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European Pharmacopoeia Monographs on Extracts: Reflections following recent discussions

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1. INTRODUCTION

It is a decade since the article by Lang and Stumpf [1] and the response by Helliwell [2] appeared in Pharmeuropa 11.4 and re-ignited the debate on the definition and classification of extracts used in herbal medicinal products. In response, the European Pharmacopoeia Commission established a Working Party, composed mainly of experts from industry, to reach a consensus on the issues involved. The results of the Working Party deliberations were presented during the symposium *Herbal Medicinal Products: Quality Evaluation - Contribution of the European Pharmacopoeia*, Nice (France), November 2000, and the proposed revision to the general monograph on Extracts (0765) was published in Pharmeuropa 12.4 [3]. Many comments were received on the proposed revisions. These were considered by the Working Party leading, eventually, to the publication of the revised general monograph on Extracts (0765) with an effective date of January 2003[4].

Despite the attempts of the Working Party to reach a consensus, the debate has continued unabated during the intervening years fuelled by the introduction of many more extract monographs into the European Pharmacopoeia (Ph. Eur.), the publication of numerous documents by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMEA) and the different interpretations placed on both Ph. Eur. monographs and HMPC documents by the various National Regulatory Authorities. These differences were clearly in evidence at a workshop [WS3]: *Are European Pharmacopoeia Monographs on Extracts a useful basis for the development of Herbal Medicinal Products?* This workshop formed a part of the 57th International Congress & Annual General Meeting of the Society for Medicinal Plant and Natural Product Research (GA) which took place in Geneva in August 2009 and at the EDQM (European Directorate for the Quality of Medicines & HealthCare) and GA Conference on *Herbal Drugs and Herbal Drug Preparations* in Vienna (Austria) in September 2009.

However, during the last 18 months, an encouraging development has been a closer working relationship between the Ph. Eur. and the HMPC, with representatives from the Ph. Eur. Secretariat attending, as observers, various meetings of the HMPC and representatives from the HMPC Quality Drafting Group (QDG) attending, as observers, meetings of the relevant Groups of Experts of the Ph. Eur. This, together with proposed annual meetings between the Chairs and Secretariat of the relevant Groups of Experts of the Ph. Eur. and the HMPC QDG, leads to the hope of an eventual resolution to many of the outstanding issues which are currently the cause of much concern to the various stakeholders involved in the Herbal Medicinal Products industry. It was as a result of the first of these annual meetings, in April 2009, that it was agreed that an open and honest assessment of the current issues should be presented for discussion. This article attempts to go some way towards fulfilling that objective.

2. MONOGRAPHS ON EXTRACTS

It is agreed by all parties that monographs on herbal drugs (herbal substances) are an essential inclusion in the Ph. Eur. to define the quality of the materials from which extracts are manufactured. However, there is no such consensus as to whether monographs on extracts should be included in the Ph. Eur. The argument against their inclusion being that there are many extracts on the market, incorporated into herbal medicinal products, which fall outside the scope of the extract monographs included in the Ph. Eur. The major differences appear to be concerned with the solvents used for extraction and the constituents used as the basis for assay.

Currently several categories of extracts are defined in the Ph. Eur. – ***Standardised, Quantified, 'Other'*** and ***Refined***. Each of these is considered below highlighting some of the issues requiring resolution.

2.1 - Standardised Extracts

According to the Ph. Eur. definition:

Standardised extracts are adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity; standardisation is achieved by adjustment of the extract with inert material or by blending batches of extract.

Whereas, the HMPC definition is:

Standardised herbal substances/herbal preparations are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardisation is achieved by adjustment of the herbal substances/herbal preparations with excipients or by blending batches of herbal substances and/or herbal preparations.

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Criticism of the Ph. Eur. definition arises from:

(a) defining these extracts in terms of '*…constituents with known therapeutic activity…*', a non-quality parameter when the remit of the Ph. Eur. is solely from a quality perspective; (b) giving a range of values for content of assayed constituents in the definition of individual extract monographs, for example, Frangula bark dry extract, standardised (1214) [5] where the content is stated as '*15.0 per cent to 30.0 per cent of glucofrangulins, expressed as glucofrangulin A…; the measured content does not deviate from that stated on the label by more than +/- 10 per cent'*.

