Risk Based Approach to Drug Delivery System Change Management

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PDA Universe of Pre-filled Syringes 2017 Post-Conference Workshop: Drug Delivery Systems: Global Technical, Regulatory and Quality Challenges

Discussion Topics

- Regulatory Framework for Change Management
- Sources of Change and Challenges of Change Management
- Change Assessment - *Draft* ISO 20069
- Summary

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Change Requirements – 21 CFR 820

Quality System Regulation

- **§820.30(i) – *Design Changes.*** Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of **design changes** before their implementation.

- **§820.40 – *Document Changes.*** **Changes to documents** shall be reviewed and approved…communicated to the appropriate personnel…maintain records of changes ...

- **§820.70(b) – *Production and process changes*.** Each manufacturer shall establish and maintain procedures for **changes to a specification, method, process, or procedure.** Such changes shall be verified or where appropriate validated according to §820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with §820.40

ISO 13485 and ISO 9001 include similar expectations for changes

Change Requirements – ICH Q10

- **Change Management -** A systematic approach to proposing, evaluating, approving, implementing, and reviewing changes.

- **IV.B.3. Change Management System:**
  - Ensures continual improvement is undertaken in a timely and effective manner
  - Provide a high degree of assurance there are no unintended consequences of the change
  - Should Include:
    - Evaluate using QRM – effort & formality commensurate with level of **risk**
    - Evaluation against the marketing authorization, including design space…current **product and process understanding**.
    - Assessment to determine whether a **change to the regulatory filing** is required under regional requirements
    - Evaluation of proposed changes by **expert teams** contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs, and Medical)
    - **Effectiveness of change** assessed after implementation to confirm the change objectives were achieved and that there was no deleterious impact on product quality

Purchasing Controls

§820.50 - *Purchasing Controls*. Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

(a) Evaluation of suppliers, contractors, and consultants….on their ability to meet specified requirements, including quality requirements…Define type and extent of control to be exercised…Establish and maintain records of acceptable suppliers, contractors and consultants

(b) Purchasing data…maintain data clearly establishing that suppliers, contractors and consultant meet specified requirements….documents shall include an agreement that the suppliers, contractors, and consultants agree to **notify the manufacturer of changes** in the product or service so that **manufacturers may determine whether the changes may affect the quality of a finished device.**

Purchasing Controls

Critical for managing changes throughout the lifecycle

- Successful implementation of purchasing controls can make for proactive rather than reactive manufacturing, supply and regulatory strategy
- Vital for combination products, as most include purchased materials/components/device assemblies
- Design only as good as purchasing controls
  - ➢without strong purchasing controls, design can change ***without you even knowing***
- Supply agreements:
  - Customers and suppliers should agree on notification and approval of changes and include these terms in agreements
  - Suppliers should ensure that **THEIR** suppliers have adequate change control programs in place

