

**Consultation response: Dissolution testing in  
BP finished products monographs for solid  
oral dosage forms**

## Background

Oral dosage forms are the most convenient and widely used drug presentations. For solid oral dosage forms it is necessary to determine the rate and extent of dissolution of the active ingredient during development, in stability testing, and as part of the control of the finished product. A pharmacopoeial dissolution test is a crucial analytical procedure which needs to be robust and reproducible. Ideally, the test will identify critical changes to the performance of a product and be able to discriminate between differences in batch quality of multiple formulations. The release of the active pharmaceutical ingredient (API) from the dosage form is a Critical Quality Attribute as defined in ICH Q8(R2) and should be suitably controlled.

The importance of dissolution testing in compendial standards has been recognised by many pharmacopoeias including the USP<sup>1</sup> and the WHO<sup>2</sup> International Pharmacopoeia. Feedback from users has also indicated the value of dissolution testing in public quality standards

The British Pharmacopoeia (BP) also recognises the importance of dissolution testing in ensuring product quality and therefore launched a consultation on how dissolution testing in BP finished product monographs for solid oral dosage forms could be improved.

In January 2017 a public consultation was published, which closed in April 2017. The purpose of the consultation was to invite key stakeholders and those with an expert opinion to provide feedback and advice on how the BP could improve its processes with regard to dissolution testing. This original consultation can be found at the following link:

<https://www.pharmacopoeia.com/content/file/Consultation-Dissolution-testing.pdf>

The responses received from the consultation were from a range of valued stakeholders including pharmaceutical manufacturers; trade and regulatory bodies; academia/researchers; and analysts. The responses were reviewed by the BP's Expert Advisory Group for Pharmacy (EAG PCY) during a meeting in September 2017. Figure 1 shows how the feedback from the various stakeholders was initially handled.



Figure 1 - initial workstream for dissolution public consultation

This report contains:

1. Introduction to the consultation
2. Key themes from the consultation responses
3. Outcomes and key points
4. Implementation

<sup>1</sup> <http://www.usp.org/chemical-medicines/dissolution-explained>

<sup>2</sup> [https://www.who.int/medicines/publications/druginformation/issues/WHO\\_DI\\_29-4\\_Pharmacopoeia.pdf](https://www.who.int/medicines/publications/druginformation/issues/WHO_DI_29-4_Pharmacopoeia.pdf)

## 1. Introduction to the consultation

The following four statements were used as a basis for a series of open questions asked to stakeholders in the consultation:

- i. For BP finished product monographs for conventional-release solid oral dosage forms published prior to 2008, the established BP criteria using either the basket or the paddle apparatus specified under 'Monographs of the British Pharmacopoeia' in *Appendix XII B. Dissolution* are currently applicable.
- ii. For BP finished product monographs for conventional-release solid oral dosage forms published after 2008, the harmonised "Q" acceptance criteria are currently applicable, where Q = 75% of label claim in 45 minutes.
- iii. A large number of BP finished product monographs for solid oral conventional-release dosage forms do not refer to the Q acceptance criteria within the monograph.
- iv. For BP finished product monographs for prolonged-release solid oral dosage forms, a Production statement is currently included rather than including a dissolution test in the monograph.

## 2. Key themes from the consultation responses

Specific questions were utilised to allow for a focused approach for gathering the feedback on the above statements.

### 2.1 What are your general comments on the current situation in the BP outlined above and how could it be improved?

An understanding of the relationships between the requirements of the pharmacopoeia and the competent authorities is key to maximising the benefits of compendial dissolution tests, the consensus among responses from stakeholders suggested that the pharmacopoeia could further define these relationships for the user.

The responses from industry and trade bodies stated that the adoption of Q criteria across both existing and new monographs is preferable. (The quantity, Q, is the specified amount of dissolved active substance, expressed as a percentage of the labelled content<sup>3</sup>).

The responses from independent stakeholders and consultants highlighted that the supporting information for dissolution testing and the relating policy could provide greater clarity. The BP should take this opportunity to update the relevant supplementary chapter.

Regulatory bodies commented that it would be beneficial to clarify further that competent authorities can have different requirements than those stated in the pharmacopoeia. The regulatory bodies also highlighted that applicants did not know the contents or whereabouts of the supplementary chapter, SC I E: Dissolution testing of Solid Oral Dosage Forms, and that there should be greater visibility and easier access to this informative chapter and appendices on dissolution.

