PATH WORKSHOP: OVERCOMING CHALLENGES TO ADVANCE MODERN METHODS AND ENSURE THE SAFE SUPPLY OF MEDICINE

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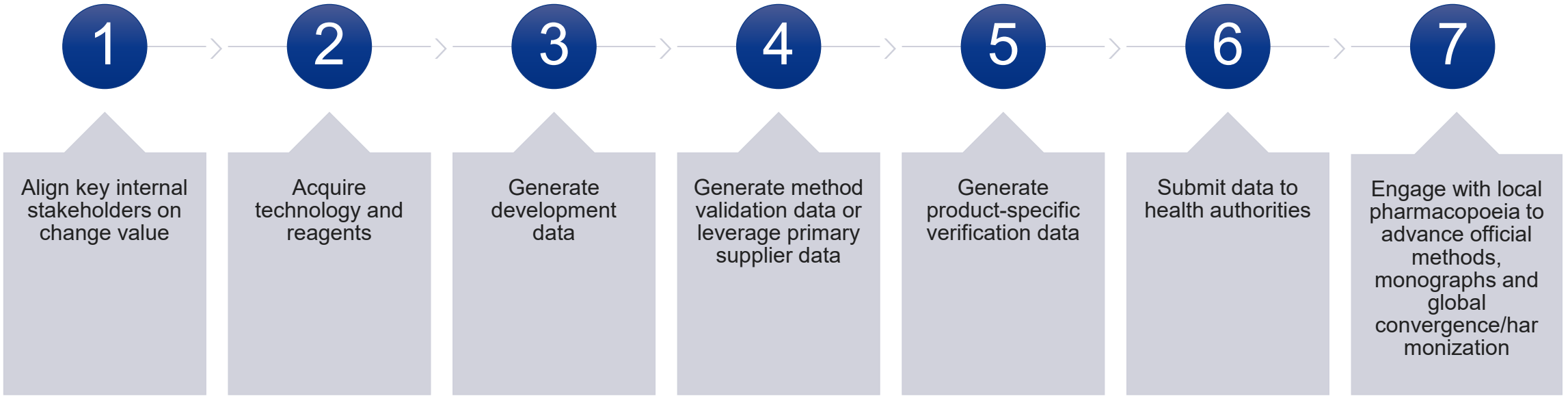
A process for evaluating and advancing new endotoxin test methods for medicines



Considerations and challenges in the adoption of recombinant reagents as an alternative to traditional LAL-based methods

Barrier	Current Status
Suppliers	3 known commercial rFC suppliers 4 known commercial rCR suppliers
Equipment	Fluorescence (rFC) or Absorbance (rCR) readers required Improves Data Integrity position
Pharmacopoeia	General Chapters in Europe (2020); UK, Eurasia, United States (2024) Guidance Chapters in China, Japan, Korea
Data Equivalence	Pharmacopoeia Expert Committees have advanced chapters based on the underlying biotechnology science and available comparability data
Regulatory Acceptance	More than 10 products approved using rBET in at least 75 countries

Global Health Authority Approvals

Argentina	Hong Kong	Pakistan
Australia	Hungary	Peru
Austria	Iceland	Philippines
Bahrain	India	Poland
Bangladesh	Indonesia	Portugal
Belgium	Ireland	Qatar
Bosnia And Herzegovina	Israel	Romania
Brazil	Italy	Russian Federation
Brunei Darussalam	Japan	Saudi Arabia
Bulgaria	Kazakhstan	Serbia
Canada	Korea, Republic Of	Singapore
Chile	Kuwait	Slovakia
China	Latvia	Slovenia
Colombia	Lebanon	South Africa
Croatia	Liechtenstein	Spain
Cyprus	Lithuania	Sweden
Czechia	Luxembourg	Switzerland
Denmark	Malaysia	Taiwan
Ecuador	Malta	Thailand
Egypt	Mexico	Turkey
Estonia	Netherlands	United Arab Emirates
Finland	Netherlands, Kingdom Of The	United Kingdom (Great Britain)
France	New Zealand	United Kingdom (Northern Ireland)
Germany	Norway	United Kingdom Of Great Britain And Northern Ireland
Greece	Oman	United States Of America

Compendial Status – Momentum & Convergence

Compendial Method

2020: Ph.Eur. 2.6.32
2024: BP XIV C
2024: EAEU 2.1.6.12
2024: USP <86>
2025: Brazil, WHO (proposed); PDG Statement

Compendial Monograph & Guidance Chapters

2023: Ph.Eur. Water for Injection Monograph

2020: ChP 9251
2021: JP G4-4-180
2023: KP

Appendix: PDG position

PDG is committed to making efforts to develop and revise existing test methods, for example, the test for Bacterial Endotoxins (BET), to decrease the use of animals or animal derived reagents.

In PDG's general chapter Bacterial Endotoxins (Q-06), six methods are described that use Limulus or Tachypleus Amoebocyte Lysate (LAL/TAL) as a reagent. This reagent consists of cells (amoebocytes) derived from the horseshoe crab.

PDG recognizes the availability of non-animal derived recombinant reagents as alternatives to replace LAL/TAL in the BET. These alternatives include recombinant factor C (rFC) and synthetic mixtures that mimic the coagulation cascade, referred to as "recombinant cascade reagents" (rCR).

The pharmacopoeias of PDG and the regulatory framework they are embedded into are at different stages of acceptance regarding the performance of recombinant reagents compared to LAL/TAL.

PDG's goal is to include new methods using recombinant reagents in the harmonised chapter.

World Health Organization

WHO/BS/2025/2488
ENGLISH ONLY

Guidelines on the replacement or removal of animal tests for the quality control of biological products

Risk assessments should take into account the nature of the product, the starting/raw materials and the product-related impurities. Careful consideration should be given to the selection and implementation of pyrogenicity/endotoxin assays at the appropriate stages of product development, manufacture and quality control. In all cases, the use of the RPT is no longer recommended, and it should be replaced with the alternative pyrogenicity/endotoxin tests described above. Where there is a risk of non-endotoxin pyrogens being present, the use of the MAT is recommended. In cases where non-endotoxin pyrogens are unlikely to be present, endotoxin testing using the rFC assay or rCR assay is recommended.

Key hurdles and practical approaches to facilitate the transition from compendial method validation to regulatory acceptance

Hurdles	Approach
Communication & Alignment	Understand the underlying science and be able to articulate your motivation
Quality and Regulatory Strategy	Generate, submit and defend your data Commit to your change and expect/compel consistency
External Environment	Benchmark Understand the global landscape
Efficiency of Acceptance	Seek regulatory and pharmacopoeia innovation to speed transition

We can and must implement new approach methods to achieve supply chain resiliency and the safe supply of medicine while realizing positive and sustainable benefits.