In answer to (a), this category of extracts is dependent upon the recognised therapeutic activity of their known constituents and there appears to be no other way of distinguishing and, hence, defining them. In answer to (b), the Ph. Eur. is required to be inclusive for all extracts from a particular herbal drug which are ingredients in licensed/registered products in countries which are signatories to the European Pharmacopoeia Convention. The intention is that, although in certain individual monographs a range for the assayed constituents of an extract is stated, any given commercial extract will have been adjusted to a defined single content, within the stated monograph range, with an acceptable tolerance (usually +/- 5.0 per cent to +/- 10.0 per cent) depending upon the assayed constituents and assay method.

The approach adopted by the Ph. Eur. Working Party on Extracts in 2000 in defining *Standardised Extracts* can be illustrated by the following from an article by Brand *et al* [6], who were other early contributors to the extract debate: *If there are any constituents with known therapeutic activity which, if being isolated, exert the same or similar therapeutic effects as the total extract and which show a dose-response relationship, emphasis should be laid on these constituents. In this case the extract must be adjusted (standardised) to a constant defined, narrow-range content of this/these constituent(s).* Here, the emphasis is on the therapeutic effect of the extract and a dose-response relationship of the constituents. This is easy to understand for a standardised extract of a hydroxyanthracene glycoside containing herbal drug where the dose can be adjusted to give either a mild laxative effect or a drastic purge. However, how does a standardised extract, such as that from ipecacuanha used as an emetic, giving an all or nothing response, fit this model?

An alternative approach to defining *Standardised extracts* is exemplified by the following given by Länger [7] during the 2009 Geneva Workshop [WS3] previously referred to:

Therapeutic activity of extract = therapeutic activity of isolated constituent with known therapeutic activity.

This approach also causes problems because other constituents in the extract may either modify or act synergistically with the known therapeutically active constituents. This was acknowledged by Länger when referring to the content of triterpene glycosides in Horse-chestnut dry extract (20 per cent of the content of the extract in this example), when he stated that there was no evidence that the remaining 80 per cent of the extract did not contribute to the activity. Such interactions would produce differences in the response of an equivalent quantity of the same constituent(s) present either as part of an extract or as the isolated constituent(s). Thus, the dose-response relationship between an isolated constituent and its presence in an extract may not be an equivalent single plot but, more likely, similar but separate plots more or less parallel with each other.

This is why the observation by Brand *et al* (6) is so important because no extract is fully characterised for all constituents and monographs are developed using the most appropriate, generally accepted, knowledge at that point in time. Ph. Eur. Groups of Experts can only elaborate monographs for those extracts used as ingredients in existing licensed/registered medicinal products and cannot become involved in judging the validity of the latest research data related to the efficacy of *in vitro* or *in vivo* studies. This must be judged by regulatory authorities when such data is submitted as the basis of a marketing authorisation which, if successful, may lead to either the revision of an existing Ph. Eur. monograph or the request for an additional monograph to be included in the Ph. Eur.

Standardised extracts are the only category of extracts which are allowed to be adjusted to a given content of constituents using inert excipients in addition to adjustment by the blending of batches. The rationale being that, because the assayed constituents are responsible for the majority of the therapeutic activity, adjustment based solely on such constituents is both acceptable and desirable in order to provide a consistent level of therapeutic activity in the medicinal product into which the extract is incorporated.

It is generally recognised that only a small number of extracts will fulfil all of the criteria required for standardised extracts.

2.2 - Quantified Extracts

When the Ph. Eur. Working Party on Extracts met in 2000 to re-assess the general monograph on Extracts (0765) following various criticisms that the then monograph did not adequately define the extracts on the market, the Working Party was well aware of a small, but significant, number of extracts which were neither extracts where the majority of the therapeutic activity could be related to one or more known constituents (Standardised extracts) nor extracts where it was not possible to link any supposed therapeutic activity with identified constituents (*'Other' extracts*). The Working Party also recognised that this small number of extracts where the basis of a range of herbal medicinal products in which certain organisations had invested substantial financial resources to attempt to demonstrate, by clinical trials, the effectiveness of these products in the treatment of certain conditions. Such extracts were defined (sometimes through patents) on 1 or, usually, several constituents whose contents were controlled within defined ranges. This control of the extracts and similarly of the herbal medicinal products into which the extracts were incorporated satisfied a number of regulatory authorities that the necessary data had been generated to allow reasonable batch to batch therapeutic effectiveness. Such extracts were termed *Quantified extracts*.

