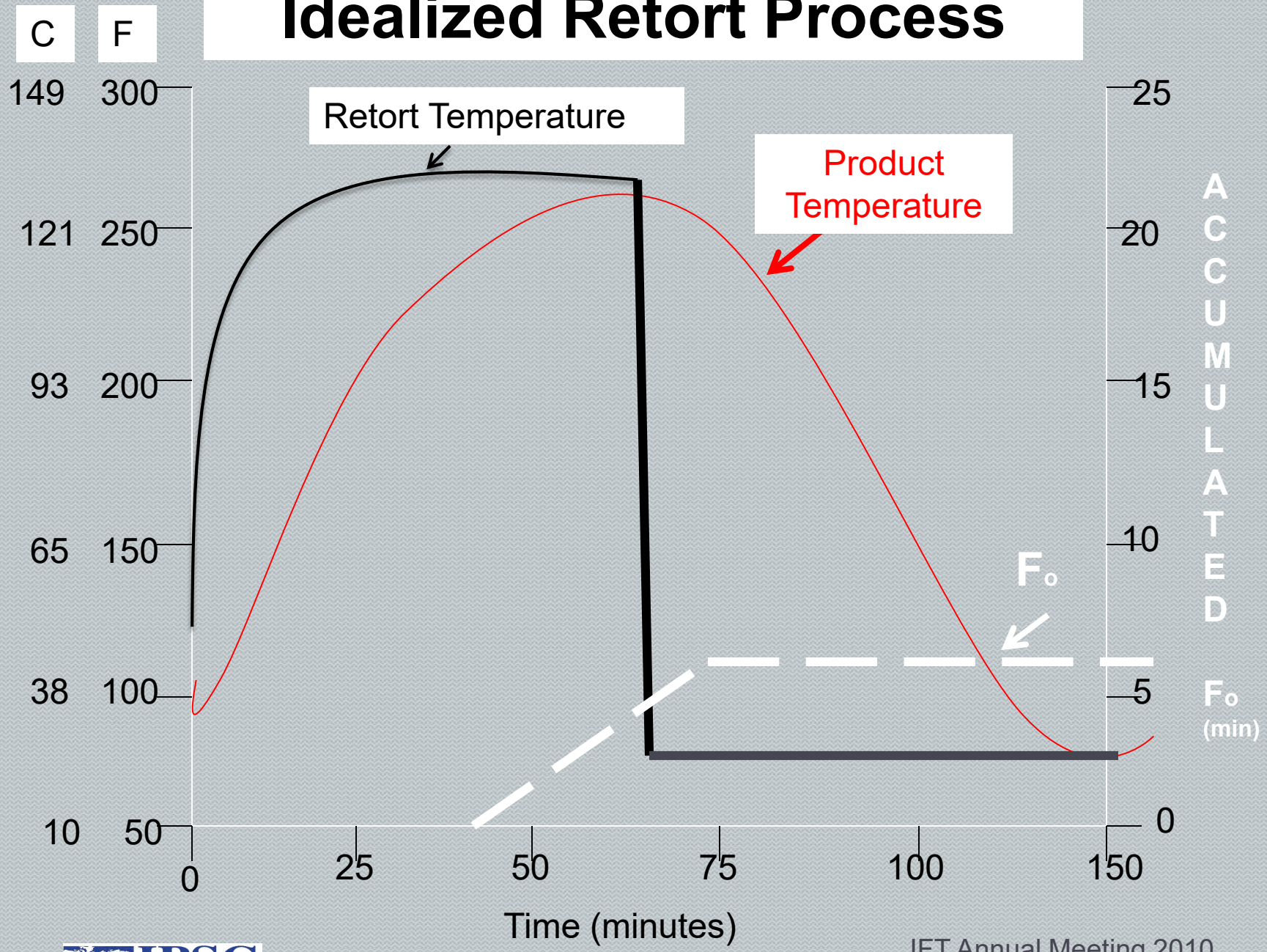
Idealized Retort Process



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Mechanics of Process Validation

1. Form and train a multi-functional team in validation procedures
2. Develop a “Master Validation Plan”
3. Seek expert reviewers (peer review)
4. Develop “Process Validation Protocols“
5. Involve regulatory officials
6. Initiate trials according to Protocol
7. Analyze the data
8. Report findings

Elements of Process Validation

Installation qualification (IQ) - Establishing confidence that process ***equipment*** and ancillary systems are ***capable*** of consistently operating within ***established limits*** and ***tolerances***.

