IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

Welcome to the IPAC-RS Supplier and Pharma Workshop on Device and Container Closure System Quality

Assessing the IPAC-RS Baseline Requirements: A Practical Tool for Enhancing Communication and Reducing Risk in the Supply Chain?

November 8, 2018

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International Pharmaceutical Aerosol Consortium on Regulation & Science

November 08, 2018

The IPAC-RS Baseline Requirements for Materials used in Orally Inhaled and Nasal Drug Products (OINDP)

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November 8, 2018

Washington, DC

Topics

- What is the Baseline Requirements document?
- Why was it developed?
- Who is it for?
- Why do suppliers need to meet the various requirements/expectations?

IPAC-RS

International Pharmaceutical Aerosol Consortium on Regulation and Science

Vision

IPAC-RS is and will remain the leading technical resource and advocate of the orally inhaled and nasal drug product (OINDPs) industry, with a focus on Chemistry, Manufacturing and Controls aspects.

Mission

Advance scientifically driven approaches to enhancing product quality of inhaled and intranasal drug products for the benefit of patients.

IPAC-RS

Advances

regulatory science of aerosol drug products through joint research and experimental work, benchmarking surveys, and technical publications.

Provides

members with timely regulatory and scientific updates and analyses, access to the IPAC-RS research results, networking opportunities, representation at the national and international level.

Works

with regulatory agencies and standard-setting bodies:

- **US FDA**
- **EMA**
- **Health Canada**
- **Ph. Eur., USP**
- **ISO**
- **CFDA**
- **ANVISA**

Engages Stakeholders

broader industry, trade associations, patient advocacy groups, clinicians, academicians, etc. to discuss key regulatory science topics of orally inhaled and nasal drug products (OINDPs)

IPAC-RS Members

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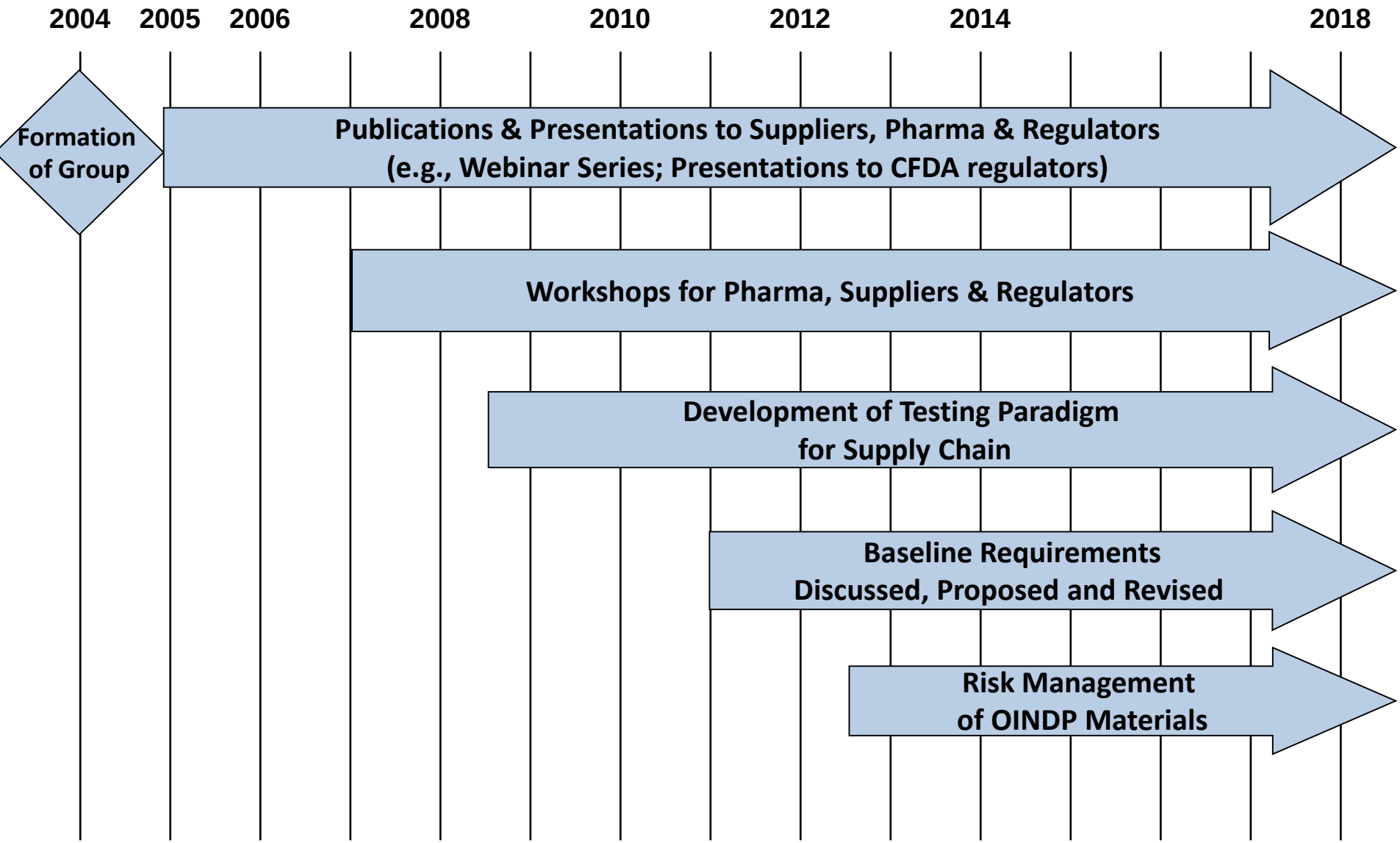
OINDP Materials Working Group

Mission

To improve packaging and device materials quality and integrity, reduce supply chain problems and promote rational testing approaches.