According to the Ph. Eur. definition:

Quantified extracts are adjusted to a defined range of constituents; adjustments are made by blending batches of extracts.

Whereas, the HMPC definition is:

Quantified herbal substances/herbal preparations are adjusted to a defined range of constituents (active markers); adjustment is exclusively achieved by blending batches of herbal substances and/or herbal preparations.

The HMPC definition introduces the concept of *active markers* which it defines as: *constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.*

This is a workable concept providing that the HMPC or its QDG is prepared to state the *active markers* on which assessments have been made and define acceptable ranges for these *active markers* within the herbal medicinal product/extract. Such information could then form the basis for the elaboration of Ph. Eur. monographs. Clarification is also required as to whether quantified extracts are only to be defined on *active markers* or if, in certain circumstances, they might be defined on a combination of *active markers* and *analytical markers* (see '*Other' extracts*). St. John's wort dry extract, quantified (1874) [8] being a good example of how, over the years, there has been a pendulum-like opinion as to the therapeutic role of the markers assayed.

There is little difference in concept between the definition and control of quantified extracts as envisaged by the HMPC and Ph. Eur. The original Ph. Eur. Concept, as explained at the Symposium in Nice (France) in 2000 [9], is illustrated with Figure 1. However, it is clear that a more comprehensive definition for this category of extracts is required in order that extracts satisfying these requirements may be clearly identified.

The content of analysed constituents in quantified extracts cannot be adjusted by the use of inert excipients. The only permitted use of such excipients in this category of extract is for technological purposes, for example, as a processing aid to give adequate flow characteristics to dry extracts for the production of solid dosage forms. The rationale for this being that the analysed constituents are only '*generally accepted to contribute to the therapeutic activity'*, therefore, there are 1 or more as yet unidentified constituents which are also contributing to the therapeutic activity. If adjustment of the assayed *active markers* was by the use of inert excipients, as for *Standardised extracts*, the as yet unidentified constituents, which are also contributing to the therapeutic activity, may be diluted disproportionately or randomly. Therefore, it is considered more appropriate to blend batches in order to achieve the required levels of the assayed *active markers*, thereby, in theory, maintaining a more controlled content of the as yet unidentified constituents which also contribute to the therapeutic activity.

For example, Quantified St John's wort dry extract (1874), where the assayed constituents are generally accepted to contribute to the therapeutic activity of the extract. Such extracts do not show a typical dose-response relationship. Such extracts to be assayed for a minimum of 2 constituents and these constituents to be quantified at typically ± 10-20% (but not more than ± 25%) of the declared value. Adjustments to achieve quantification within stated limits of constituents to be by either blending suitable batches of extract and/or by blending batches of the starting material prior to extraction.

As for standardised extracts, it is recognised that only a small number of extracts will fulfil the requirements for quantified extracts.

2.3 – 'Other' extracts

All extracts not complying with the definitions for *Standardised extracts* or *Quantified extracts* belong

