Product Protection by Design

Container Closure Integrity Assurance

Austin Caudle
SmartSkin Technologies

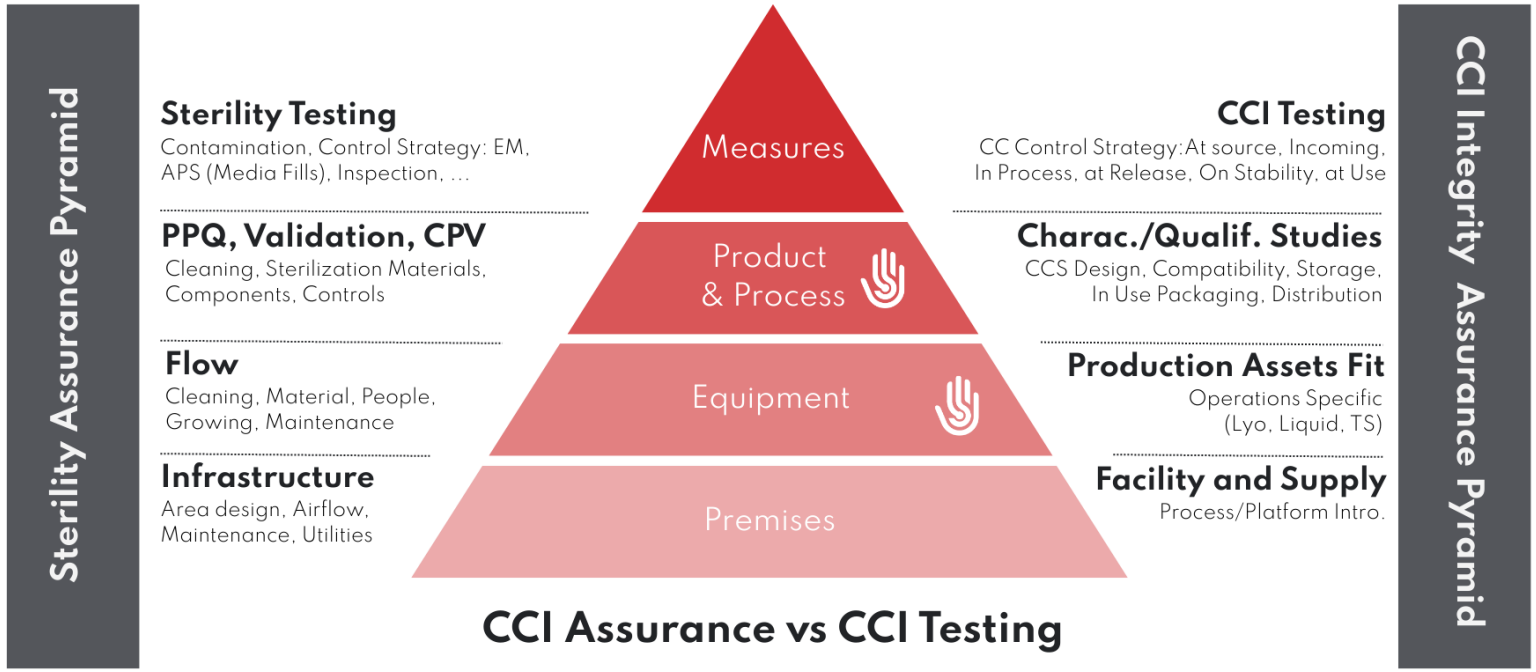
Overview

- Product Protection: Sterility Assurance and CCI Assurance
- Regulatory Context, Industry Updates: PDA TR27 and USP <1207> Revisions
- SmartSkin Technologies and CCI Assurance

Sterility Assurance & Container Closure Integrity

SMARTSKIN TECHNOLOGIES

Assurance Architecture is Pyramidal



CCI Assurance vs CCI Testing

Sterility Assurance - Container Closure Integrity Assurance Analogy Decoder

SMARTSKIN TECHNOLOGIES

- Sterility is ONLY Confirmed by Sterility Test (Pass/Fail)
- Container Closure Integrity is ONLY confirmed by CCIT (Pass/Fail)
- Sterility is assured by designing it into the facility, the aseptic production flow, its qualification and validation of aseptic and implementation of the suitable control strategy
- Similarly, Container Closure Integrity is assured by designing an integrated Container Closure System from selected components, secure it during its assembly by the qualification and validation of processes and equipment used before, during and after aseptic product filling. Its control strategy will build specific to the product presentation. “One Size does not Fit All “

CCI Assurance – A holistic approach that secures product protection until patient use (outside Aseptic Filling area!)

