Acerta® Disposable Filling System

The Evolution of a New Disposable Filling Technology for Sterile Pharmaceuticals

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Millipore Corporation

Innovative Enabling Technologies for Disposable Manufacturing

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Presentation Outline

- Introduction
- Background on Technology
- Prototype Systems
- Current Hardware Design
- Scale-up of Technology
- Disposable Component
- Validation / Qualification

Introduction

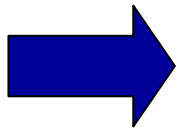
- Technology is scheduled to be launched in middle of 3rd Quarter of this year (not yet commercially available)
- This technology with disposable and pre-sterile product contacts parts was pursued as part of our *Disposable Manufacturing Initiative*
- Initiative includes expanding our product line offerings beyond our filtration product lines (Opticap® and Millipak®) to include product more complete process unit operations
- Designed to give the marketplace options to help speed the time to clinic & market and/or reduce the capital investment required for initial product development along with enhanced process security
- The initiative also has resulted in our recent Bioprocessing Alliance with Hyclone which gives us access to their Bioprocess Container product line with the CX5-14 Film

Why Adopt Disposable Manufacturing Technologies? Enhanced Process Security

PDA-Identified Major Sources of Contamination*

1. **Personnel contamination**
2. Non-routine activity
3. **Aseptic assembly**
4. Human error
5. Mechanical failure
6. Airborne contaminants
7. **Improper sanitization**
8. Surface contaminants
9. Material transfers
10. Failure of 0.2 μm filter
11. Failure of HEPA
12. **Improper sterilization**

* PDA Industry Aseptic Processing Survey 2001



Minimize Process Risk

- Eliminates cleaning after use
- Reduced CIP or SIP
- Minimizes validation efforts
- Complete containment of product
- Increase cleanliness, reducing risks for operators