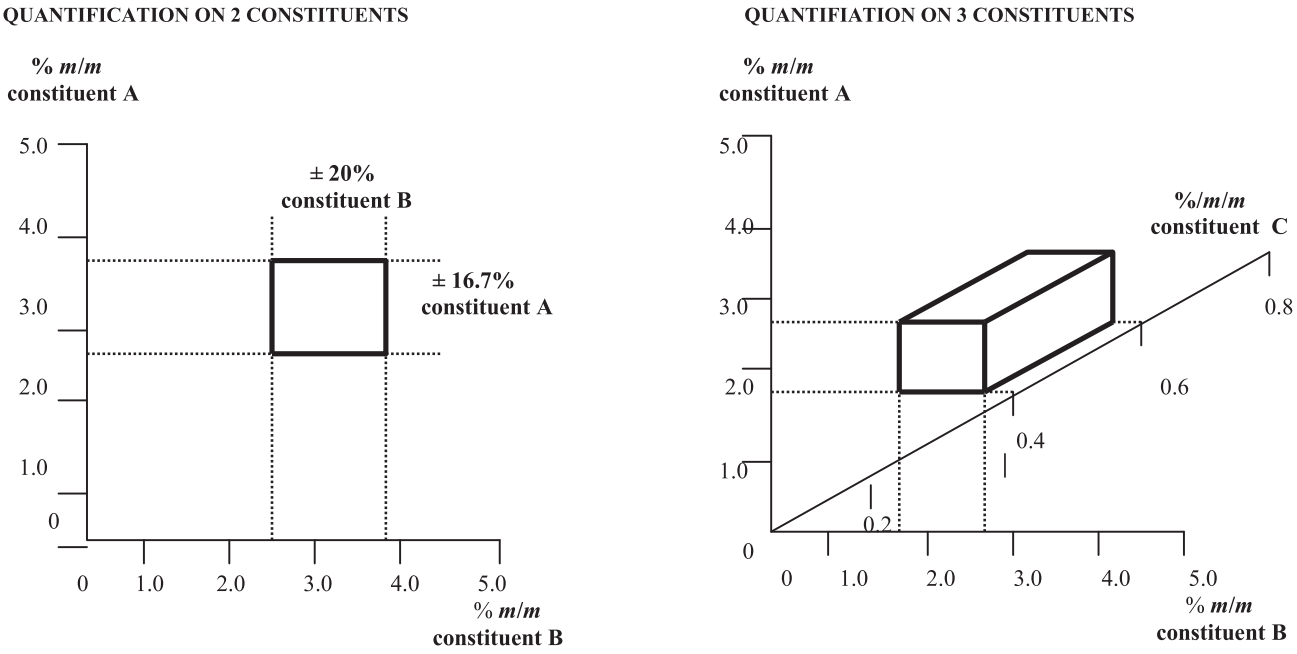

Figure 1 - *Ph. Eur. Working Party concept for Quantified extracts*

to this category. According to the Ph. Eur. definition: *Other extracts are essentially defined by their production process (state of the herbal drug or animal matter to be extracted, solvent, extraction conditions) and their specification.*

Whereas, the HMPC definition states: *Other herbal substances/herbal preparations are active substances for which neither constituents with known therapeutic activity nor active markers are known. These herbal substances/herbal preparations are not adjusted to a defined content of analytical markers.*

The HMPC definition introduces the concept of *analytical markers* which it defines as: *constituents or groups of constituents that serve for analytical purposes.*

Neither of these definitions for *'Other' extracts* reflect reality in that the Ph. Eur. definition suggests that only *'Other' extracts* are defined by their production process. Whereas, an integral part of the definition for all categories of extract is their production process combined with their specification. The HMPC definition states that these extracts are not adjusted to a defined content of *analytical marker*. However, commercial batches of *'Other' extracts* have remarkably consistent levels of *analytical markers* which are not reflected by the wide range of content of these same *analytical markers* in the herbal drug (herbal substance) upon which the extracts are based.

The name *'Other' extracts* is unsatisfactory and it is proposed that an alternative name, for example, *Characterised extracts* or *Non-Standardised/Non-Quantified extracts* should be introduced. However, unlike the terms *Standardised* and *Quantified*, the chosen term would not be included in the extract title.

A common criticism of the category *'Other' extracts* arises from the fact that, in individual Ph. Eur. monographs, only a lower limit is given for the assayed constituents. This is apparently being used as a basis for the argument that provided that the content of *analytical markers* in the extract/herbal medicinal product remains in excess of this lower limit, the extract/herbal medicinal product is of an acceptable quality. However, this lower limit for the *analytical markers* in an extract is intended to indicate a minimum content which would be expected using the criteria given in the production section of that extract monograph when using herbal drug (herbal substance) complying with the minimum content for the same *analytical markers* stated in the Ph. Eur. The majority of commercial operations would use herbal drug (herbal substance) in excess of the minimum content of *analytical markers* stated in the Ph. Eur. monograph and hence the content of *analytical markers* in the extract will often be substantially higher than the minimum content in the Ph. Eur. monograph on the corresponding extract. Therefore, as only a lower limit for *analytical markers* is stated in the monograph on the herbal drug (herbal substance), the inclusion of lower and upper limits for the *analytical markers* in the extract would seem inappropriate. However, unless otherwise justified, the normal HMPC guideline requirements for the stability of the *analytical markers* in the extract/herbal medicinal product will apply. That is, an alteration of no more than 10 per cent in content of assayed constituents during the shelf-life of the product. Therefore, the minimum content of *analytical markers* stated in an extract monograph has no bearing on the shelf-life requirements for the content of *analytical markers* in the extract/herbal medicinal product.