Process performance qualification (OQ) - Establishing confidence that ***the process*** is effective and ***reproducible***.

Product performance qualification (PQ) - Establishing ***confidence*** through appropriate testing that the ***finished product*** produced by a specified process meets all pre- determined release requirements for ***functionality and safety.***

Source: USFDA

Validation Protocols?

A written plan stating how validation will be conducted including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

- **Determine *what* to measure**
- **Determine *how* to measure**
- **Determine *how many* to measure (statisti significance)**
- **Define acceptance/rejection criteria**
- **Define required documentation**

List of Protocols

1. Calibration of temperature measuring devices including traceability and known standards
2. Procedures for measuring/verifying pressurization
3. Mounting and configuring thermocouples to product pouches
4. Heat distribution studies for carrier in hot water tank with SOP for hot tank operations
5. Heat penetration studies for product in hot water tank
6. Thermal mapping of HPP vessel using empty an empty carrier
7. Heat distribution studies within HPP unit
8. Heat penetration studies within HPP unit
9. Product filling and net weight confirmation
10. Vacuum sealing of pouches and seal integrity testing
11. Product formulation and physical testing methods
12. Biological Validation - Microbiological challenge testing protocols – spore production, calibration, and inoculated pack protocol

Product Considerations

- **Formulation** – Critical factors for FDA
- **Key performance attributes** - Thermal conductivity, moisture, Aw, pH, viscosity, solids, salt
- **Background microbiological** - Assessment of normal flora and microbiological stability studies

Packaging Consideration

- MRE US Military-type polymeric pouches
- Pre-formed with three of four seams formed (at receipt)
- Net weight
- Filled pouch profile and thickness
- Thermocouple mounting
- Setup and operation of closing machine
- Headspace (vacuum)
- Seal integrity testing
- Polymer performance under extreme pressure and heat (cosmetic defects v. functional defects)

Equipment Considerations

- All-Pak liquid filler –**setup and calibration**
- Hot water tank (Avure Technology) Resistance Thermal Device (RTD), Transmitter: Inor APAQ-LR and RTD: Watlow RFJBOTK150BB300 - **Thermal distribution and Heat Penetration**
- Product Cage and Carrier – **Loading, Assembly and Lock**
- Type K beaded wire thermocouples -Omega Eng., Product TC P/N: KMQSS-062U-60-RP; Response time: is 0.3 sec. to 63.5% of temperature, ungrounded 304SS sleeved style. Pressure vessel thermocouples –Avure - **(calibration)**
- Omega Type K –EXFF-K-24 Wire thermocouples- **(calibration)**
- Pressure transducers - Omegadyne Inc., P/N: PX91P1-120KPSI, Linearity: +/- .5% fso **(calibration)**
- Intensifier- **water temperature and speed verification**
- QUINTUS Food Autoclave Press QFP-35L-600 High pressure vessel (Avure)- **Pressure and temperature verification**

Key Processing Consideration

1. Product cage/carrier assembly immersed in hot water-filled tank to achieve specified **product initial temperature** (based on heat penetration studies)
2. Carrier/Cage transfer time and associated thermal losses
3. Pressure vessel temperature – **wall and process water**
4. **Process initial temperature** at onset of pressurization
5. Pressurization – **temperature of high pressure water**
6. Come-up-time- for both **processing pressure** and **processing temperature**
7. Holding time - temperature and pressure
8. Product Temperature during pressurized hold
9. Accumulated lethality under worst case conditions
10. Decompression and cooling