Impact

The Patient is best served when we provide quality packaging and device components that are both safe and effective throughout the shelf life of the drug product.


2004
2005
2006
2008
2010
2012
2014
2018
Formation of Group
Publications & Presentations to Suppliers, Pharma & Regulators
(e.g., Webinar Series; Presentations to CFDA regulators)
Workshops for Pharma, Suppliers & Regulators
Development of Testing Paradigm
for Supply Chain
Baseline Requirements
Discussed, Proposed and Revised
Risk Management
of OINDP Materials

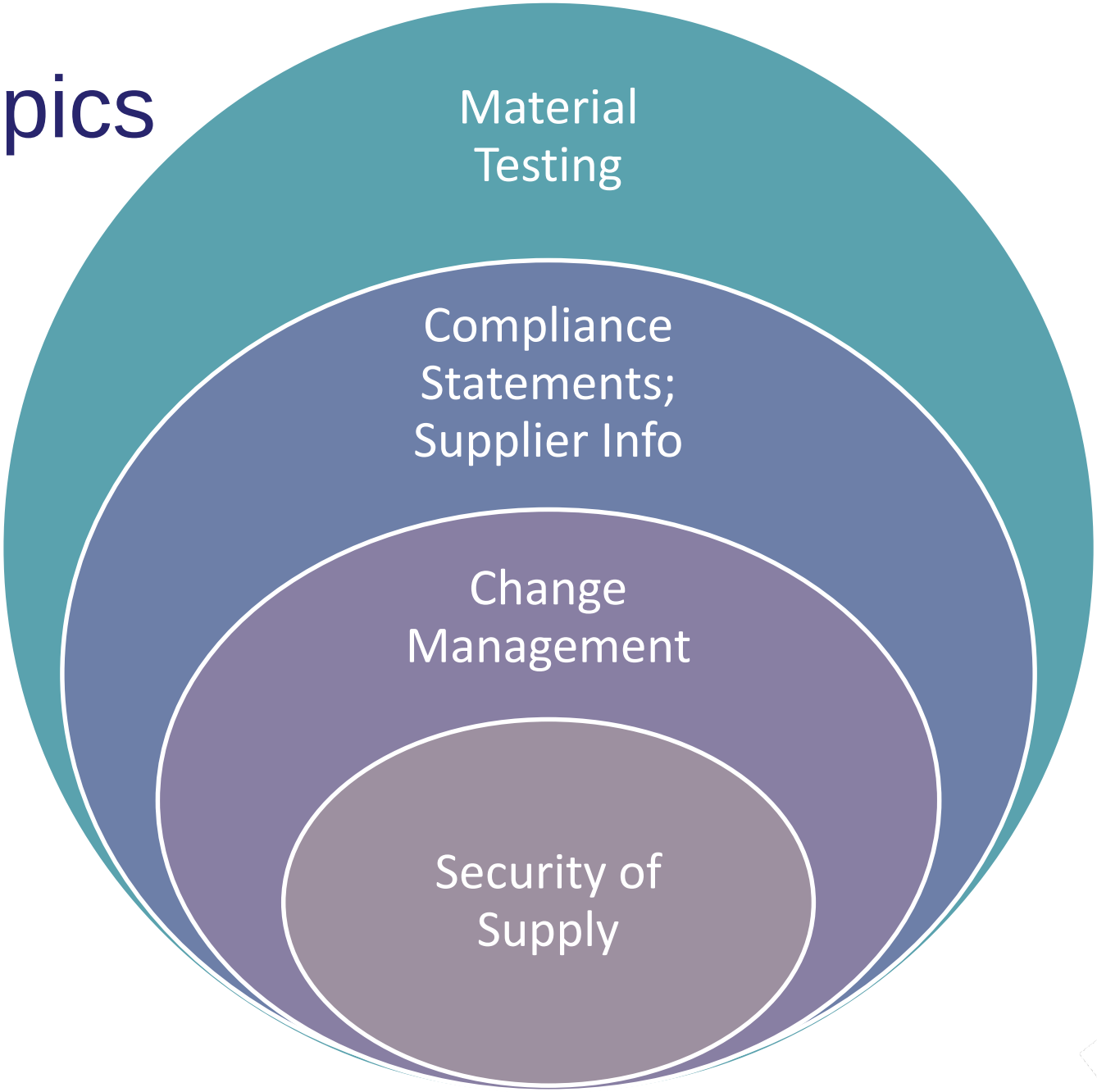
What is the Baseline Requirements document?

Describes current basic requirements for materials used to manufacture container closure, packaging, and device components for OINDP

- Compiled from international regulatory and compendial requirements
- Applies to all types of materials
- References in the document are not comprehensive, but capture current expectations

➢ Materials meeting the requirements are considered by IPAC-RS to have quality necessary for OINDP.