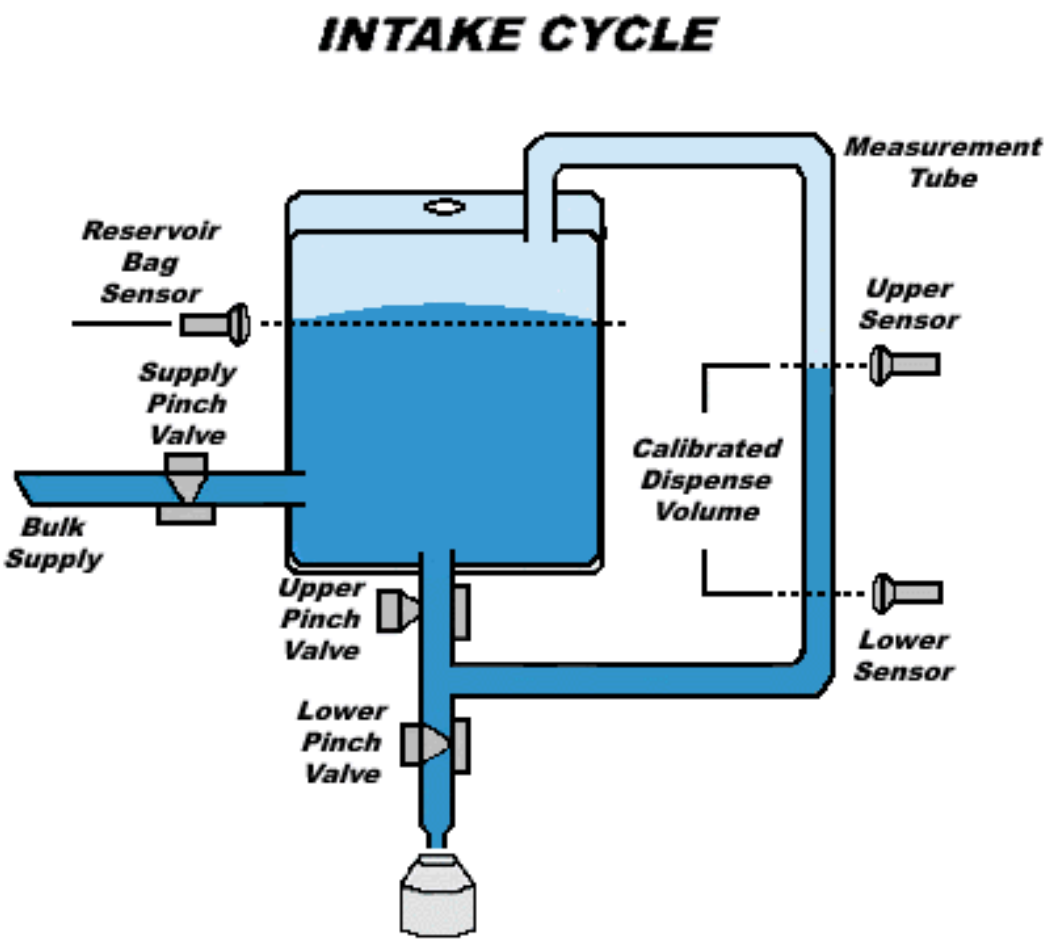
Background on Technology

- Short History
- The patents covering the technology “Volumetric Fluid Dispensing Apparatus” by Denis Keyes et. al. were licensed by Millipore
- Before licensure there were a few iterations of the technology produced
- We took the last iteration, made some improvements in design and performance and designed a system for demonstration and testing with the assistance of a consulting engineer with a background in filling machine technology
- The effort lead to Millipore’s first prototype system

Technology Highlights

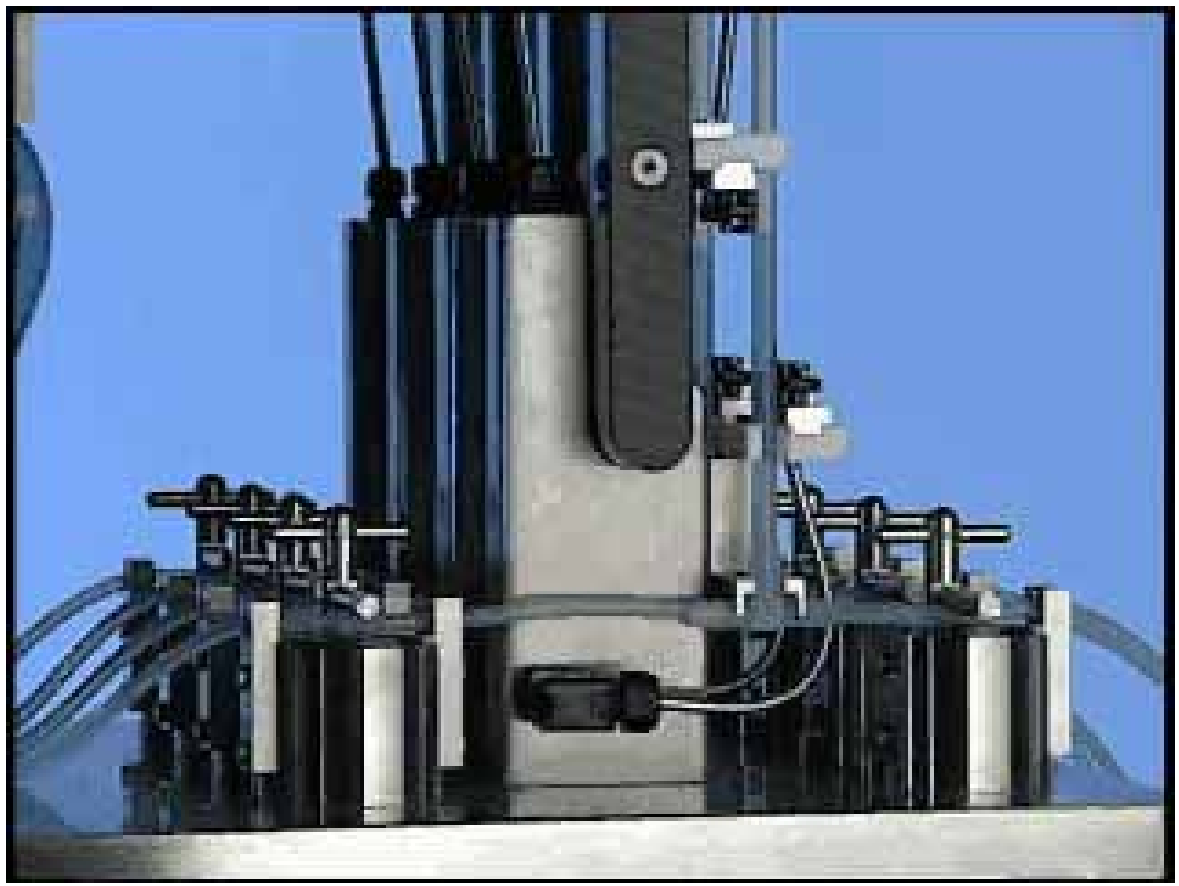
- It enhances product and operator safety
- Does not require autoclaving or steam-in-place
- Eliminates aseptic assembly of parts
- Offers the total containment of product
- Disposable component eliminates the need for post-use cleaning
- Disposable assembly easily snaps to hardware component
- Multiple head flexibility
- Designed for new or existing filling lines
- Patented gravimetric / volumetric dispensing system based mainly using the interaction of optical sensors and pinch valves
- Intended for use with final sterile injectables- initial filling capability for small volume, aqueous liquids (approx. 0.2 to 10 grams)