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<sup>3</sup> British Pharmacopoeia Commission. *British Pharmacopoeia 2018*. London: TSO; 2017. Appendix XII B. *Dissolution*

## **2.2 For monographs requiring dissolution testing, what methods would be useful to include to enable users to carry out the test?**

All stakeholders indicated that the current methods in the BP were acceptable for use and generally no changes were thought necessary. The industry and trade bodies mentioned that there could be further information in a supplementary chapter that would help the analyst in developing alternative procedures.

Independent stakeholders mentioned that clearer guidance on the use of alternative methods should be provided. It was also noted that the industry was moving towards mechanical calibration of equipment.

The desire to maintain a single dissolution test for each monograph was raised as this assists in the comparison of products. It was noted and reiterated that dissolution tests in a monograph should always be considered the minimum requirement for that product.

## **2.3 Should multiple dissolution tests be included in the BP to reflect the methods used for available products?**

Across both industry and regulatory bodies, there was a clear and strong view that the inclusion of multiple methods for dissolution testing within the monographs was not the preferred option. There were however comments that indicated multiple dissolution tests should only be included in exceptional circumstances and when they can be fully justified. The regulatory bodies indicated that where a secondary test is included, a clear statement should be made in the monograph to indicate when the alternative test should be applied.

## **2.4 Do you believe that dissolution tests and acceptance criteria should be included in BP monographs for prolonged-release preparations? If yes, please indicate what tests and criteria you would propose including in the monograph.**

There was a shared opinion across industry, regulators and independent analysts that it would be difficult to achieve an inclusive test or set of dissolution tests for the same prolonged-release product from different manufacturers. However, the responses from regulatory stakeholders suggest that a dissolution test for prolonged-release preparations would be beneficial, so that there is an analytical method available to enforce and control the quality of prolonged-release products.

The majority of the responses focused on ensuring the inclusivity for products with different release profiles, while also postulating that there should be a minimum standard that products are required to meet. It was suggested that this could be achieved by setting sampling points for products within adapted and revised production statements.

## **2.5 Should Q acceptance criteria be included in the BP for solid oral dosage forms in future new monographs and included as part of a revision for current monographs?**

A large majority of the responses proposed that all new and current monographs should use Q as the acceptance criteria. This view was shared across regulatory bodies, industry and independent analysts. Stakeholders from industry requested that any changes that would have a regulatory impact should be appropriately managed over a suitable timeframe. A phased implementation of the change was also suggested; this would allow licence holders time to submit variations if required.

**2.6 In your opinion, how could Q values be set to ensure that they are appropriate for the preparation? For example, current BP policy is a default Q = 75% at 45 minutes. However, such default values may not be appropriate in practice.**

The common theme observed across the range of responses, was that a default Q value across all monographs is not appropriate and a more meaningful requirement should be selected based on the products covered by a specific monograph. A number of stakeholders stated that BP Q criteria should be the minimum quality requirement for marketing authorisation holders (MAHs). Industry groups also reiterated that current licensed product specifications should be considered when setting the Q criteria.

**2.7 What criteria are important to consider in a compendial quality standard when setting the acceptance criteria in dissolution testing?**

The responses to this question were varied, but overall, suggested that stakeholders believe that the methods and acceptance criteria included in monographs should ideally be clinically relevant, however it was acknowledged that this is not always possible or necessary. The methodology and acceptance criteria need to be capable of rejecting batches whose performance is significantly inferior to those used in the clinical/bioequivalence studies. It was also noted that the limits in dissolution tests should not be so strict as to inhibit licensing of safe, effective medicines but not so loose as to provide limited control.

The responses across industry imply that the amount of information in the monographs should be dependent on several factors including; information gained during development of the product, what other measures are in place as part of a wider control strategy, and ease of use for the individual analyst.

### 3. Outcomes and key points

The responses were discussed in depth by EAG PCY, a number of key points emerged from these conversations. These key points have been collated and are detailed in section 3.2

#### 3.1 Outcomes

The BP recognises the importance of maintaining up to date standards and guidelines and this review discusses the detail from stakeholder comments and EAG PCY members to formulate a clear directional strategy.

There are currently more than 400 pre-2008 BP monographs that do not use the 'Q' approach for dissolution<sup>4</sup>. This causes confusion for users and emerged as a key theme from all the responses received and discussions undertaken. Figure 2 details the current procedure to assist users of the BP to identify different criteria for dissolution testing of a product.