Main Topics



Publicly available document on the IPAC-RS website

IPAC-RS

International Pharmaceutical Aerosol Consortium on Regulation and Science

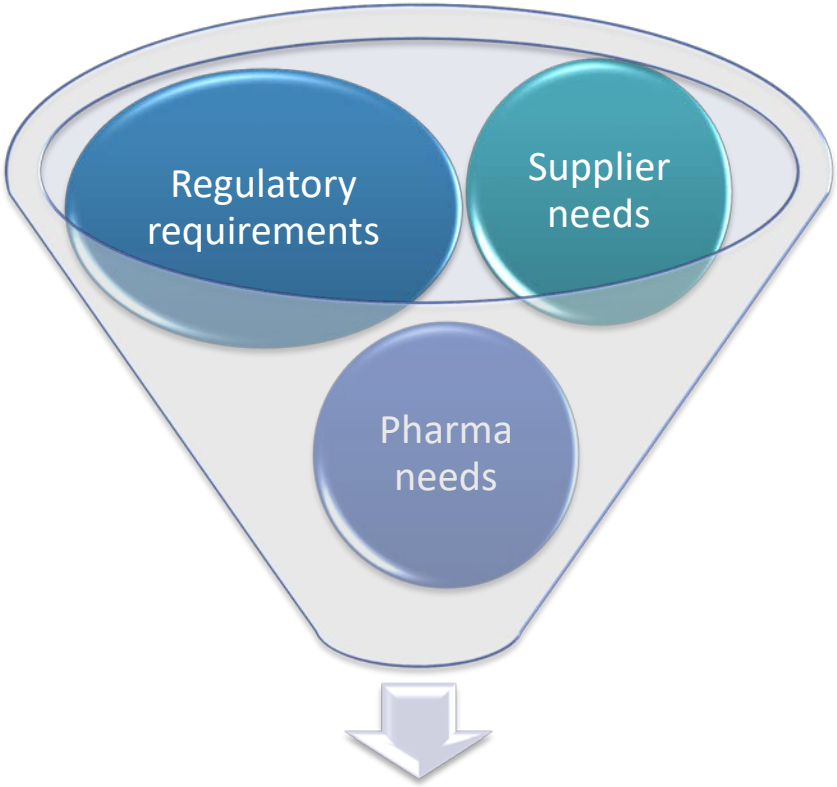
9 February 2017

Recommended Baseline Requirements for Materials used in Orally Inhaled and Nasal Drug Products (OINDP)

This document describes baseline requirements for materials used to manufacture components for OINDP, and is the first revision of the original document presented in 2011.[i] This revision is primarily driven by changes in the regulatory landscape since 2011. We note that national and international guidelines and standards are continuously evolving, and that references noted in this document are not comprehensive, but do capture current expectations. As there is no single guidance for these types of materials, these requirements were compiled from a variety of international regulatory and compendial requirements. The impetus for this document was based on a clearly articulated need for a uniform set of requirements that arose out of several discussions between pharmaceutical manufacturers, regulators and multiple suppliers in meetings sponsored by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The recommendations originally put forth by the Polymer

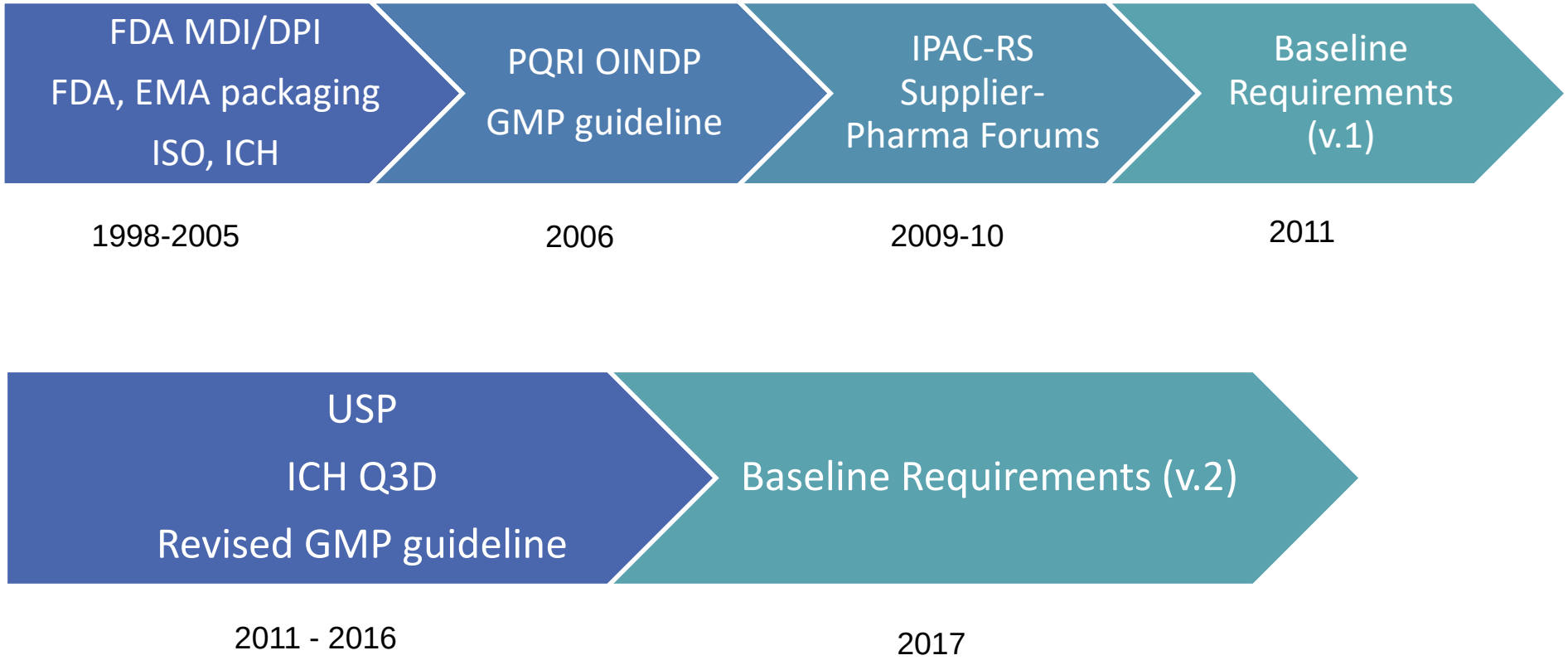
Why was it developed?