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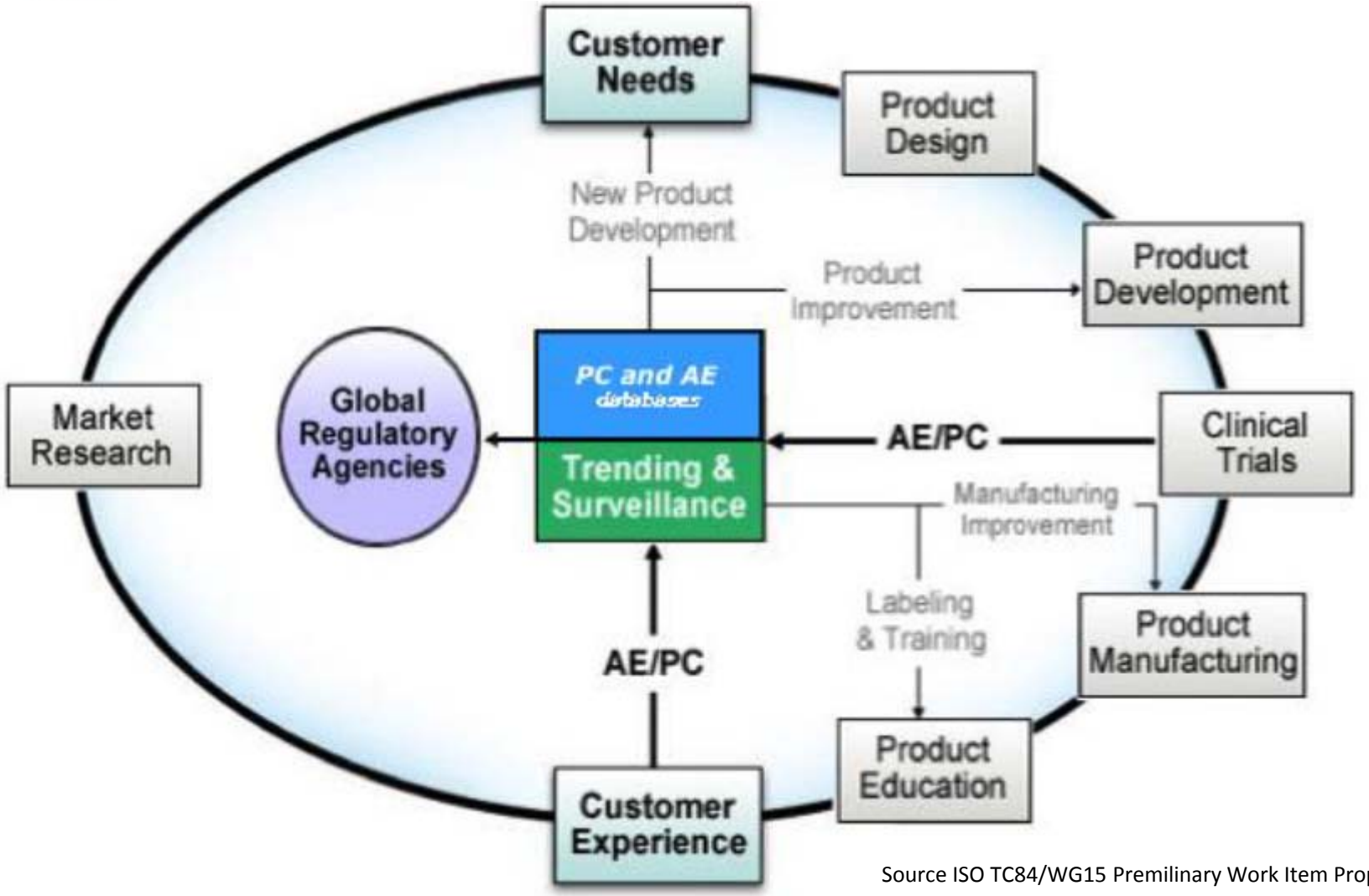
Sources of Change



Source ISO TC84/WG15 Premilinary Work Item Proposal (N033)

Supply Chain Linkages
Sources of change

- Base polymer
- Raw rubber
- Antioxidants
- Pigments
- Stabilizers
- Regulation changes

- N-2 Changes
- Cleaning process / cleaning agents
- Component molding process (time / temp / pressure)
- Processing aids (i.e., mold release agents)
- Regulation changes

- N-2 Changes
- N-1 Changes
- Assembly process changes
- Site changes
- Packaging changes
- Regulation changes

Slide ref: Riddell/Roan – IPAC-RS Supplier GMP Training Course, May. 2008

Design Change Controls

Purpose: To ensure that the changes are appropriate and that the device/ combination product will continue to perform as intended