Animation of Filling Process with the Acerta System

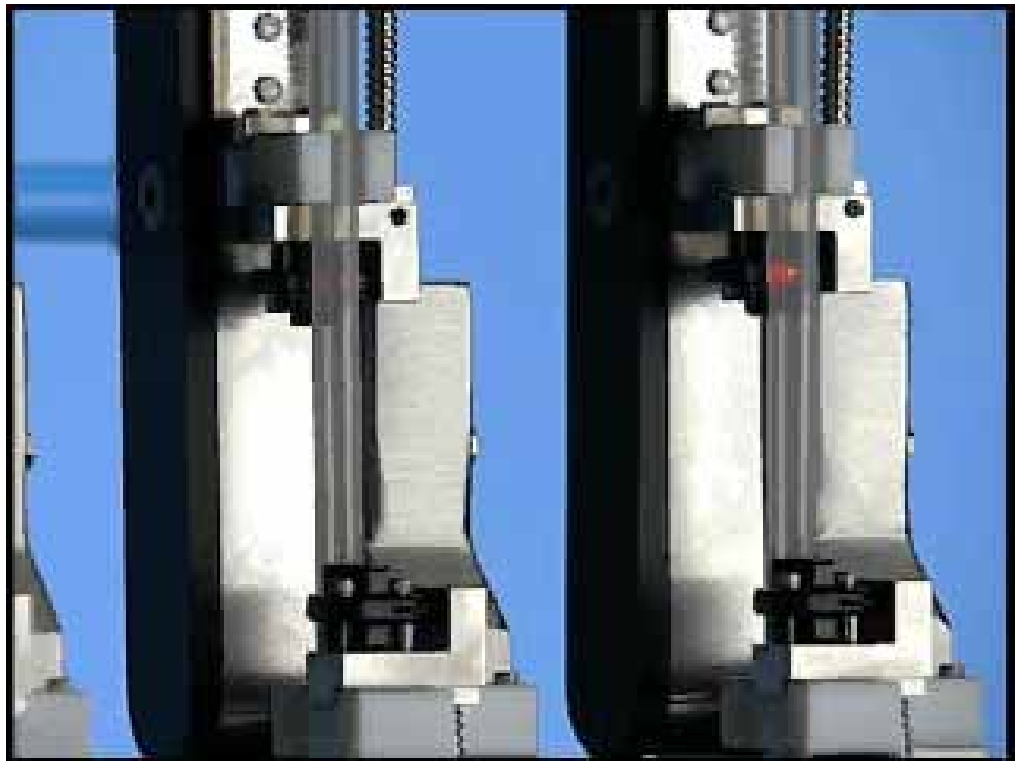


Prototype System

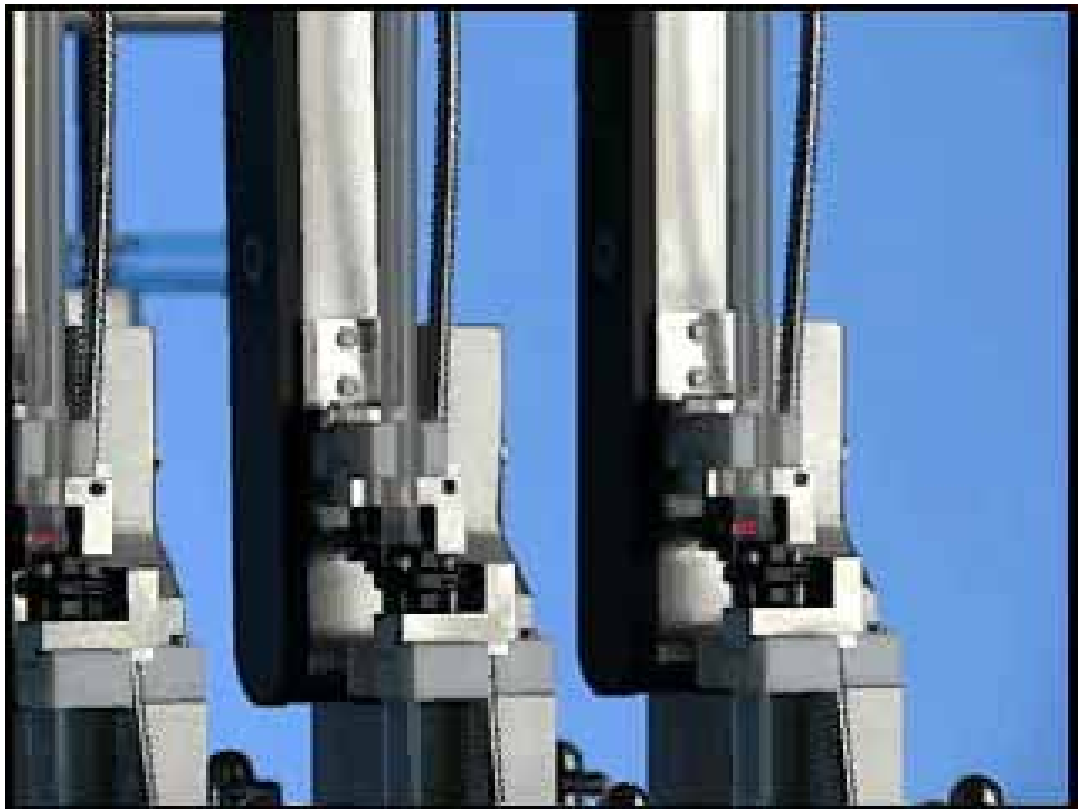
Prototype System Operation-
Interation of Light Sensors and Pinch Valves



Light Sensor-
Detects Liquid to Activate Cycle Change



Volume Adjusted-
by Changing Upper Sensor Position



Data From Trial of Acerta Prototype System

- Trials completed in November 2002 at Pharmacia (now Pfizer) in Nerviano, Italy
- Complete Presentation first delivered by Per Sivertsson from Pfizer at the PDA Conference in Prague- February 2003
- Presentation Title “Disposable systems
an interesting alternative for aseptic manufacturing”
- Excerpts now presented courtesy of Pfizer

Pharmacia-PDA presentation modified for PDA Chapter meeting- Acerta Only.ppt

Outcome of Market Analysis (Including Testing at Pfizer)

- Design improvements to make it more sanitary for an aseptic processing area
  - Optimized for wipe down
  - Removal of fan for cooling the control panel
- Improvement in setting the initial target fill weight
- Easier to use operator interface for production personnel
- Functionality to prevent product loss and downtime
- Have a version to be used for small scale production
  - Designed for low hold-up volume
  - Designed for optional use in a Biological Safety Cabinet for Manual Filling (small foot print)
  - Scalable to a Four Head (or multi-head) system

Current Hardware Design- Modular Design

Single Head - Designed for Integration to Filling Line or used in a BSC (to be avail.)