International regulatory and compendial requirements and discussions between pharmaceutical manufacturers, regulators and suppliers pointed to a need for a uniform set of requirements



Baseline Requirements

Originally published 2011; revised 2017 due to evolving regulatory landscape



Key Regulatory Guidance and Standards (~ 2005)

- 1993 CDRH - Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators
- 1998 FDA - Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products
- 1999 FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics
- 2002 FDA - Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products
- 2002 EU Directive 72: plastic materials and articles in contact with foodstuffs
- 2005 EMA - Guideline for Plastic Immediate Packaging Materials
- 21CFR 170-189
- EP 3, USP <381>, <660>, <661> (Physicochemical)
- ISO10993, USP<87>, USP<88> (Biocompatibility)

Key Regulatory Guidance and Standards (~ 2005 - 2011)

- 2006 PQRI - Recommendations: Safety Thresholds & Best Practices For Extractables & Leachables in OINDP
- 2006 Health Canada/EMA Guidance: Pharmaceutical Quality of Inhalation and Nasal Products
- 2007 European Parliament/Council: Medical Device Directive 93/42/EEC as amended
- 21CFR 170-189
- 2011 Commission Regulation (EU) No 10, plastic materials and articles in contact with food
- 2011 IPAC-RS, PQG, CQI PS 9000:2011 “Pharmaceutical packaging materials for medicinal products, with reference to Good Manufacturing Practice (GMP)”

“New” Documents

- 2012 IPAC-RS (Wiley) Leachables and Extractables Handbook
- 2012 EU cGMPs Chapter 7, “Outsourced Activities”
- 2014 ICH Q3D “Guideline for Elemental Impurities” (Step 4)
- 2015 USP <1663> “Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems”
- 2015 USP <1664> “Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems”
- 2016 USP <232> “Elemental Impurities-Limits”
- 2016 USP <661> “Plastic Packaging Systems and Their Materials of Construction”
- 2016 USP <661.1> “Plastic Materials of Construction”
- 2016 USP <661.2> “Plastic Packaging Systems for Pharmaceutical Use”
- 2016 USP <1661> “Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact”
- 2016 IPAC-RS, PQG PS 9000:2016 “Pharmaceutical packaging materials for medicinal products, with reference to Good Manufacturing Practice (GMP)”
- 2016 FDA Guidance Contract Manufacturing Arrangements for Drugs: Quality Agreements

Continuous Improvement (initiated 2015)

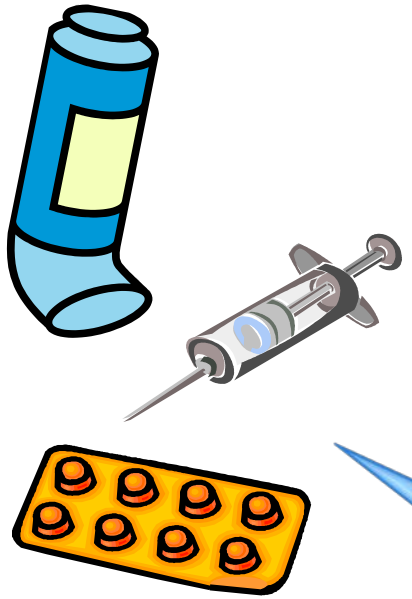
- How can the “Baseline Requirements” be kept relevant to current scientific, manufacturing, and regulatory context?
  - Development and manufacturing processes are changing
  - Risk management, control, and testing paradigms are changing
- Who is using them?
- How are they being used?
- What are “critical components”?
- Can these requirements be expanded to other “high-risk” dosage forms?

Revision Process

- Materials Working Group created draft
- Discussed with stakeholders in various forums to receive feedback
  - IPAC-RS Members
  - Material Suppliers
  - Contract Manufacturers
  - Contract Analytical Testing Labs
  - Regulators
- Post final document on IPAC-RS website

Each container closure system/ medical device and their components must be suitable for its intended use.