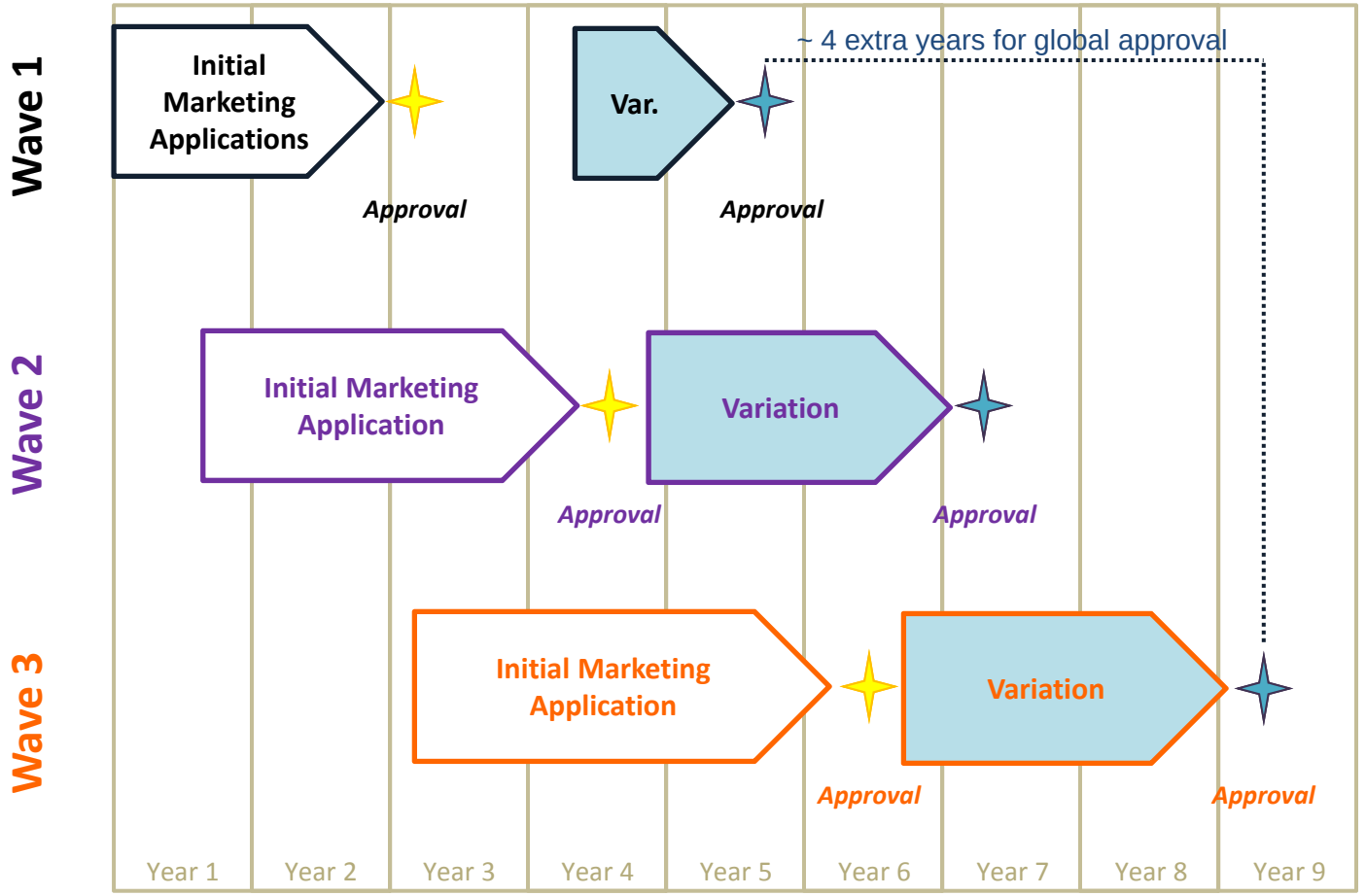
Pre- and Post-Design Transfer

Examples:

Container Closure	**Drug Formulation**
Fluid Path	**Process Change**
Delivery Mechanism	**Labeling**
User Interface	**Packaging**
User Population/Environment	**Supplier Change**

Slide ref: Neadle/Roan – Xavier Health Fundamentals of Combination Products, Sept. 2017

Realities of Global Changes



Global implementation timeline impacted to a greater extent due to ongoing initial reviews

Aim to minimize commitments in Wave 2/3 markets to shorten overall implementation timelines

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What is the need?