CCI Assurance is built and secured across the Product Life Cycle

Product Protection for Injectables

SMARTSKIN TECHNOLOGIES

- **Aseptic Manufacturing:**
  Focus on Sterility Assurance by Design
- **Sterile Product and Process Lifecycle**:
  Focus on CCI Assurance to Secure Product SISPQ
- **Synergy and Knowledge**
  Science based Process Understanding *(i.e Annex 1)*

Container Closure Integrity is a Governing Rule for Injectables

Assuring CCI is a Product Life Cycle Journey (Annex 1)

Regulatory Hierarchy: How CCS Fits

FDA

SMARTSKIN TECHNOLOGIES

Federal Food, Drug, and Cosmetic Act

21 CFR Part 211
(Current Good Manufacturing Practice)

Subpart E: Control of Components and Drug Product Containers and closure

§§ 211.80 - 211.94
(Specific CCS Requirements)

Guidance Documents & Industry Standards
(USP, CCIT Guidance)

SMARTSKIN TECHNOLOGIES

Key Risks Controlled by Subpart E

Ensures Container-Closure Integrity (CCI)	• Evaluation of container-closure systems • Assurance they protect against microbial ingress
Prevents Introduction of Microbial Contamination	• Components tested and controlled before use • Containers and closures (e.g., vials, stoppers) are suitable for sterile use
Controls Pyrogen/Endotoxin Risks	• Testing and qualification of incoming materials • Supplier quality oversight • Depyrogenation process validation
Prevents Chemical and Particulate Contamination	• Qualification of suppliers • Defined specifications for components with lot to lot traceability
Requires Supplier Qualification and Material Traceability	• Materials that leach chemicals into product - compatibility studies required • Materials that shed particles - Visual inspection and particulate testing

21 CFR 211.94 – Container Closure Requirements (Sterile Focus)

FDA

SMARTSKIN TECHNOLOGIES

Container-closure systems must **protect, not interact, and maintain sterility**

Compatibility (211.94(a))

- Not **reactive, additive, or absorptive**
- No impact on **identity, strength, quality, purity**
- Controls **leachables & extractables risk**

Sterility Protection (211.94(b))

- Provides **barrier against microbial & particulate contamination**
- Maintains **Container-Closure Integrity (CCI)** through shelf life

Cleaning, Sterilization & Depyrogenation (211.94(c))

- Must be **cleaned and sterilized** as appropriate
- **Depyrogenation processes validated** (critical for parenterals)

Handling & Storage (211.94(d))

- Prevent **contamination, mix-ups, and environmental exposure**
- Controlled conditions from **receipt → use**

Container Closure Integrity Testing (CCIT) Expectations for BLA

FDA

SMARTSKIN TECHNOLOGIES

CCIT in lieu of sterility testing as a component of a stability program	• To ensure that containers are able to maintain sterility throughout the drug product's shelf life (every 12 months until expiry). *Guidance : Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products* (February 2008)
CCIT performed as part of capping/crimping parameter validation for vials	• To demonstrate the integrity of the vials after worst-case capping/crimping conditions
CCIT performed after the assembly of the pre-filled syringe and device	• To demonstrate that the assembly process did not affect CCI

11

Revision of PDA TR27 on Parenteral Packaging and CCI Assurance

SMARTSKIN TECHNOLOGIES

Why Revise TR 27 and Incorporate TR 86?