Safety:
- Biocompatibility
- Extractables
- Leachables



Compatibility:
- Loss of Potency
- Degradation
- Precipitation
- Discoloration
- pH change
- Brittleness of Package

Protection:
- Light
- Solvent loss/leakage
- Microbial contamination
- Water vapor
- Gas

Performance:
- Functionality
- Drug delivery

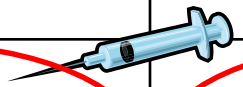
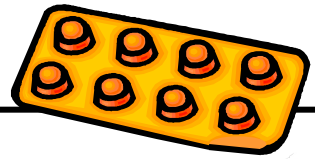
How can suitability be demonstrated?

Quality cannot be tested into products, quality should be built in by design.

- Quality is designed by :
  - Scientific understanding, information and knowledge and
  - Quality risk management
  - Of attributes critical to product quality
- Processes, specifications and controls are established

For the intended performance of the product

Variety of OINDP types, each with different risk profiles

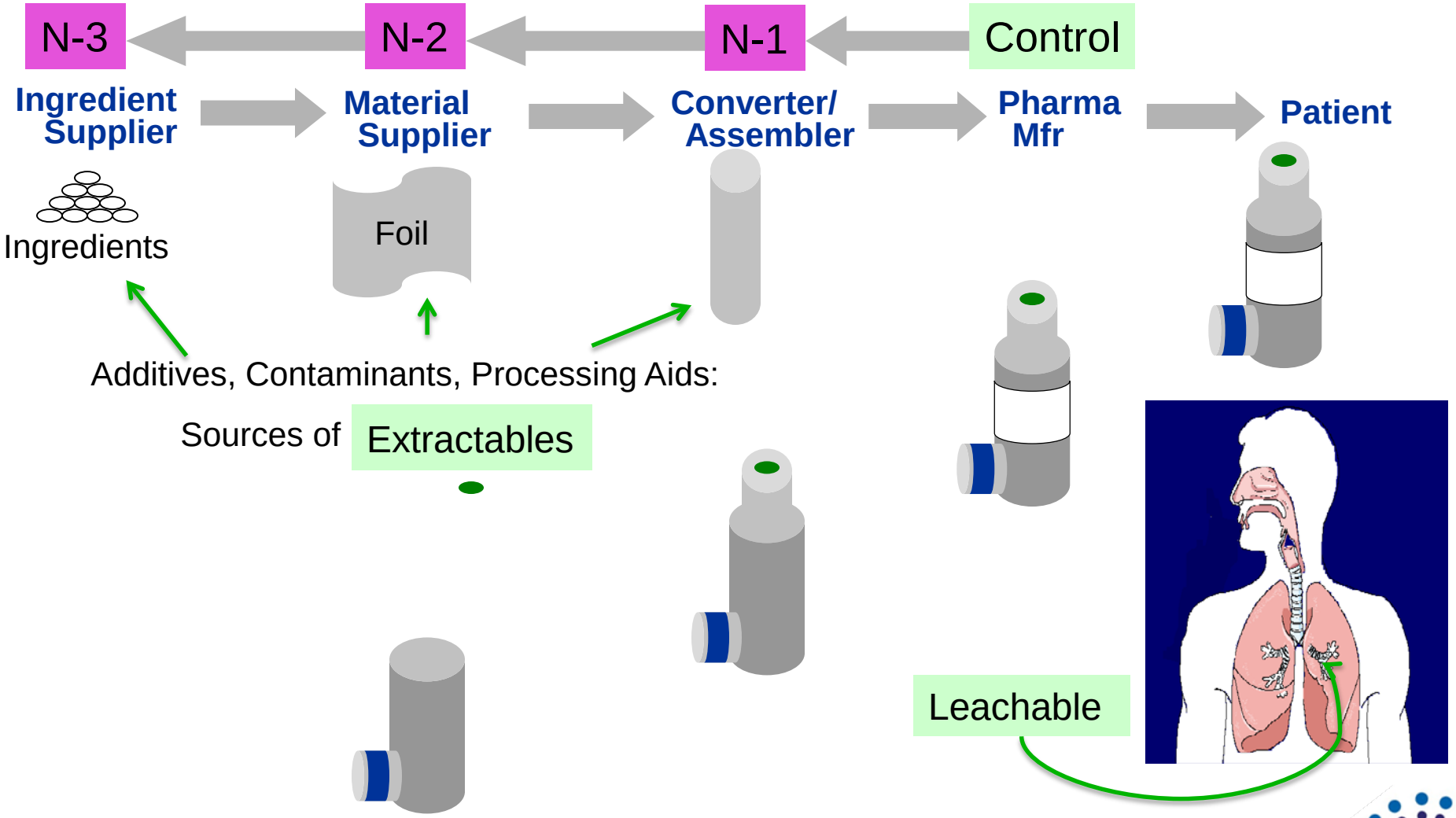
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest 	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions 	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions / Suspensions; Nasal Aerosols and Sprays	
Low	Topical Solutions / Suspensions; Topical / Lingual Aerosols; Oral Solutions / Suspensions		Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders 

Source: USP <1664> **Modified** FDA/CDER/CBER Risk-Based Approach to Consideration of Leachables
FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999