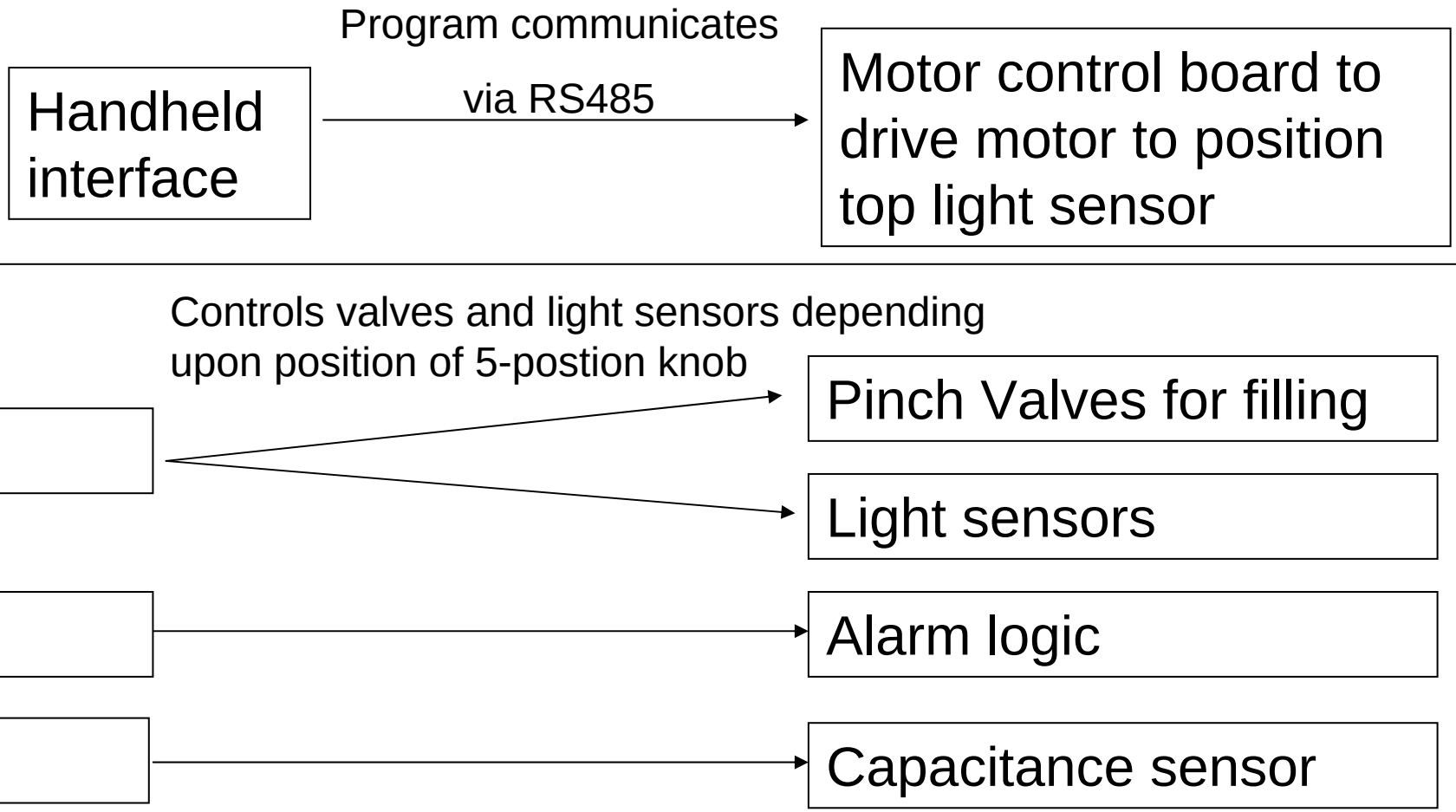
Four Head - Designed for Integration to Filling Line (only beta version now)

Acerta™ Hardware Components Filling Line Integration

Main Components (excluding enclosure):

- Power Supply (not shown)
- Integrated Circuit Board (ICB)
- Capacitance sensor for product reservoir level control system
- Pinch Valves
- “Towers” consisting of:
  - Servo positioning motor w/control board
  - Light sensors
  - Slide mechanism to move the top sensor
- Handheld Computer (with preprogrammed firmware)

Logic


Program communicates
via RS485
Handheld interface
Motor control board to drive motor to position top light sensor
Controls valves and light sensors depending upon position of 5-postion knob
ICB
Pinch Valves for filling
Light sensors
ICB
Alarm logic
ICB
Capacitance sensor

Manual Filling Specific Qualification- Microbiological Challenge Successful

- Test Completed in Biological Safety Cabinet - SG603 from The Baker Company
- Product Protection Test - Challenged with a bacterial aerosol spore concentration of 8 X 10^6 spores per ml delivered each 5 minutes (as per NSF).
- Personnel Protection- Challenged with a bacterial aerosol spore concentration of 8 X 10^8 spores per ml delivered each 5 minutes (as per NSF)
- Tests run in triplicate
- Results - Pass