SIGNIFICANT

in how companies manage device design changes

An Example…

Survey performed by IPAC-RS

Scenario:

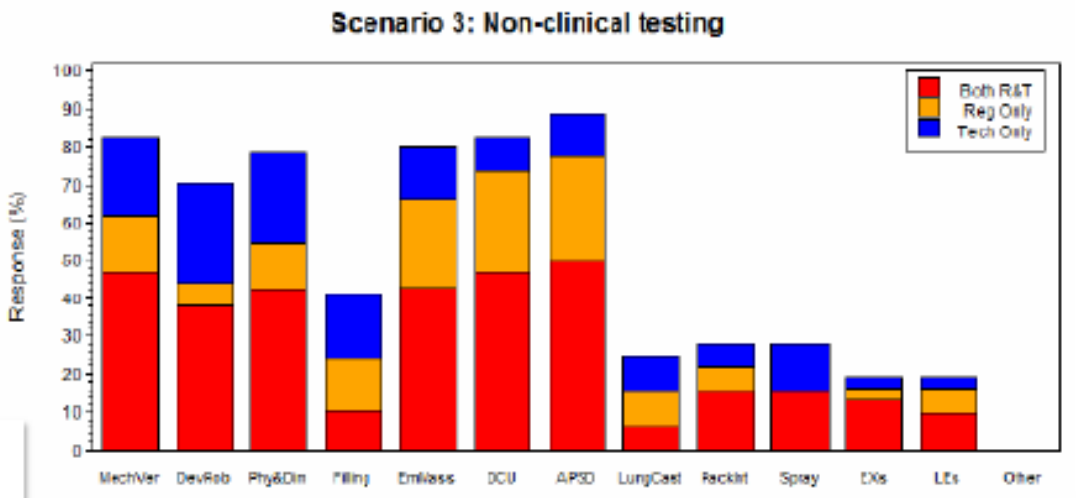
A novel beta 2 agonist inhaled drug product (DPI) is under development. Feedback from participants in several focus groups indicated that the mouthpiece should be longer and wider

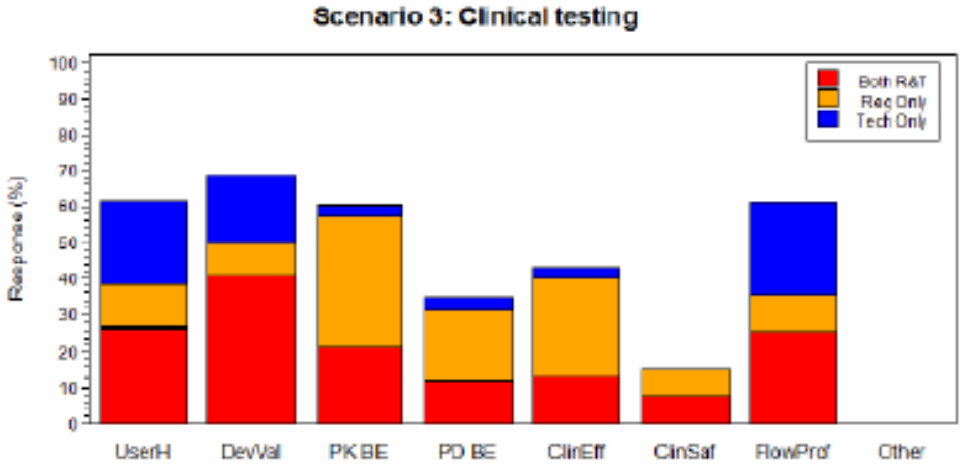
Survey Responses

Context	N
NDA or EQ	30
ANDA or EQ	7
No Answer	68

Submission	N
Update IND/CTA	24
PAS or EQ	4
Suppl. CBE30	2
Suppl. CBE	1
Ann. Rep or EQ	1
No Submission	1
No Answer	72

Months	25/60	30/60	40/75
No Test /0	12	12	12
3	3	3	5
6	3	2	12
9	0	1	0
12	4	6	1
18	0	0	0
24	9	3	0
No Answer	74	78	75