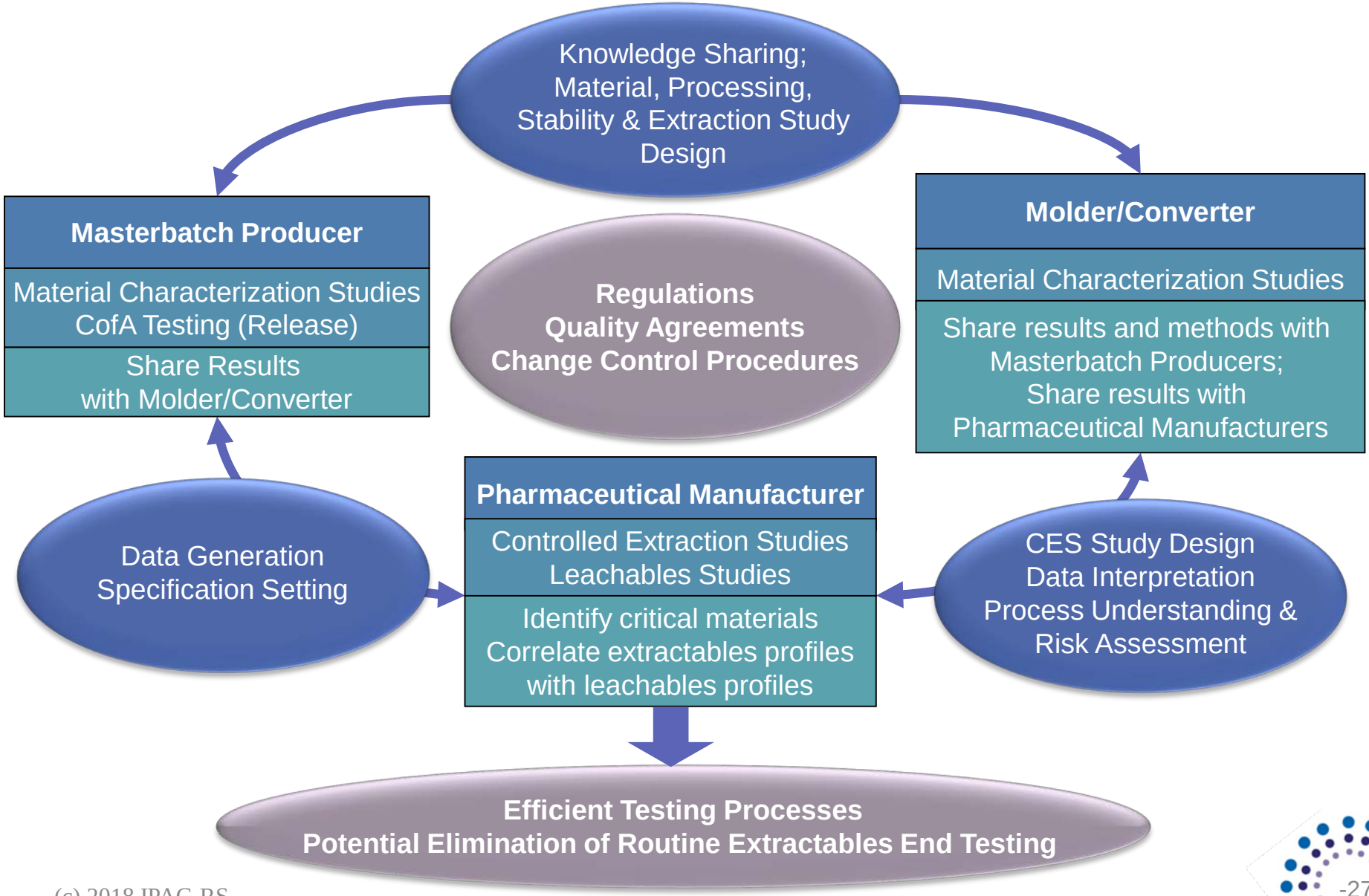
Who is it for?

- OINDP or other drug product manufacturers to guide primary packaging/device production, material selection and control
- Container closure system and device component suppliers
- Materials suppliers (materials of construction)
- Suppliers providing materials for dosage forms with a high degree of concern can consult these recommendations

