

Holistic CCI (a framework)

- QbD Focus on design phase testing
- Predictable vs. un-predictable defects
- SPC still needed
- Deterministic methods directionally drive holistic capability: reduced testing frequency, increased assurance, clarifying data, data capable of greater scientific inference (QbD)
- Novel concept subject to ICH Q8 & Q9

ICH Q8

- Holistic lifecycle approach to product quality • Guidance for pharmaceutical drug product development with emphasis on Identify and control risks to quality QbD principles
- Critical aspects of the container closure system (CCS) need to have a control strategy
- Establish critical physiochemical properties
- Container Closure Integrity (CCI) should be tested and evaluated
- Critical Quality Attributes and quality product profile must be established (the MALL)
- Sources of variability that affect quality should be controlled
- Real-time release testing and SPC full product testing at recommended intervals



Occurrence

- Common Failure
- Systematic Failures in process
- Uncommon Failure
- Debris in seal area • Micro-cracks
- Defective components; mis-molded closures

Severity

- A measure of the possible consequences of a hazard.
- What are the potential hazards of sterility breaches/CCI failures?

Detection

- Accuracy of detection
- Level of detection

USP <382>

- Purpose: "Fitness-for-intended-use functionality requirements of packaging/delivery systems that are intended for injectable dosage forms and include primary packaging components partially or completely made of elastomeric material"
- Section 4. Package integrity Requires inherent integrity testing of elastomeric closures and components,
- included but not limited to: Needle shield interface
- Vial stoppers
- Syringe/cartridge plungers
- Covered piercing area of BFS Containers
- Access Ports to infusion containers • Requires testing of 30 samples per elastomeric component/seal interface
- Detection must meet the MALL for the product-package

ICH Q9

- Scientific and practical approach to assessing probability, severity and detectability of risk
- Quality identified as fulfilling on explicit or implicit needs or expectations of the patient
- Provides a series of risk management assessments to apply to broad industry needs
- Provides examples of areas to apply QRM principles, including evaluating container closure system, container quality and statistical sampling approaches



Elastomeric Closure Functionality in Pre-filled Syringe **Delivery Systems/Requirements for Container Closure Integrity**

Phase 1 of Pharmaceutical Product Lifecycle Package Development

100% He Flow Apparatus

Device allows a measured flow of helium into a container or package for continuous 100% helium flow method testing. Flowmeter calibrated specific to Helium gas



Induction Seal Vacuum Fixture



Plastic Vial Test Fixture



Plastic Vial Test Fixture

Bottle Package Application



Ophthalmic Bottle Container Components



Initial Bottle He Leak Testing: Data Table

Sample Number	Bottle Cavity	Cap Color	Tip ID	Helium Leak Rate from Test Fixture ^{1,2}	Helium Leak Detected (Y/N)?
1	24	Gray	XD30551	2.8 E-04	Y
2	43	Gray	XD30551	1.0 E-05	Y
3	40	Gray	XD30551	2.2 E-06	Y
4	41	Gray	XD30551	5.8 E-06	Y
5	22	Gray	XD30551	4.3 E-06	Y
6	35	Gray	XD30551	1.6 E-04	Y
7	45	Gray	XD30551	7.6 E-05	Y
8	34	Gray	XD30551	2.1 E-05	Y
9	38	Gray	XD30551	4.9 E-05	Y
10	21	Gray	XD30551	3.7 E-06	Y
11	25	Gray	XD30551	4.0 E-06	Y
12	20	Gray	XD30551	7.9 E-06	Y
13	32	Gray	XD30551	3.7 E-05	Y
14	44	Gray	XD30551	9.6 E-06	Y
15	40	Gray	XD30551	7.0 E-05	Y
16	35-21	Pink	XD30686	2.1 E-09	N
17	33-13	Pink	XD30686	1.8 E-09	N
18	28-13	Pink	XD30686	6.9 E-10	N
19	29-13	Pink	XD30686	1.4 E-09	N
20	43-13	Pink	XD30686	8.7 E-10	N
21	45-13	Pink	XD30686	1.1 E-09	Ν
22	26-13	Pink	XD30686	2.8 E-09	Ν
23	46-13	Pink	XD30686	2.7 E-09	Ν
24	35-13	Pink	XD30686	8.3 E-10	Ν
25	43-13	Pink	XD30686	3.0 E-09	Ν
26	23-13	Pink	XD30686	1.4 E-09	Ν



Cartridge fixture with stopper supports

Helium Leak Detection: Most sensitive technology for inherent integrity

- Smallest inert atom used as a tracer gas
- Component isolation
- Suitable for polymer packages

Syringe Barrel Needle Fuse Leak Test Fixture



Glass Jar – Closure Seal Fixture

100% Flow



Helium Flow Meter



Bottle Test Fixtures



Bottle Containers During Leak Test Cycle



Examples of Custom Vacuum Text Fixture Modules for Syringes & Cartridges – 100% Helium Flow method



Cartridge secured in test position



Syringe Fixture – Needle Shield Test