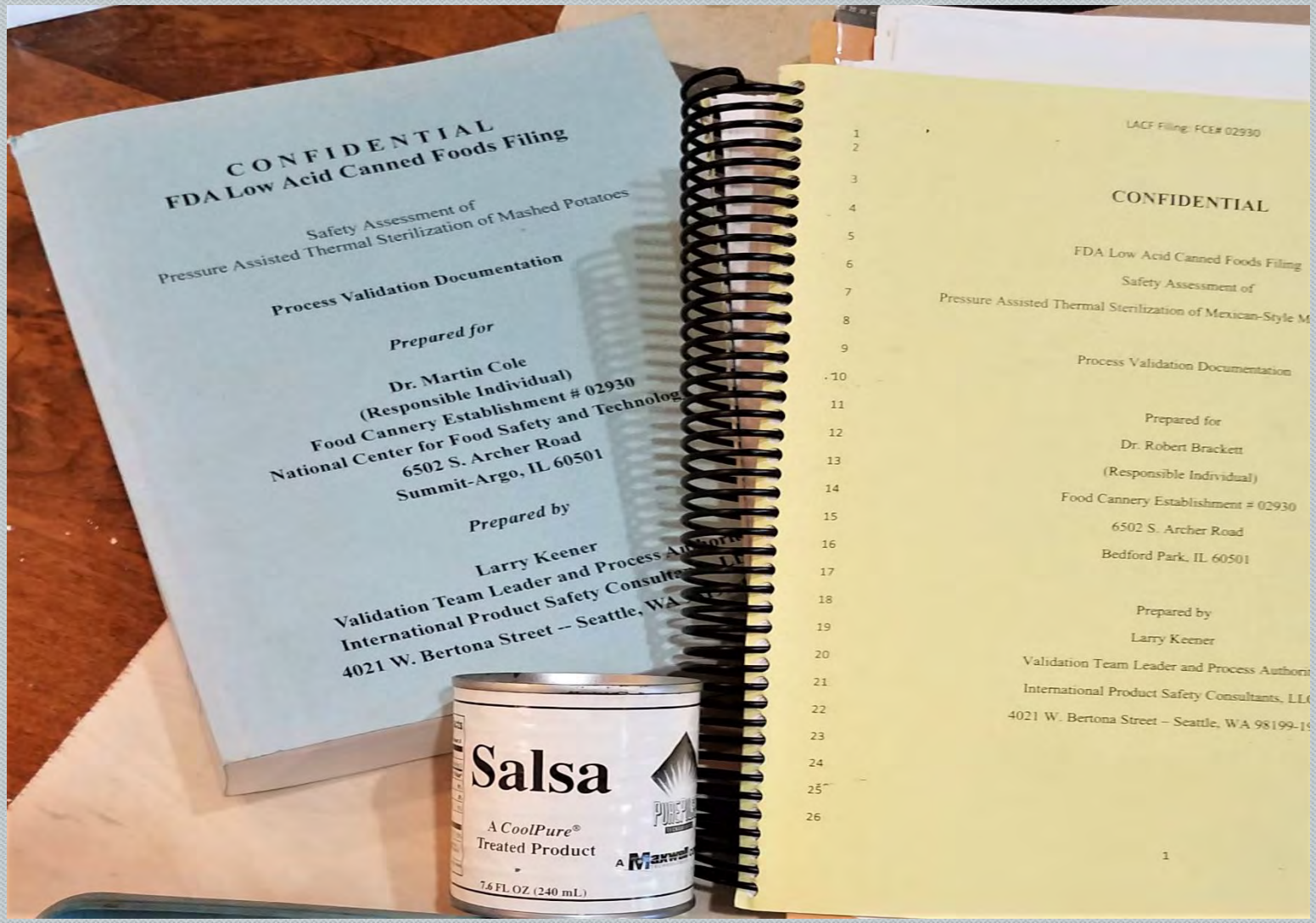
Trial Runs and Process Qualification

- Equipment shake-down trails (reliability studies)
- Qualification of temperature and pressure measuring devices (process critical measurement devices)
- Thermal distribution studies (steps 1 and 2)
- Thermal penetration studies (steps 1 and 2)
- Worst case production trials – numerous
- Preliminary inoculated pack studies (PA 3679)
- Biological validation trails (C. botulinum)

Data Analysis and Reporting

1. All data evaluated- Equipment, Process and Product
2. PATS Process calculated
3. Challenge study data evaluated
4. 2541(a)
   - **A**. Product (21CFR108.35/113)
   - **B**. Processing Method – QFP35-600 High Pressure Press – Method(PATS)-Pouches
   - **C**. Critical Factors – Formula, net content, headspace, product I.T., applied pressure, hold time at pressure and process temp.
   - **D**.- Scheduled process- **Step 1** criteria achieving product I.T. **Step 2** sterilization parameters 690MPa, 121.1C for 3 minutes

Outcome



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Thank You