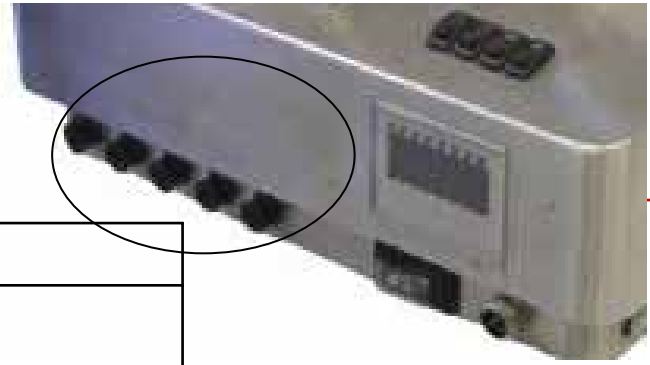
Acerta System in Action

- Single Head System ..\Video\2004 Videos\Single head on a filling line\Acea.mpg
- Four Head System ..\Video\2004 Videos\AcertaTS.rm

Three Modes of Operation

- Manual Dispense Button
- Foot Switch
- Signal From a Filling Line

I/O Connections



Connector	Signal
J1 Computer	RS485
J2 Pump	Peristaltic Feed Pump Control
J3 Inputs	Dispense Signal From Filling Line Signal from Filling Line if Vial is Missing
J4 Outputs	Fill complete signal External Alarm Signal
J5 Footswitch	Foot switch input

Scale-up of Technology to Multi-head Systems

- Partner with Filling Machine Manufacturers (OEM Program)
  - Have discussed the technology with the major companies in the industry
  - At an end-users request, they are willing and able to integrate the system to their filling line
  - Market Survey was conducted on their expectations from Millipore to support the OEM Program
  - They liked the modular design
- We want to stick to our core competence in the area of in the delivery of process solutions in the area of the disposable assemblies (where the OEMs have little expertise and experience)

Scale-up of Technology Options

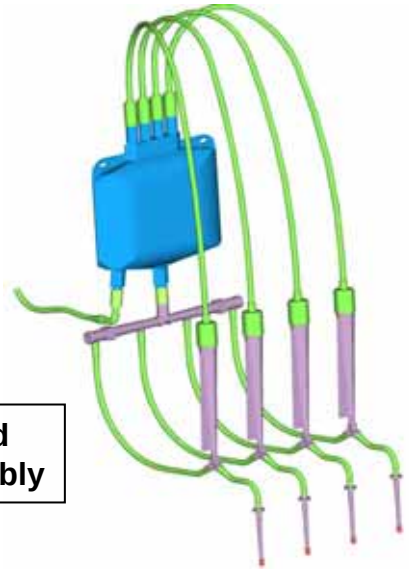
- Portable System (shown previously)
- Integrated System (here)

Sterifill F 200 , photo courtesy of www.ima.it

Acerta Disposable Assembly

Single Head

Four Head Beta Assembly



- Arrives triple-bagged and sterile (by gamma)
- All liquid contact parts are completely disposable
- Removes the need for validated cleaning procedures and increases safety

Acerta Disposable Assembly Highlights

- Materials
  - Reservoir — LDPE product contact layer
  - Tubing — Platinum cured Silicone and Pharmed
  - Fittings — HDPE
  - Needles — Polycarbonate
- All materials not toxic per USP Class VI Biological Test for Plastics
- Pre- Sterilized - Gamma Radiation using validated methodology
- Tripled bagged and boxed and tested per ISTA 2A
- LAL Bacterial Endotoxins Test $\leq$ 0.5 Eu/mL
- Meet TOC Specifications for WFI (<0.5 ppm TOC)
- 100% Integrity Tested using a validated leak test
- Must maintain integrity after being pressurized at 1 psi for 8 hours
- Meet USP 26-NF21 sec 788 for particles

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Acerta Hardware Highlights

- Filling Performance
  - 0.2 – 1g @ 40 fpm
  - ≤ 5g @ 20 fpm
  - ≤ 10g @ 10 fpm
  - ≤ 20g @ 7 fpm
    (0.5 – 1g at +/- 5mg; > 1g at +/- 0.5%)
- CE Compliant
- IP 54 Enclosure rating
- Easy access to pinch valves for maintenance