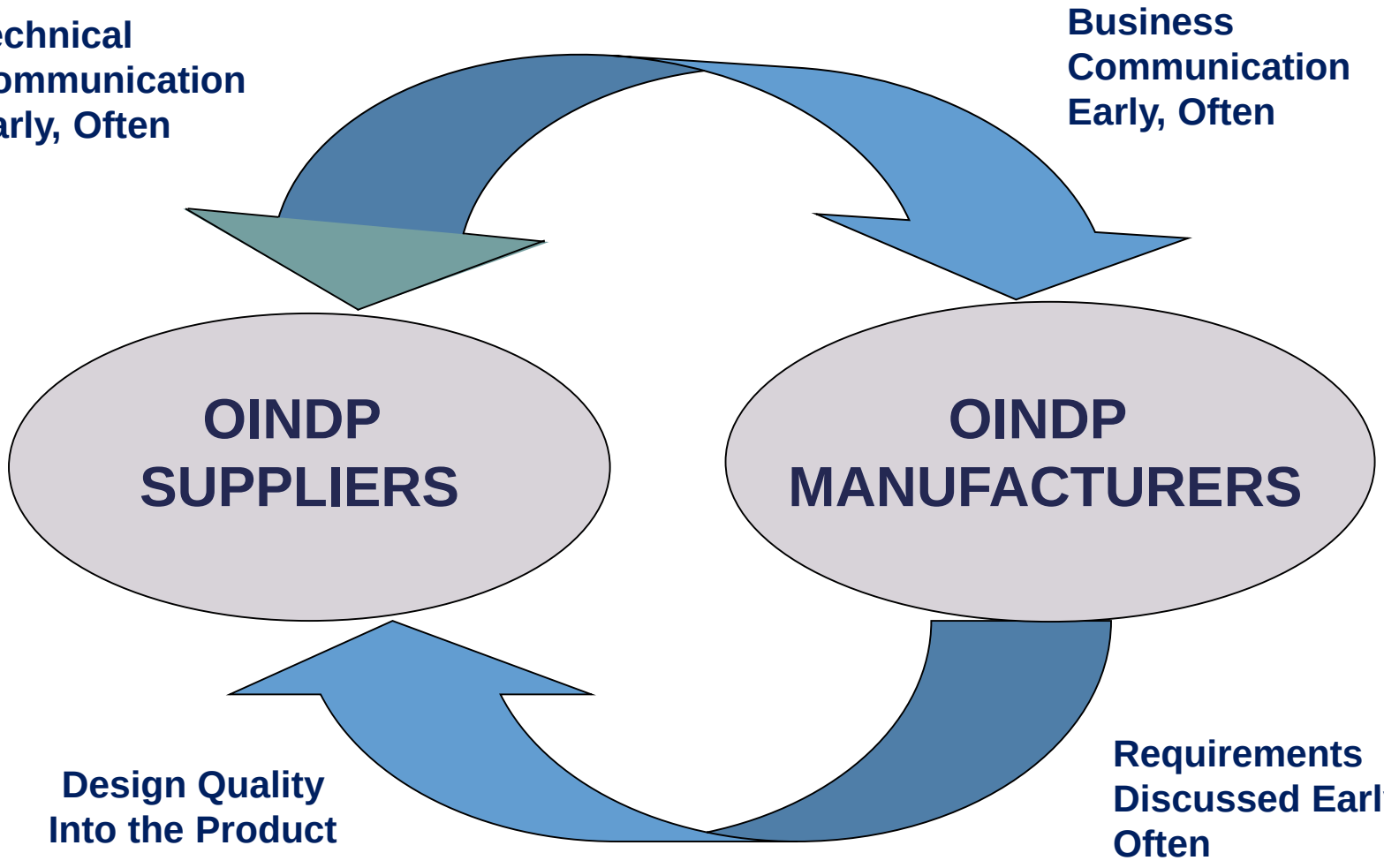
Supply Chain is Key in Helping Ensure Quality – E&L Example



Proposed Testing Paradigm (2016)



OINDP Supplier, Manufacturer Communication



Revised Baseline Requirements

Security of Supply

- Shelf-life of material when stored according to manufacturer's recommendations
- Adequate notice period (minimum 12 months) to qualify new material according to regulatory requirements
- *Last-call option*: notice to customers to allow bulk purchase before production discontinuation, to guarantee supply to patients, where practicable

	Notice Period with Last Call Option	Raw Material Shelf Life	Finished Component/Assembly* Shelf Life	Resulting Material Availability
Material #1	12 mo	---	24 mo	36 mo
Material #2	12 mo	12 mo	12 mo	36 mo
Material #3	18 mo	12 mo	6 mo	36 mo

*Assembly could be, e.g., valve, multilayer foil, inhaler

Change Management

- Part of supply and/or quality agreements between supplier and customer
  - Changes requiring notification, notification period, and approval process for changes
  - Responsibility matrix, change control for documents, materials, specifications, processes, facility and equipment

Compliance Statements and Other Supplier Information

- Compliance statements, e.g.,
  - Food additive compliance
  - TSE/BSE
  - Elemental impurities
  - REACh
- Other information, e.g.,
  - Phthalates Content (required for labeling in EU); DEHP Content (Canadian Requirement); BPA Content (Canadian Requirement)
  - Aromatic Amines content
  - Mercaptobenzo thiazole (MBT) content
  - N-nitrosamines content
  - Polycyclic aromatic hydrocarbons (PAH) content

