AstraZeneca's Perspectives on the Prospective Harmonisation Pilot

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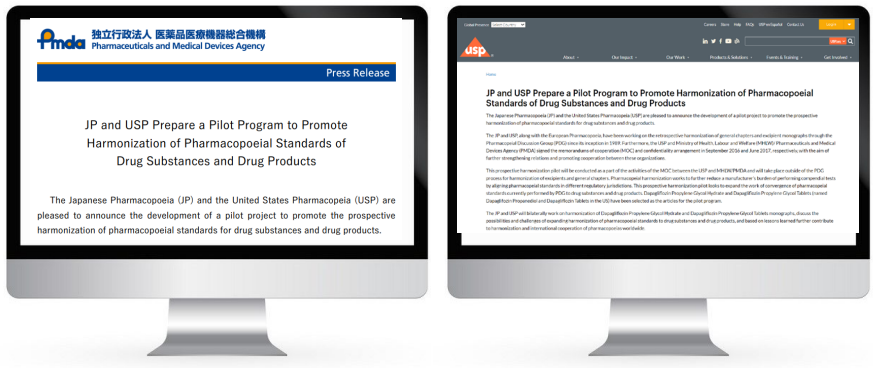
History of JP Dapagliflozin Propanediol monograph elaboration



PMDA & USP announced the prospective harmonisation pilot on the Dapagliflozin Propanediol monographs on their respective websites in Oct 2023

Request for bilateral monograph elaboration documents in Oct 2023

Document submissions in Dec 2023 & Jan 2024

	API	Drug Product
USP	Adopted (1 Dec 2023)	To be published
JP	Public comment (1 Sep 2024)	Public comment (1 Sep 2024)
Ph Eur	To be published (1 Jan 2025)	To be published (1 Jan 2025)

EXTERNAL

Expert Committee on Chemicals, Working Group, established in Sep 2023

This enables AZ to significantly speed document submission preparation and delivery

Prospective Bilateral Harmonisation Kick-off meeting in Aug 2023

Established a team that was exclusively responsible for data package

INTERNAL

Interest expressed in May 2023

Setting tactical & strategy plans in projects

Development & Enterprise thinking

Aligned standards disperse risk and ensure a stable product supply

Pharmacopoeia monograph benefits

Basic role and attribute

- Lists essential pharmaceuticals, provides information on quality, and offers explanatory guidance
- Demonstrates official standards of appropriate quality for medicinal purposes
- Supports innovation and consistency in global pharmaceutical quality assurance

Simplification

- Harmonised monographs with approved test methods and specifications, minimising effort for adoption
- In the case of API/Products already listed in JP, abbreviated entries permitted

External Advocacy

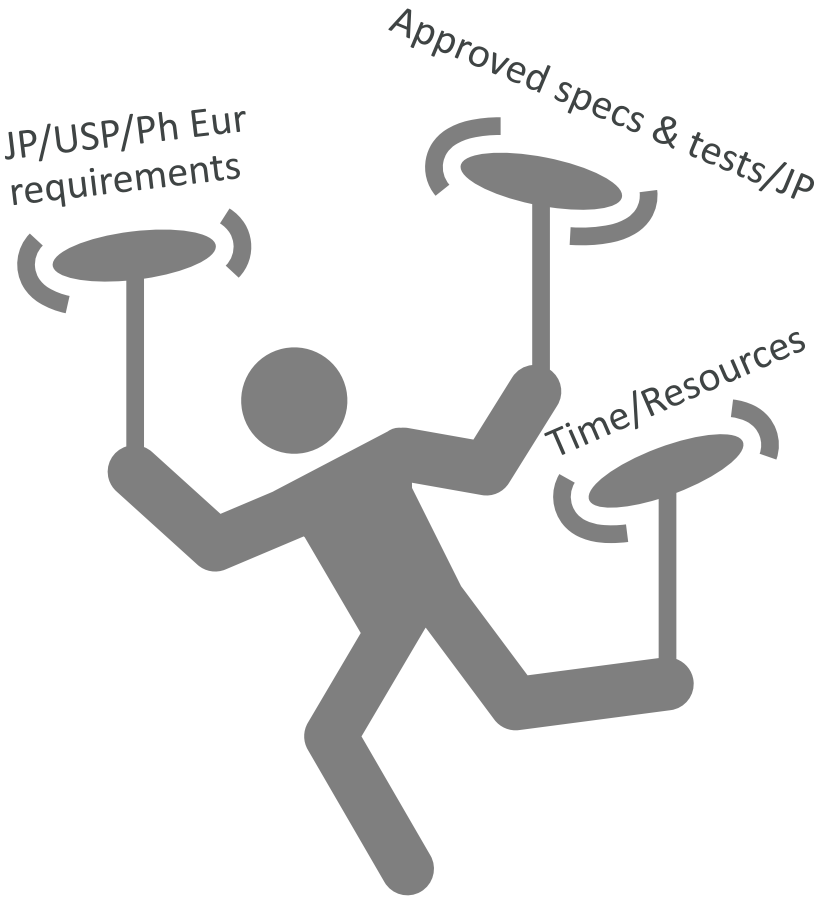
- System suitability calculation harmonised globally, enabling adoption of our test methods without change
- Aligned standards are dispersing risk and ensure more stable supply of products