- TR 27 was last revised in 1998 (28 years ago!)
- Innovation in therapeutics and drug delivery technologies
- Industry best practices have evolved and changed
- Holistic risk-based and product life cycle approach
- Emphasis on building "CCI assurance" into the product development and manufacturing process to reduce risk
- TR 86 (published in 2021) discusses challenges with CCI technologies and testing at cryogenic storage conditions
- Scope includes syringes, drug delivery devices, flexible bulk containers, and IV bags

Images from pda.org

PDA TR27 on Parenteral Packaging –Revision will Include

SMARTSKIN TECHNOLOGIES

- Lifecycle Management of Pharmaceutical Packaging/ Integrity Assurance Through Product Development and Product Life
- Package Integrity and Leak Rate Specifications
- Inherent Package Integrity and Closure Assessment
- Manufacturing and Process Control
- Pharmaceutical Packaging/Integrity Assurance through Product Shelf-Life
- Package Integrity Testing Technologies

TR 27 Parenteral Packaging Revision Progress

SMARTSKIN TECHNOLOGIES

What are the Next Steps?

- Technical Peer review
- Scientific Advisory Board ballot
- Board of Directors ballot
- Publication

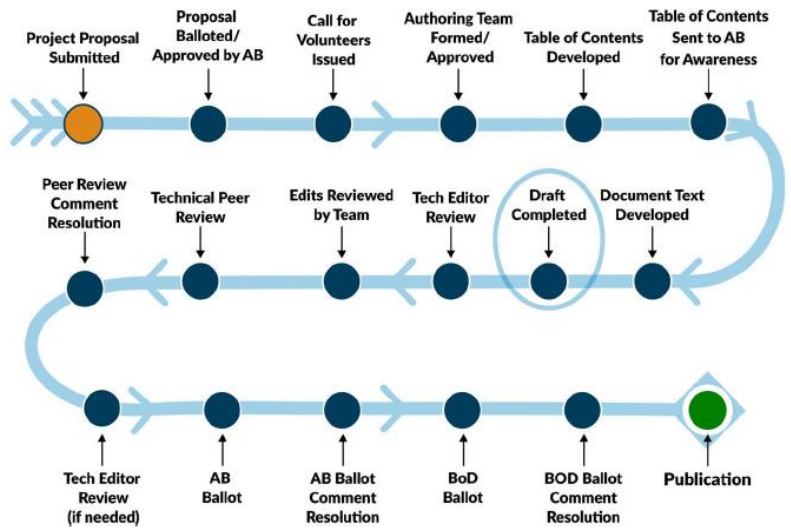


Image from the PDA Technical Report and Points to Consider Team Handbook, PDA Inc.

UPCOMING USP <1207> REVISION

Discussion Topics: Potential Revision

1 Risk-based, holistic CCI assurance strategy and lifecycle management based on the concepts of EU Annex 1

- QbD approach to CCI Assurance (QTPP and CQAs)
- Emphasize using an in-process control strategy to build CCI assurance into the manufacturing process to reduce risk

Which CCI technologies should be used during each phase of the product life cycle?

2 MALL Clarification

- How to determine MALL when the Kirsch Limit isn't applicable
- Correlation to microbial ingress risk – not industry standard

MALL for polymeric rigid and flexible packaging?

3 CCI testing with empty or surrogate-filled containers

- Biologics interfere with CCI tests (i.e., clog small defects)
- The manufacturing process is agnostic of product fill
- Cell and gene therapy batch sizes are too small

Can CCI testing be performed using empty or surrogate-filled containers in a holistic CCI assurance program?

4 Sub-ambient CCI

- Permanent vs. transient leaks
- Cold storage and freeze/thaw considerations
- Shipping and distribution studies

Which CCI technologies should be used for sub-ambient testing and what should be the temperature range of the method?

**Announced at 2025 PDA Parenteral Packaging Conference, Desmond Hunt, Sr Principal Scientist at USP*

UPCOMING USP <1207> REVISION

Discussion Topics: Potential Revision

5 Challenges with Positive Controls

- Industry best practices for creating positive controls
- How to handle clogged positive controls
- The number of positive controls that should be used during method establishment and routine testing

What does it really mean when a positive control does not meet the acceptance criterion?

6 Drug-led combination products, IV bags, and polymeric rigid and flexible packaging

- Best practices for testing these container-closure systems
- Typical detection limits

What is the recommended strategy for testing fully-assembled autoinjectors and pen injectors?