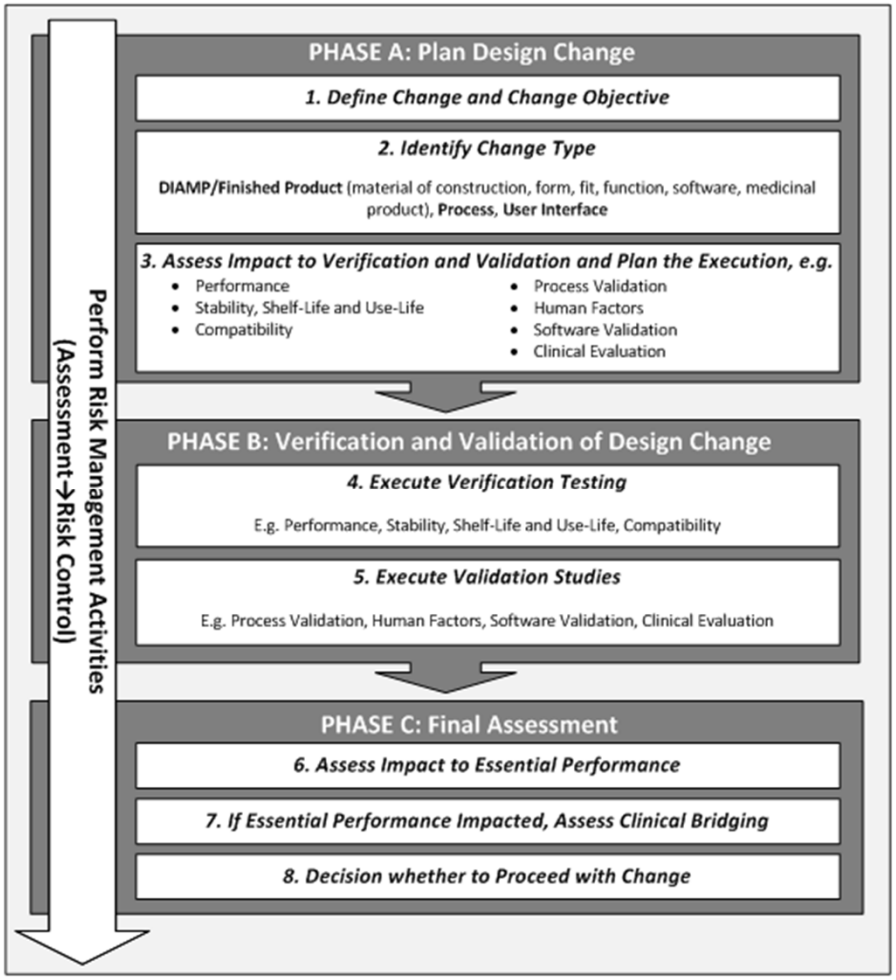




Slide ref: Jansen – PDA UPS EU, Nov 2015

ISO 20069: Change assessment of devices for administration of medicinal products*