Material Testing

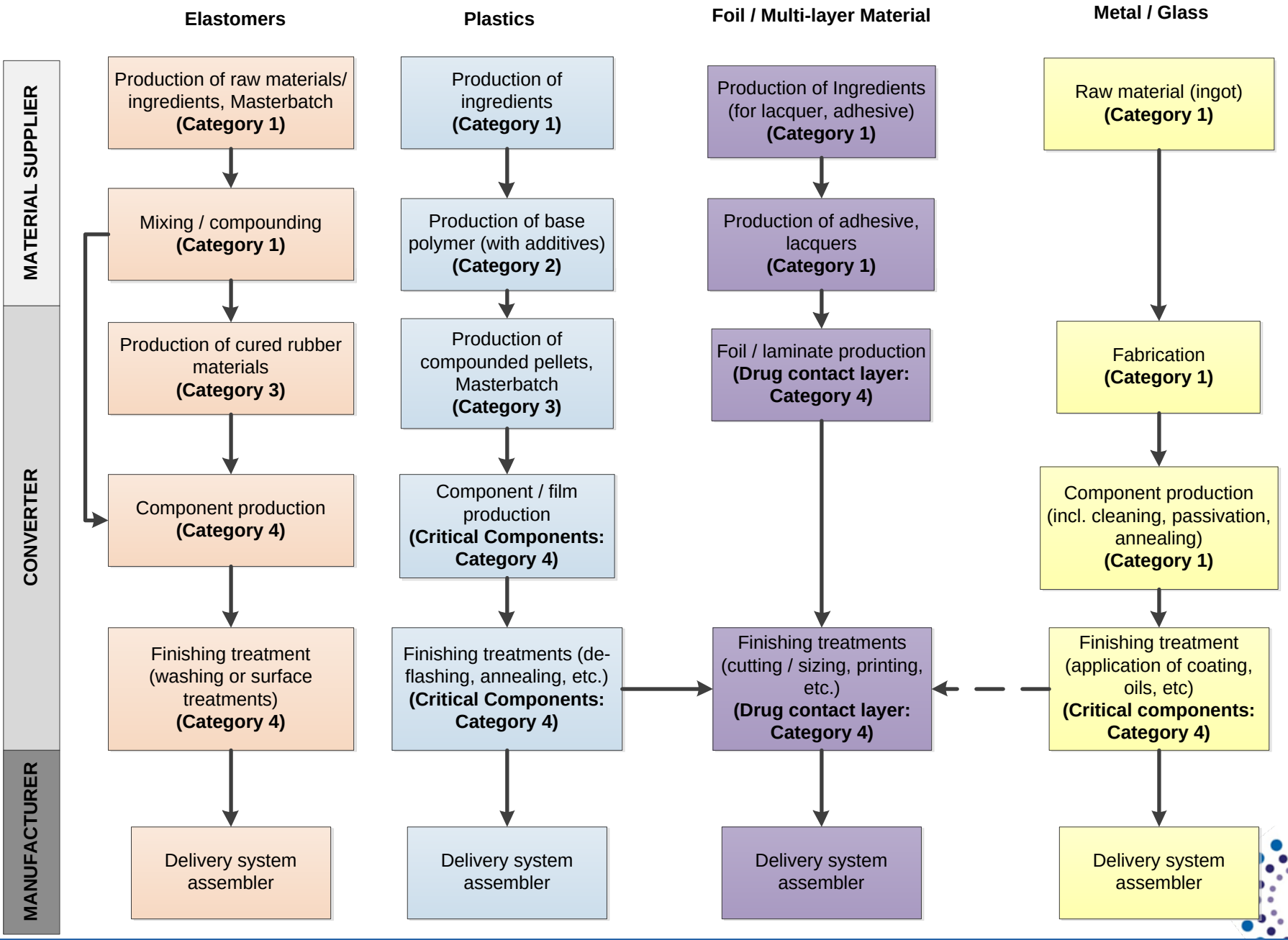
- Supplier's specifications (e.g., ISO, dimensions),
- Pharmacopeias/Standards Compliance:
  - Biocompatibility: based on product use (patient contact and duration), e.g., ISO 10993, parts 5 and 10 (sensitization, irritation), or USP <87>; classification of plastics per USP <88> preferred.
  - Physicochemical testing: compliance with, e.g., EP Chapter 3; USP <661>; <381>, JP XV
- Controlled extraction studies; minimum requirements based on best practices, e.g., PQRI
- Routine extractables testing
- Foreign particulates

Requirement Categories for Testing

Test	Category 1	Category 2	Category 3	Category 4
Biocompatibility - compliance ISO 10993, USP <87> and <88> Deliverable: Cert of Compliance (required) and report with test results (upon request)		One-time test* for plastics only	One-time test* for plastics only	One-time test*
Physicochemical Testing - compliance with EP3, USP <661>, USP <381>, USP <660>; ISO 10993-1, JP XV Deliverable: Cert of Compliance (required); Cert of Analysis (on request)		One-time test* for plastics only	One-time test*	One-time test*
Controlled Extraction Studies Deliverable: Report with results (complete data package)	No test; Provide composition information.	One-time test* Or provide composition and processing aids or additives	One-time test* Or provide composition and processing aids or additives	One-time test*
Routine Extractables Testing Periodic, Quantitative / Qualitative Validated method Deliverable: Certificate of Analysis			Routine Test.▲ At request of customer, in connection with Category 4 routine extractables testing	Routine Test.▲ Commercial requirement may be adjusted based on product needs

* Test once at the beginning of materials selection, or if significant change has occurred.
▲ Test material according to schedule developed in agreement with customer.

Materials Manufacture Flowchart with Testing Categories



Appendices describing

- Rationale for security of supply
- Quality Agreements
- Rationale for Controlled Extraction Studies
- Rationale for Routine Extractables Testing
- Rationale for “one-time” testing
- Key references

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Stephen Warren, AstraZeneca
Atish Sen, AstraZeneca
Andrew Feilden
Lee Nagao, IPAC-RS

Questions

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