7 Sampling plans for products using systems other than fusion, large volume products, and stability testing

- Guidance on establishing a scientifically justified sampling plan for CCI testing
- Recommended sample size for stability and shipping distribution testing

How many samples should be tested for lot release and commercial product stability?

8 Modeling/in silico evaluation techniques to generate evidence of CCI assurance

- Statistical analysis of component dimensional fit
- Finite element analysis of interference fit
- Sensor-based estimation of seal quality

How can modeling or in silico evaluation techniques be used to generate evidence of CCI assurance?

11

LIGHTHOUSE

SMARTSKIN TECHNOLOGIES

CCI best practices will continue to evolve

Regulatory Landscape

Sterility in the ICH Q1 revision

Today	→	Tomorrow
ICH Q1A		
ICH Q1B		
ICH Q1C		
ICH Q1D		ICH Q1
ICH Q1E		
(ICH Q1F)		
ICH Q5C		

Acknowledgement: Andrew Lennard, Amgen

Augmented Manufacturing Intelligence is Needed to Change Status Quo

SMARTSKIN TECHNOLOGIES

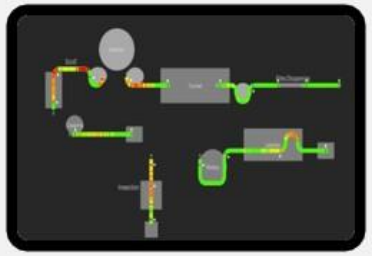
Digital Container Twin (Physical) + Software (AI)

Sensor-enabled replica Digital Containers Twins

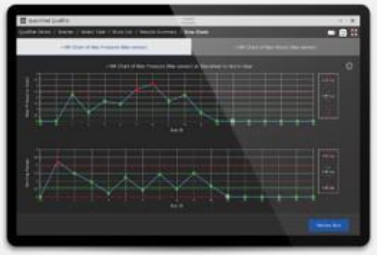
Forces Measured

To Make Visible, Measure and Eliminate Interactions at Product/ Equipment Interface

Diagnose



Optimize



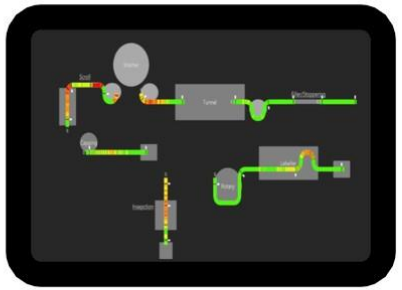
Qualify

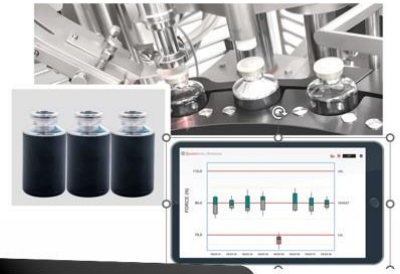
Manufacturing (Physically Assisted) Intelligence for Fill/Finish and Packaging Operations

SMARTSKIN TECHNOLOGIES

SmartSkin Technology and Product Protection CCI Assurance

Product Development Path Stages of Validation &Control	Technology Transfers
---------Stage 1 Validation -----	Tech Transfer (I)
Product & Process Design	*Production Of Clinical Materials*
--------Stage 2 Validation -----	***Tech Transfer (II)***
Process Qualification	*Clinical and Commercial Supply Validation and Registration Batches*
--------Stage 3 Validation-----	**Transfer (II-III-IV-----)**
CPV-Continuous Process Verification	Commercial Supply Expansion