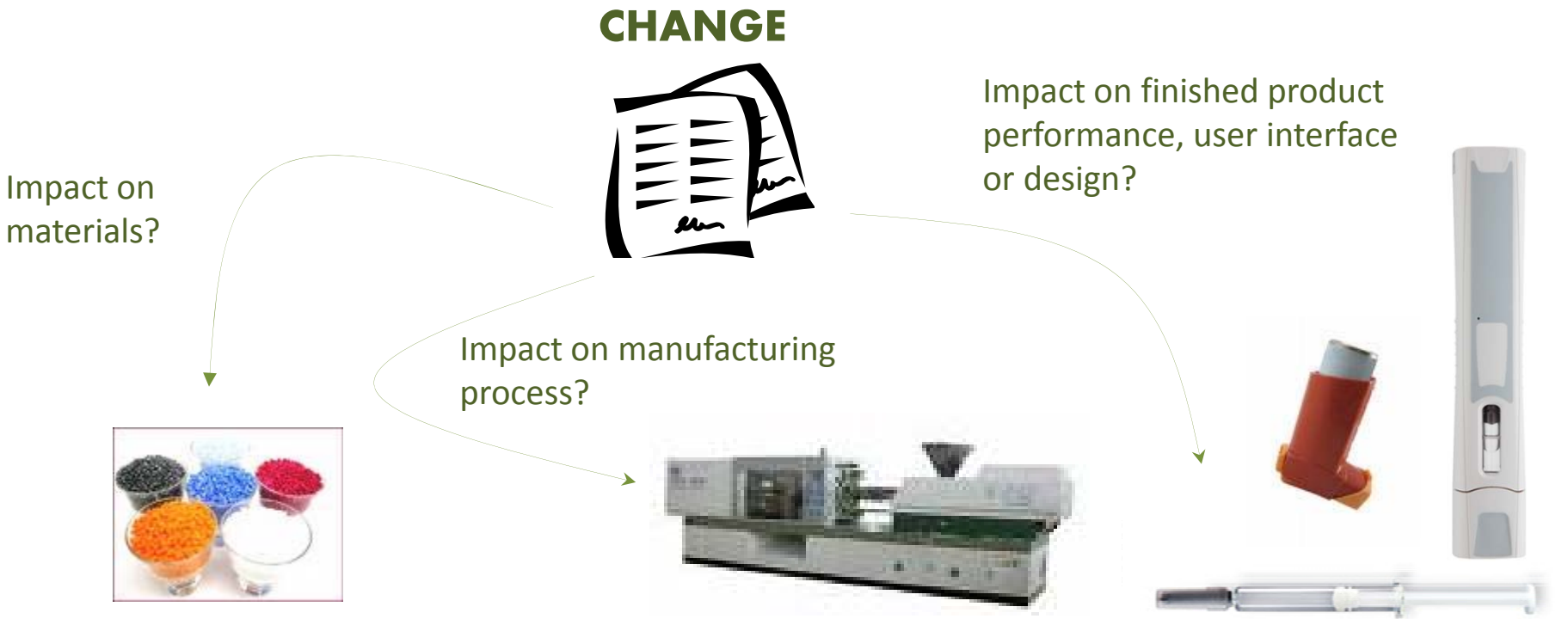
- Intended as a **guidance** for manufacturers providing a framework to manage assessments for changes to **device and medicinal product** components of a drug delivery system
  - NOT prescriptive
- Current Approach:
  - Linked to **risk management** & assessment of **impacts to essential characteristics**
  - Process flow central to standard with analysis approaches presented
- Standard not intended to address regulatory reporting requirements (defers to national legislation)



**Draft principles, under development by ISO/TC 84 WG15; final title TBD*

Understanding & Evaluating Changes

- Determine impact on product quality, safety & efficacy, usability, and process validation
- Understand the current/proposed future state – including any differences in function or user experience, overall risk profile
- ISO 20069 will provide a framework for assessing changes



ISO 20069 Key Concepts

Intended characteristics – physical, functional, chemical, biological, microbiological, and/or usability characteristics of the drug delivery system/medicinal product medicinal product that are required for the finished product to meet its design requirements

Essential characteristics – intended characteristic necessary to achieve freedom from unacceptable risk and/or achieve acceptable delivery of the dose

*Note that the Expert Technical Committee is proposing **Essential Characteristics** instead of the previously used terms essential performance, essential functions to differentiate from EU MDD/MDR and IEC 60601-1 terminology*