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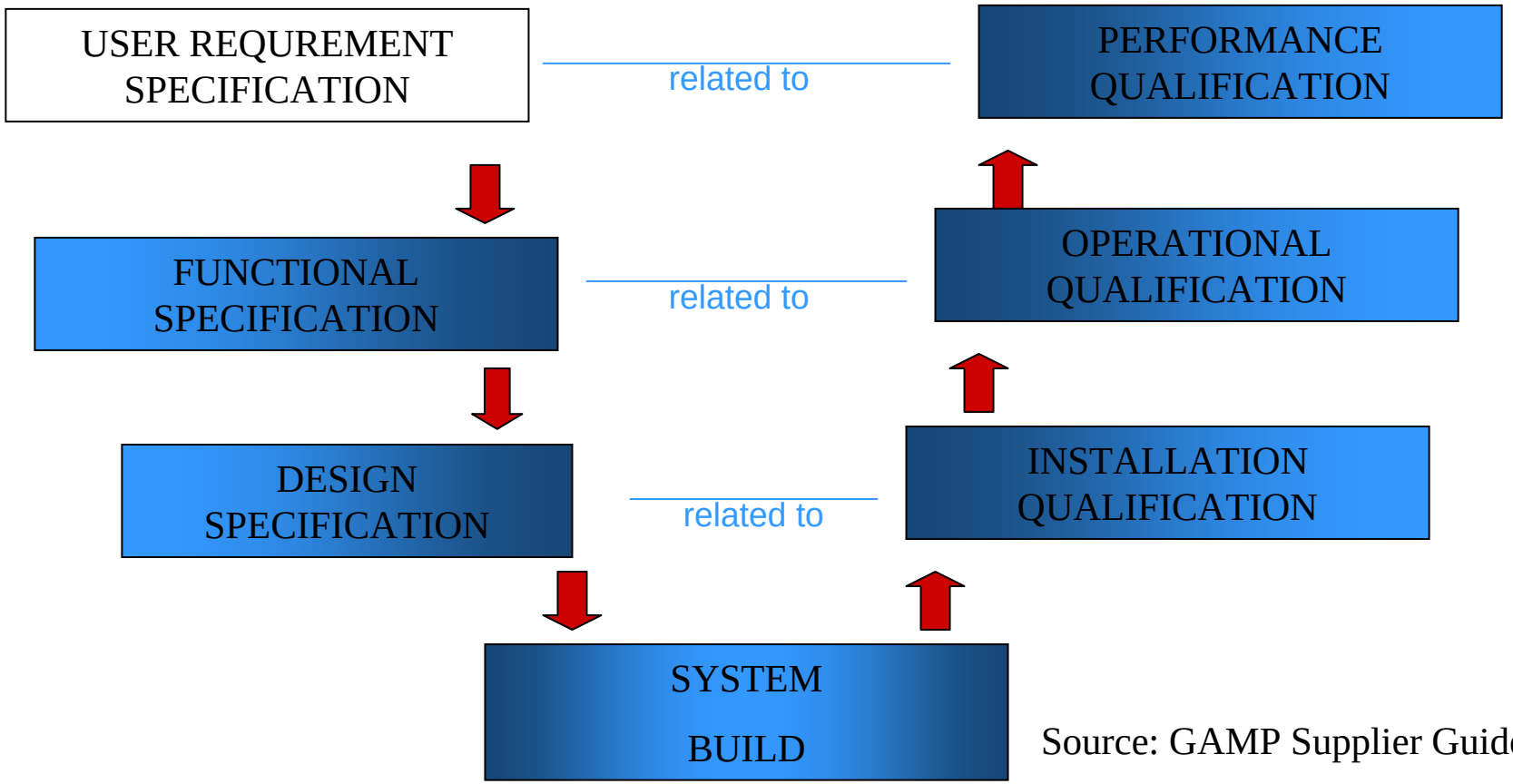
Validation, Qualification, and Implementation of Acerta System Into Your Process

- Application Support: "Will it work with my products attributes?"
  - Handled by local Applications Specialist with support from R&D Applications Engineering via demo systems
- Will have available cost model
- Extractables from Disposable Assembly
  - Will offer Extractables Validation Support Program similar to filter extractables program via our state-of-the-art Access^{sm} Service Labs
  - Components were optimized in R&D Program
  - Protocol developed System Acceptance Testing
- Support customers in product adsorption protocol development
- Disposable Assembly Certificate of Quality with Lot Release Criteria (Including lot sterilization information)