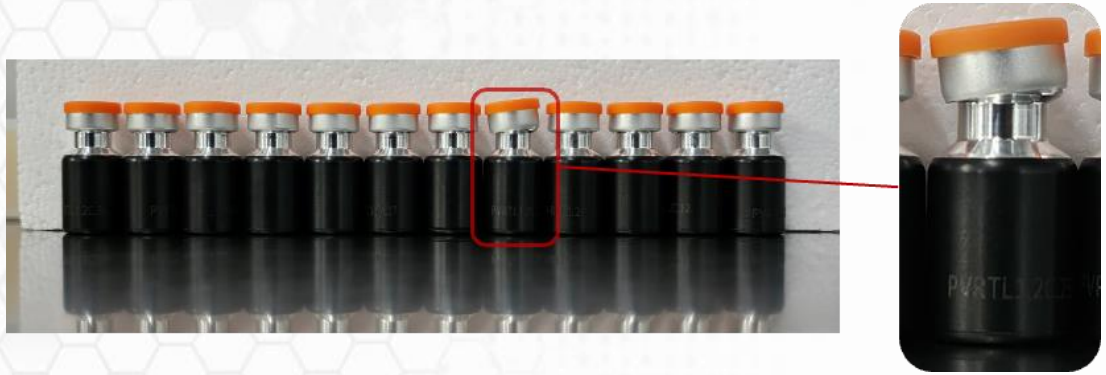
Anatomy of a Capping Event

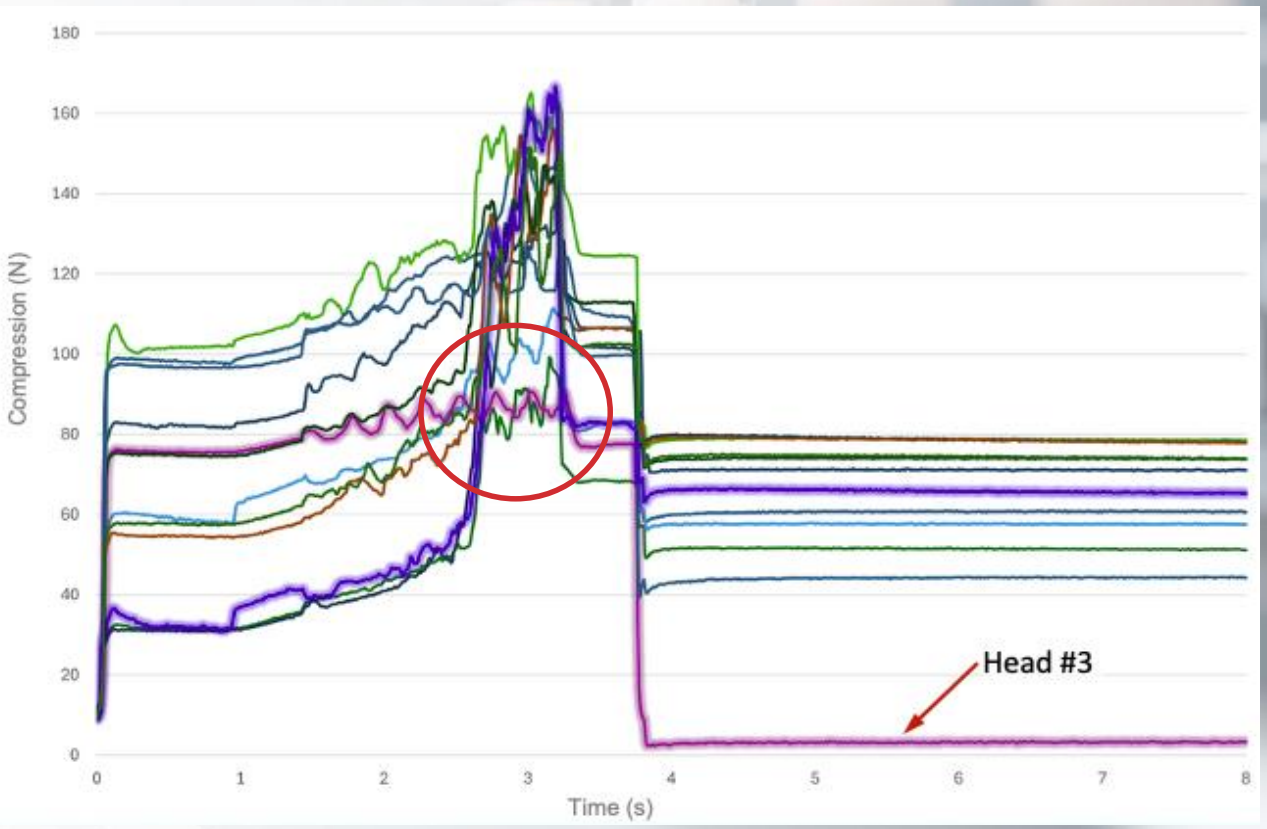
Multiple Capping Heads – Capping Seal Force Uniformity – Capping OQ/PQ

SMARTSKIN TECHNOLOGIES

Data from the container twin processed by Head #3 indicates insufficient crimp force.