There are also a number of herbal medicinal products containing *'Other' extracts* where the chosen *analytical markers* are other than those specified in Ph. Eur. monographs. This is because the Ph. Eur. is concerned primarily with monographs on herbal drugs (herbal substances) and herbal drug preparations (herbal preparations) and the choice of *analytical markers* tends to reflect this. However, when an extract is used in an herbal medicinal product, in some cases in combination with other extracts or herbal drugs (herbal substances), the *analytical markers* in the Ph. Eur. may not be the most appropriate to demonstrate the content of an extract in the herbal medicinal product. Therefore, it would seem reasonable to introduce into the Ph. Eur. general monograph on Extracts (0765) a statement as follows:

In an individual monograph for an 'Other' extract, the chosen analytical marker(s) constitute one method of assaying the extract. This does not preclude the use of alternative analytical markers which may be more appropriate for the intended application of the extract.

As for quantified extracts, using the same reasoning concerning unidentified constituents which may have therapeutic activity, excipients are only permitted for technological purposes, for example, as processing aids.

2.4 - Refined extracts

The Ph. Eur. defines these as follows:

Extraction with a given solvent leads to typical proportions of characterised constituents in the extractable matter; during the production of standardised and quantified extracts, purification procedures may be applied that increase these proportions with respect to the expected values; such extracts are referred to as 'refined'.

The purpose of refining extracts is to increase the content of constituents with known or generally accepted therapeutic activity in order to improve the therapeutic activity of the extract. The purification procedures are, therefore, only applicable to standardised and quantified extracts. Recently, the HMPC has produced a *Reflection Paper on level of Purification of Extracts to be considered as Herbal Preparations* [10]. This posed the question, when is an extract still an extract and when is the purification procedure such that the end product can no longer be considered an extract but 1 or more isolated constituents, some of which may have been chemically modified?

The original purpose of defining *Refined extracts* was to take account of a small but significant number of such extracts that were on the market and used in herbal medicinal products. The intention was to indicate that these are still extracts and that the only purification procedures permitted were those which increased the proportion of the selected constituents with respect to the levels which would be expected under 'normal' extraction conditions. Therefore, any kind of chemical manipulation was not anticipated or intended. A basic requirement was that it should still

be possible to demonstrate the presence of constituents from the original matrix of the extract but with an enhanced content of the selected constituents. The Ph. Eur. definition of *Refined extracts* would be improved by indicating the types of purification procedures (e.g. solvent/solvent extraction, certain solid phase binding/exclusion techniques, etc.) which were permitted in order to achieve a refined extract.

3. MORE RECENT ISSUES

3.1 - Traditional Herbal Medicinal Products Directive [THMPD]

The process of implementation of the THMPD [11] and the interest in registering products formerly sold without any marketing authorisation has revealed certain anomalies concerning the types of extracts available as items of commerce and incorporated into herbal medicinal products for which registration under the THMPD is being sought. One such issue is the use of the term 'standardised'. There are currently a number of extracts on the market where the assay is based upon constituents which according to HMPC definitions would be classed as either *active markers* or *analytical markers* but where inert excipients are being used to adjust the content of these assayed constituents to a defined, fixed content and the term 'standardised' is being applied to these extracts. An informed discussion is required and a decision taken as to how to categorise such extracts, many of which were in existence prior to the revision of the Ph. Eur. general monograph on Extracts (0765) which re-defined terms such as 'standardised'.

3.2 - Categorisation of individual monographs in the Ph. Eur.

It has become apparent, as more informed discussions have taken place between the Ph. Eur. and the HMPC, that the designation of certain individual extract monographs in the Ph. Eur. will need to be altered once a consensus has been reached concerning the definition of the different categories of extract.