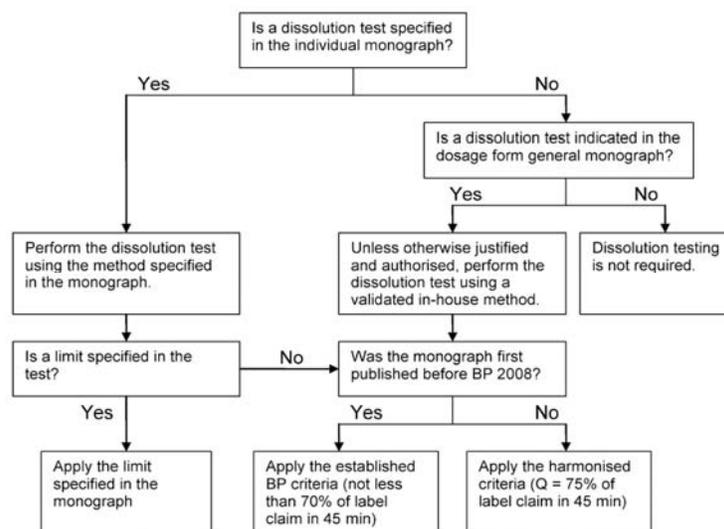


Figure 2 - Schematic diagram outlining which limits apply in the case of each monograph<sup>2</sup>

This procedure could be improved to further aid users and it has been proposed that that this schematic diagram should be updated. The diagram will be redesigned to alleviate the confusion and simplify the process, where it is necessary and data are available to do so.

Monographs that include the pre-2008 BP criteria for solid oral dosage forms, including those that do not currently contain a dissolution test will be reviewed. Monographs will be updated to include a dissolution test, with suitable Q acceptance criteria. Monographs for revision will be prioritised based on a number of factors including usage, the Biopharmaceutics Classification System (BCS) class of the drug substance and therapeutic range.

Further supporting information will be provided within the publication to improve guidelines and visibility of information regarding dissolution testing within the BP. The aim is to aid users to easily identify and access the relevant information when navigating the dissolution texts within the BP, including a clear and transparent policy for dissolution testing requirements.

The need for the BP to remain applicable to all stakeholders was identified as a key attribute and as such, the current analytical methods and techniques used in the BP will be retained. The

<sup>4</sup> British Pharmacopoeia Commission. *British Pharmacopoeia 2018*. London: TSO; 2017. SC 1 E. Dissolution testing of Solid Oral Dosage Forms.

responses and discussions indicated that there could be instances where alternative methods may be required; the BP will seek to provide sufficient guidance on the justification of alternative methods.

It is noted that competent authorities control the quality of each and every product during the licensing process and therefore specific methods for dissolution of prolonged-release products will not be widely introduced at this time. The BP recognises the importance of providing adequate controls of prolonged-release dosage forms. However, the advancements of new technology for dissolution testing are not universally available, and setting criteria that utilise these technologies does not fit with the BP's policy of remaining inclusive for all stakeholders. As a result of this, the BP will continue to explore opportunities to control prolonged-release dosage forms and this will be kept under review.

Relationships with stakeholders across the world are key to the BP's objectives. Continuing to develop and build upon these relationships will assist in the establishment of appropriate acceptance criteria for key quality attributes of medicines, including, but not limited to; dissolution.

### 3.2 Key Points

The BP should provide further guidance and clearly defined expectations for dissolution testing. These documents should be more clearly visible to the user.

Current dissolution testing methods in the BP are still relevant and should be retained as per Appendix XII B. *Dissolution* (Ph. Eur. monograph: 01/2016:20903). These tests should be maintained as a harmonised text between the Pharmacopoeial Discussion Group (Ph.Eur, USP, JP).

The BP should revise applicable monographs to include suitable dissolution tests. The revisions will be prioritised based on the use and impact of the product, also including information relating to the BCS class of the drug substance and the therapeutic range.

Dissolution requirements within monographs should all be expressed in terms of the internationally harmonised quantity, Q, of active substance dissolved in a specified time.

Control of prolonged-release solid oral dosage forms poses different and more complex challenges.

The relationships between the BP and its stakeholders remain vital to ensuring the quality of medicines. There should be continued close working with all our partners and stakeholders.

#### 4. Implementation

The key discussions have been translated into strategic objectives and these will be combined to form a defined process to develop, implement and periodically review an updated policy on how the BP addresses dissolution testing of solid oral dosage forms. This has been illustrated through the diagram in figure 3.