Consequences: Increased risk of leaks, compromised container integrity, and contamination resulting in product loss.





Seal Assurance Digital Twin

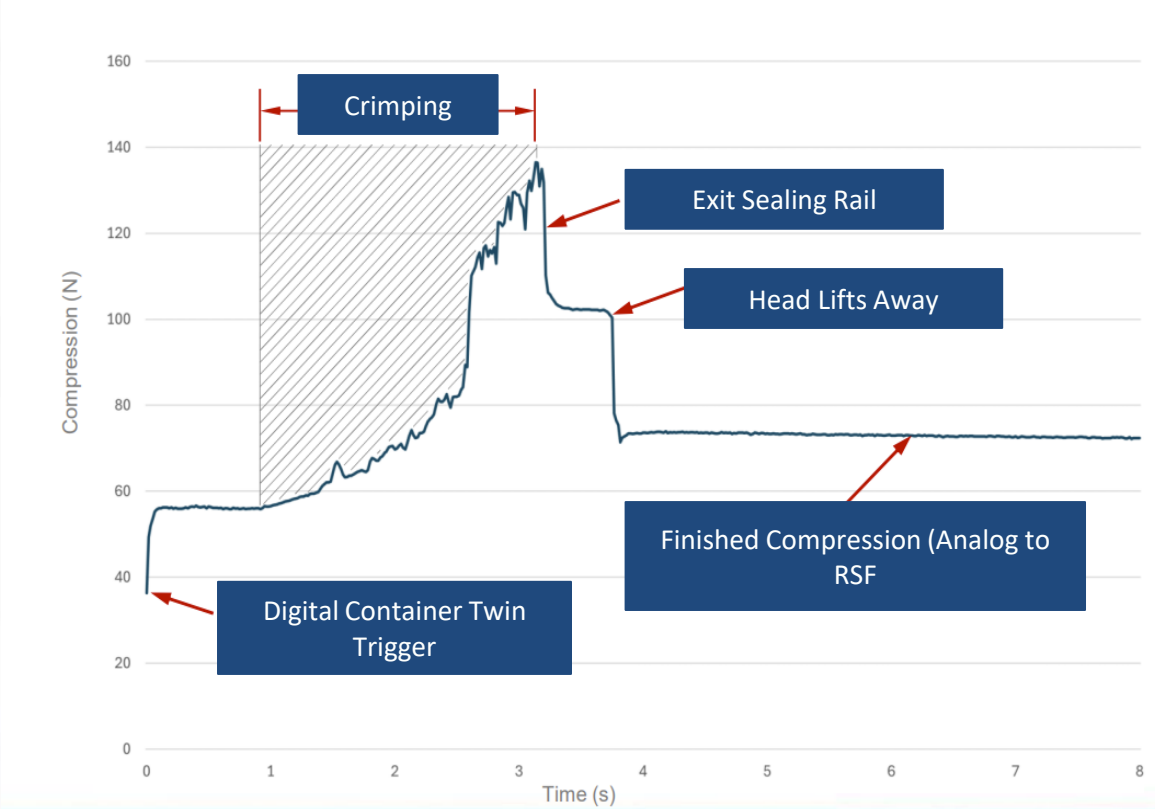
Ability to visualize process in real-time at production speeds

SMARTSKIN TECHNOLOGIES

- Measures forces at vial flange between stopper and vial flange — the interface that determines seal quality.
- Accepts standard stoppers; measures both top-load and crimp-applied force for a unique view of sealing dynamics.
- Captures compression during capping and seal tightness after head disengagement (analog to RSF).