Definitions aligned with Oct 2017 committee meeting outcomes for ISO/TC84, WG 15

Current Structure: ISO 20069

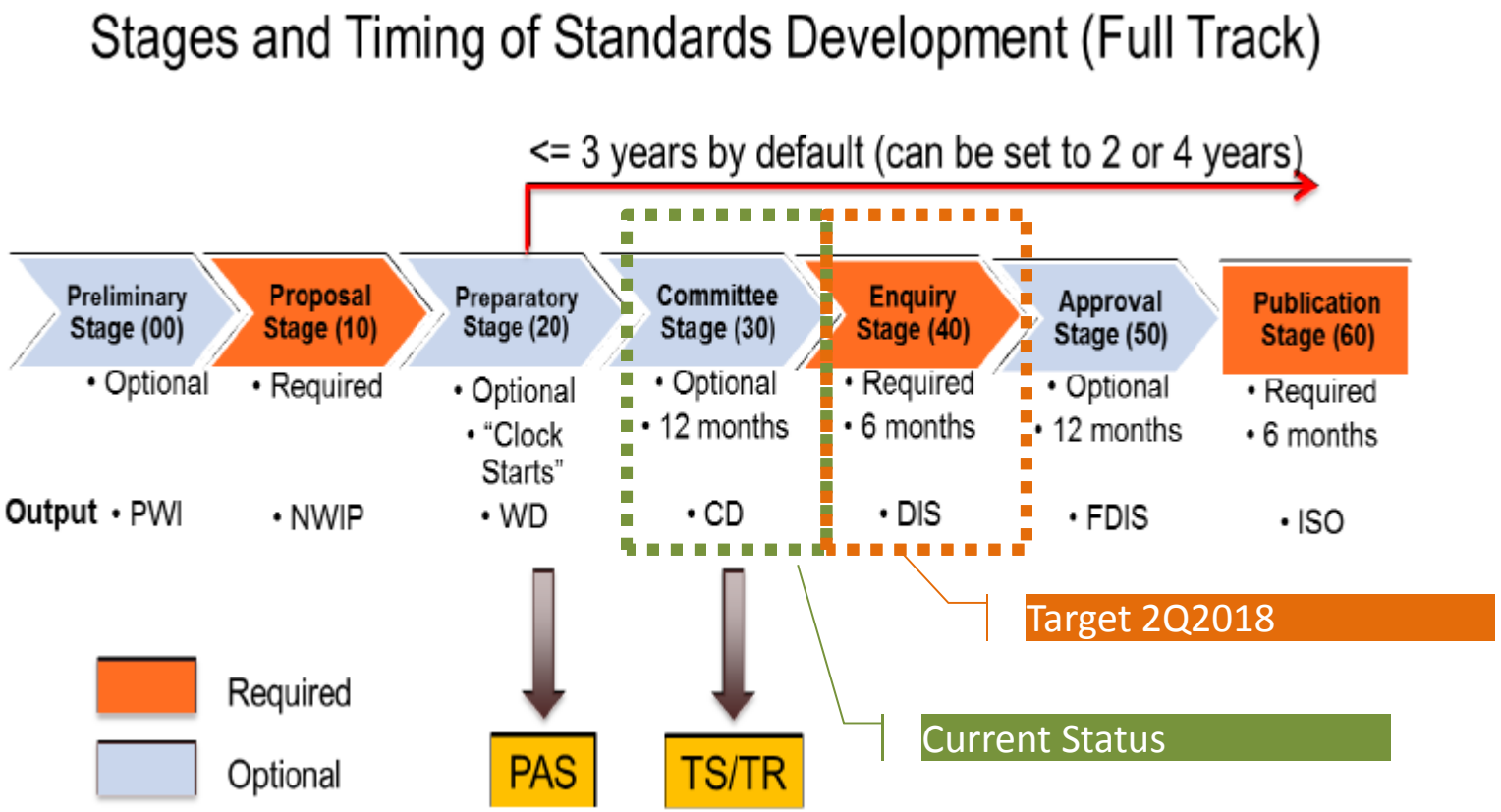
Phase A: Planning and Assessment
- Objective
- Change Category
- Impacts of Change

Phase B: Verification and Validation
- Executing Studies

Phase C: Final Evaluation
- Determine impact on Essential Characteristics
- Determine impact on Clinical Dataset
- Decision to Proceed with Change

Templates
- Templates aligned with process
- Example changes using the templates

Where are we?



Committee meetings planned Feb 2018 in US and May/June 2018 in UK

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- Change Management is a required element of the quality system
- Effective change management systems capture all sources of change
- Variability across industry regarding approaches to qualification of changes was the driver for the development of ISO 20069
- ISO 20069 is intended to provide guidance on a framework to apply for the assessment of changes:
  - Applies to changes to medicinal product and the device
  - Uses risk-based principles
  - Aligned with quality system standards (ISO 13485, ISO 14971)
  - Flow chart, explanatory text and templates

Thank you!

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Acknowledgments

- ISO/TC 84 Working Group 15 Expert Committee
- Danish Standards, ISO/TC 84 Secretariat