3.3 - Replacement of non-specific assays by specific assays in Ph. Eur. monographs

The work of the Ph. Eur. Groups of Experts in Phytochemistry has led to proposals to replace certain non-specific (spectrophotometric and titrametric) assay methods with specific (primarily HPLC) assay methods. The first examples of this, the draft monographs for Horse-chestnut dry extract, standardised (1829) and Horse-chestnut (1830) were published in Pharmeuropa 20.3 (July 2008) and Pharmeuropa 21.2 (April 2009), respectively. This has led to much discussion, for example, at the previously mentioned Workshop in Geneva and the Conference in Vienna and via articles published in Pharmeuropa 20.1[12], Pharmeuropa 20.3 [13] and Pharmeuropa Scientific Notes 2009-1 [14]. The rationale for introducing a change of assay method is that the non-specific methods tend to be less robust and can give an unacceptably high variance in assay values when compared with more specific methods. However, for the majority of herbal medicinal products, the data supplied for marketing authorisations is based on non-specific methods and, particularly for those herbal medicinal products based on standardised extracts, the dosage is also related to the non-specific methods. In most cases, the introduction of specific assay methods will lead to a decrease in the declared content of the assayed constituents. This change in content would lead, in the case of herbal medicinal products based on standardised extracts, to a change in labelling of the product with the possibility of a consumer perception that the product had been reduced in strength and, hence, efficacy. This would be an unacceptable outcome for products where the method of manufacture of the extract, the content of extract in the herbal medicinal product and the method of manufacture of the herbal medicinal product had not changed. The only change would be the method of assay which, in many ways, is outside the control of the extract and herbal medicinal product manufactures. It is difficult to understand, therefore, why a change so remote from the consumer should have the potential to affect consumer confidence in a product.

One proposed resolution to this problem is to establish a factor linking the difference in assay values between the non-specific and specific methods (12, 14). However, the value of such a factor between an inherently variable non-specific method and a less variable specific method must be questioned. The reason for introducing a specific method is intended to overcome significant variations in assay values using the non-specific method. Establishing a factor would suggest that such variations do not exist, rendering the exercise of introducing the specific method superfluous.

An alternative approach [15] would be to alter the style of declaration, for example, the current HMPC Guideline [16] declaration for *Standardised extracts*, states:

Sennae folium dry extract ethanolic 60% (V/V): 50-65 mg corresponding to ***12.5 mg of hydroxyanthracene glycosides,*** *calculated as* <u>*sennoside B*</u> *either ((a-b):1) or (equivalent to x-y mg Sennae folium).*

Where, with a change in assay, the declaration in **bold** would change, the content being reduced, and the declaration <u>underlined</u> might alter depending upon the chosen reference constituent used for the calculation.

An alternative declaration would be:

Sennae folium dry extract ethanolic 60% (V/V): corresponding to 60 mg Sennae folium dry extract ^{ARC},

where ^{ARC} is an **A**greed **R**eference **C**ontent for the per cent content of the assayed constituents.

This type of declaration has 2 advantages in that the declaration is in line with HMPC Guidelines (16) which state that: '… *the herbal substance or herbal preparation in its entirety is regarded as the active substance …'* and alterations to an assay method would affect only the ^{ARC} and would not alter the declaration. As a result, any changes to assay methods (in a monograph) would be dealt with by the pharmacopoeia, industry and regulatory authorities and would not impact the consumer or be a cause for product relabelling.

4. CONCLUSIONS AND RECOMMENDATIONS

The lengthy discussions at the meetings in Geneva and Vienna and the publication of recent articles (12, 13, 14) lead to the conclusion that there is an urgent need for industry, pharmacopoeia and regulatory authorities

to resolve the many issues detailed above. To facilitate this, it is proposed that the European Pharmacopoeia Commission be requested to re-establish a Working Party on Extracts consisting of invited participants from: the European Herbal Medicinal Products industry, the relevant Ph. Eur. Groups of Experts/Secretariat and the HMPC QDG, with the following remit:

(1) to draft more comprehensive definitions/explanations for designated categories of extracts in order to bring a common understanding to all stakeholders;

(2) to propose an approach for the replacement of non-specific assay methods by specific assay methods in Ph. Eur. monographs taking into account stakeholder requirements.

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