Anatomy of a Capping Event

Example of a Seal Assurance Digital Twin: Capping Force Profile (Equipment Specific)



ANNEX 1: Manufacture of Sterile Medicinal Products

SMARTSKIN TECHNOLOGIES

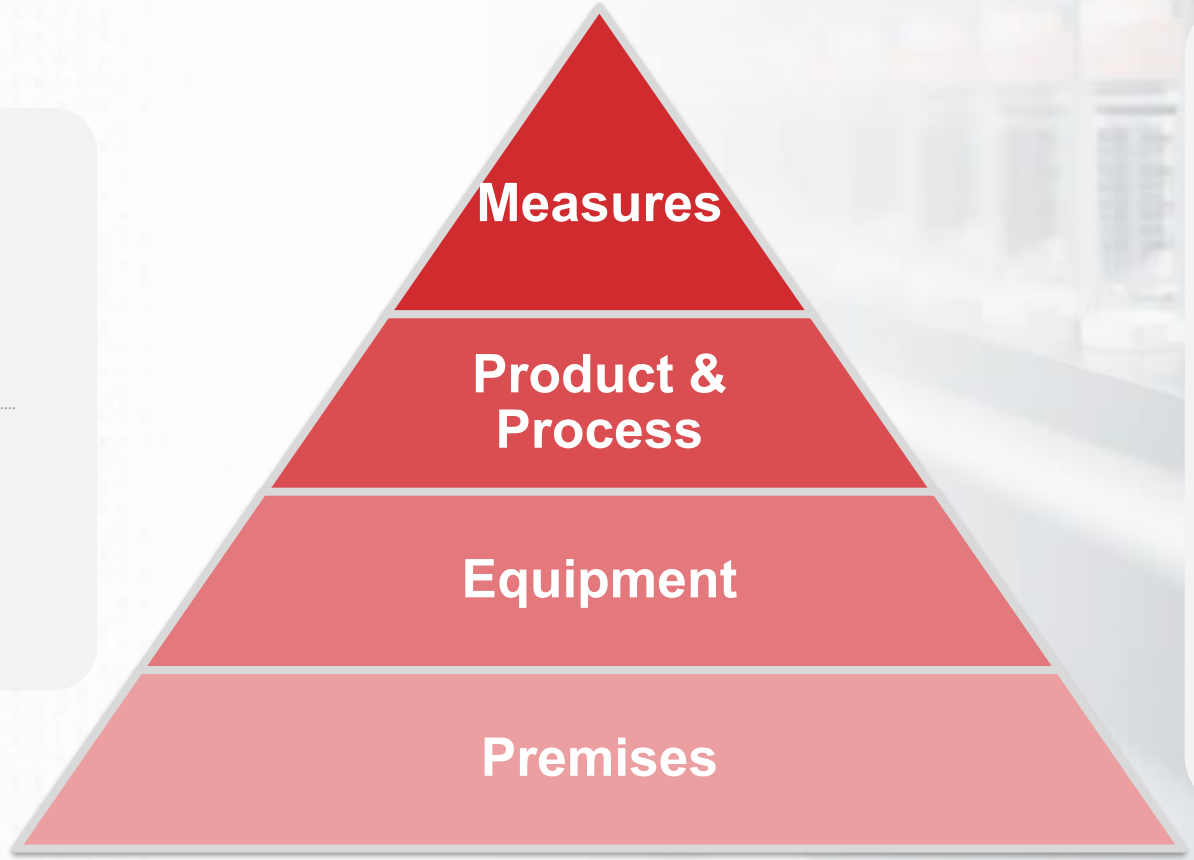
SmartSkin is enabling Annex 1 Compliance

European Commission

Contamination Control Strategy

Quality Risk Management

Production Quality Systems



SMARTSKIN TECHNOLOGIES

Contamination Control Strategy
Particles, Glass Contamination,
Proactive, Corrective Actions

Quality Risk Management
De-Risking Targeted Locations
Unit Operations / Process

Production Quality Systems
Enhanced Performance by Design

Thank You!

Q&A

Austin Caudle, MSc, MRQA
VP, Pharmaceutical

austin.caudle@smartskintech.com
(919) 217-4127, mobile / text

SMARTSKIN TECHNOLOGIES

info@smartskintech.com
+1 (855) 210-9006

SmartSkin Technologies
354 King St. Suite 195
Fredericton, New Brunswick
E3B 1E3 Canada