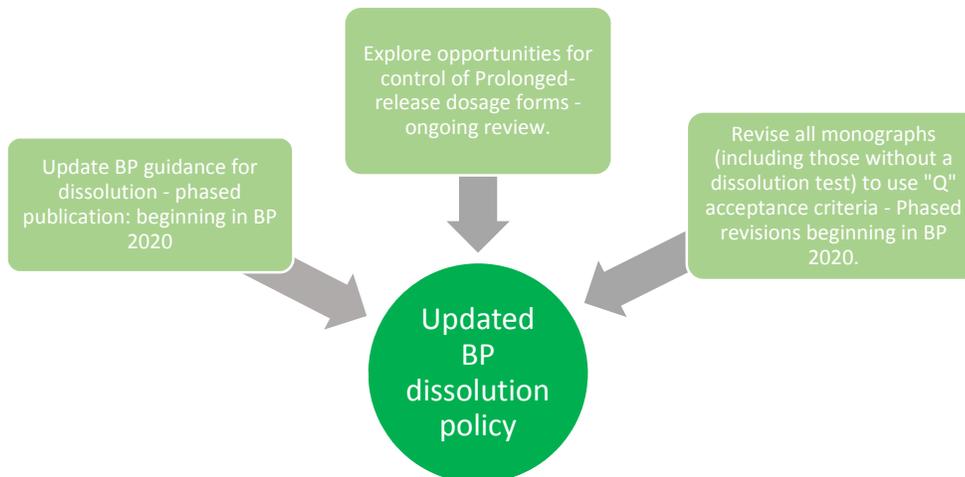


Figure 3 - Implementation process to update BP dissolution policy

The first step will include addressing the guidance in the supplementary chapter, SC I E: Dissolution Testing of Solid Oral Dosage Forms, to ensure ease of use of the methods contained within the publication. The current layout of the appendices for dissolution, which splits the dissolution methods for different pharmaceutical dosage forms into different monograph texts, can be confusing for users. The Secretariat and the members of EAG PCY have worked together to re-order these appendices, which can be seen in Table 1. This update will be published in the BP 2020. This change will help enhance the user experience in performing dissolution testing and will provide clarity on the location of information within the BP publication.

**Table 1 – Layout of Appendices for Dissolution from BP 2020**

Title	Texts
<b>Appendix XII B. Dissolution</b>	1. Dissolution Test for Tablets and Capsules (Dissolution Test for Solid Dosage Forms) (Ph. Eur. method 2.9.3)
	2. Dissolution Test for Transdermal Patches (Ph. Eur. method 2.9.4)
	3. Dissolution Test for Lipophilic Solid Dosage Forms (Ph. Eur. method 2.9.42)
	4. Dissolution Test for Medicated Chewing Gum (Ph. Eur. method 2.9.25)
	5. Intrinsic Dissolution (Ph. Eur. method 2.9.29)
	6. Apparent Dissolution (Ph. Eur. method 2.9.43)
	Monographs of the BP
<b>Appendix XII B. ANNEX: Recommendations on Dissolution Testing</b>	Ph. Eur. general texts 5.17.1

The BP appreciates that the strategy for future dissolution testing and acceptance criteria encompasses a broad spectrum of changes. Notably, the proposal to review and revise older monographs, to bring them in-line with current standards and including a suitable dissolution test, where applicable. Including this test will have a positive effect on public health. However, the BP understands that the regulatory burden on manufacturers could temporarily be increased. The BP will work closely with stakeholders to minimise the risks associated to avoid any issues with supply and quality. The BP will duly inform manufacturers in advance of the publication, matters relating to likely changes to product monographs to include dissolution tests or an update to the acceptance criteria for existing dissolution tests.

## **Conclusion**

Based on the discussions and recommendations from the consultation, the BP Secretariat, with the support of the BP Commission, aims to develop a revised BP policy on dissolution testing. The BP will address each of the points raised with a clear action plan that defines how this policy will be implemented.

Any specific changes to dissolution criteria in monographs will be communicated to the appropriate stakeholders before the change is implemented. This will include, but not be limited to, information relating to the public consultation window for each monograph; this process already occurs during each quarter of the calendar year.

The responses to the consultation highlighted the need for further clarity in the BP regarding the scope of compendial standards and their role within the regulatory framework of medicines. The BP, in conjunction with the MHRA Licensing Division, will explore how best to communicate this to our stakeholders.

The BP wishes to thank all stakeholders for taking part in the consultation. This continued cooperation and participation of stakeholders is of great value. The BP is committed to ensuring patient safety and we aim to tailor the content so that the needs of all users can be met whilst maintaining high quality standards for pharmaceutical substances and medicinal products, in the interest of protecting public health.