Harmonisation

- Leading global Pharmacopoeia engagement in monograph development
- USP, JP & Ph Eur monographs advocate other pharmacopoeias

Impacts that pharmacopoeia monographs have on product release

- **Legal Obligation:** Compliance with Pharmacopoeia monograph quality standards is mandatory in some territories
- **Change Documentation:** Adjusts the burden of change documentation and implementation
- **Alternative Procedures:** Allows alternative analytical methods if they ensure compliance with monograph standards
- **Resource Commitment:** Essential to allocate resources for monograph development to maintain operational licenses throughout the product lifecycle



- **Patient Safety:** Pharmacopoeia monographs are crucial for enhancing patient safety and access to high-quality medicines
- **Risk Dispersal:** Aligned standards disperse risk and ensure a stable product supply

Technical & regulatory challenges

Current Position	Desired Position
API identification by UV should be included in the JP monograph however this is not an identity test operated by AZ or included in the USP/Ph Eur	• **Identification by UV to not be included in the JP monograph** • **Harmonise with USP/Ph Eur and include IR and HPLC with no additional specification and test**
API identification by IR (KBr or ATR & reference spectrum or reference standard spectrum)	• **Harmonise with USP/Ph Eur – KBr or ATR adopted** • Reference spectrum not accepted – compare sample spectrum with reference standard spectrum
JP description versus rationalisation description	• **Introduction/adoption of the concept of rationalisation** • **Strive for international harmonisation**
Chromatography <*2.01*> versus <*2.00*>	• **Harmonise JP's Chromatography <*2.00*> application policy with USP, including the sensitivity calculation** • **Global unification of chromatographic conditions**

Technical & regulatory challenges

Current Position	Desired Position
System suitability test – to confirm that specificity for the test component is ensured in the assay, set resolution as well as peak symmetry in JP – this resolution is not specified in the USP/Ph Eur	• The system performance in the assay is defined only by the peak symmetry and as such is in line with the approach followed in dissolution tests.
Disintegration versus dissolution test	• **Disintegration is adopted based on prior knowledge and manufacturing experience** • While setting disintegration for AZ product is reasonable, it's not advisable to automatically apply it to other products. Control by disintegration test is permitted under QbD development in manufacturing requirements.
Non-availability of translated monograph content	• Preparation in a timely manner

Advantages of prospective harmonisation

- **Shared Documents**: Manufactures, JP and USP share the same documents and data
- **International Harmonisation**: Promotes harmonisation of technical requirements and direct communication with regulators
- **Early Adoption Support**: Encourages early monograph adoption, typically taking a few years before official adoption
- **Reduced Testing Burden**: Aligned pharmacopoeial standards across regulatory jurisdictions reduce manufacturers' burden of compendial tests
- **Standard Convergence**: A pilot initiative to expand convergence of pharmacopoeial standards for API and drug products, contributing to global harmonization and cooperation

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Any Questions?