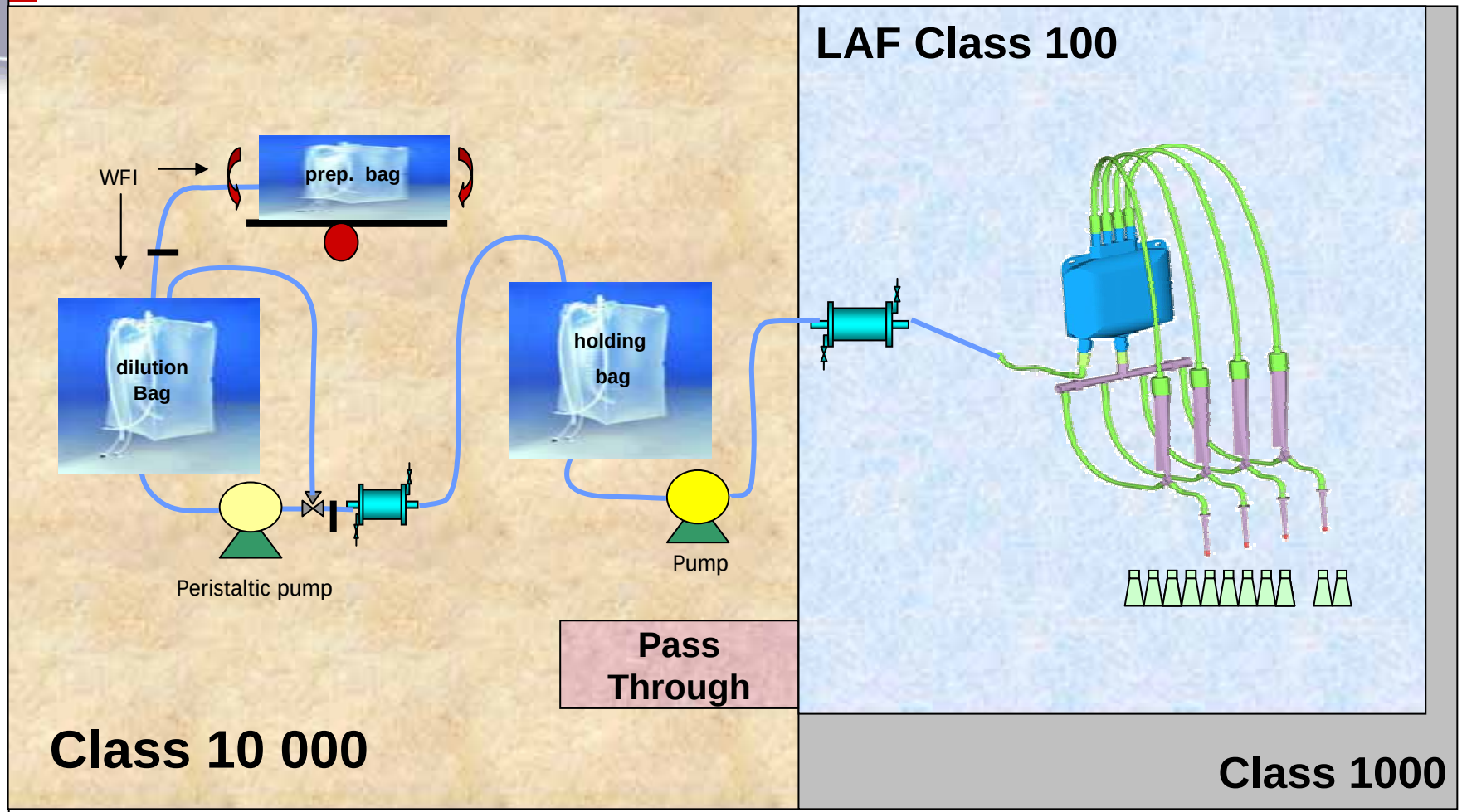
Hardware Developed Using GAMP Life Cycle Methodology GAMP 4 V-model

- Hardware Validation Documentation Package Only
- Hardware Execution services



Source: GAMP Supplier Guide

Future Disposable Final Fill and Finish Clean Room Process



Summary of Potential Benefits

Advantages of:

- **No CIP**
- **No SIP**
- **No Aseptic Assembly of Parts**

Offers potential benefits of:

- **Reduced set-up time**
- **Improved turnaround time**
- **Reduced validation efforts**
- **Reduced risk of contamination**
- **Speed in time to market**

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