European Pharmacopoeia Commission

Priorities for 2023-2025

This document presents the priorities proposed by the Presidium to the European Pharmacopoeia Commission (EPC) for 2023-2025. They are the outcome of a discussion between the Chair, the two Vice-Chairs, the EDQM Director and the European Pharmacopoeia (Ph. Eur.) Secretariat. These priorities follow on from those established for 2019-2022 and take into account the achievements of the past three years, and the outcomes of the International conference *Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition*, organised by the EDQM in September 2022 in Strasbourg (hereinafter referred to as "11th Ed. Conference").

The priorities described below comprise a number of – sometimes prospective – issues and activities that the Presidium believes merit particular attention in order to ensure that the Ph. Eur. remains up-to-date and fit for purpose and continues to be an international leader in the field. They are not ranked by importance in terms of workload and/or criticality.

The topics included in this document do not represent an exhaustive list. The Presidium may revise these priorities if new needs or points of attention are identified (horizon scanning) or if any unexpected issue arises.

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1. Non-technical priorities

1.1. Rules of procedures and guides

One of the priorities to be tackled by the last Presidium was the update of the fundamental documents governing the functioning of the Ph. Eur. beyond the Convention. The Rules of Procedures Working Party (ROP WP) was allocated this task and after a period of intense activity, the revised *Code of Practice for the work of the European Pharmacopoeia* and the revised *Guide for the work of the European Pharmacopoeia* were

approved during the 173rd session of the EPC, together with the newly elaborated *Privacy statement of the European Pharmacopoeia*. Another new document, the *Guide on the declassification of documents pertaining to the work of the European Pharmacopoeia*, will be submitted to the EPC at the 174th session, and the ROP WP is still working on the *Rules of Procedure of the European Pharmacopoeia Commission.*

Up-to-date guides on the different topics dealt with by the groups are important to improve the efficiency of their work. During its 173rd session in June 2022, the EPC approved the 8th edition of the *Technical guide for the elaboration of the monographs* of the European Pharmacopoeia, an overarching guide that influences the work of many expert groups and working parties. The time has now come to update the sectorial guides, such as the *Guide for the elaboration of monographs on herbal drugs and herbal drug preparations*, or elaborate new ones such as the *Guide for the elaboration of monographs on medicinal gases.*

1.2. Modernisation of ways of working

The COVID-19 pandemic of the last three years has forced us to make sudden and radical changes to the ways we work. We have learned to rely heavily on teleworking and to meet using an increasing number of digital platforms. Although personal contact is necessary for establishing stronger networks and increases the problem-solving capacities of the groups, it is clear that there will not be a full return to face-to-face meetings. On-line meetings help increase attendance, but may make participation in discussions more difficult. They lack the personal relationships that support group dynamics, but can save time and money and improve efficiency in certain circumstances.

The EDQM worked diligently and with great skill to face the COVID situation and ensure that the Secretariat, expert groups, working parties and EPC continued to function correctly during the pandemic. The move to on-line meetings as only one of the many changes made. For instance, the Agenda of the EPC sessions was redesigned, enhancing efficiency but also simplifying procedures with in-block adoption on topics that do not need further discussion during the meeting. However, should these changes be adopted permanently? Should other changes, such as the switch from a manual to an electronic voting system, be permanently implemented? The in-block adoption is detrimental for the visibility of the chairs of the groups: how could this be offset? How can the participation of on-line attendees in group meetings be improved?

One of the challenges of the Ph. Eur. for the next years is to analyse the lessons learned during the pandemic and establish a policy that strikes the right balance between on-line, face-to-face and hybrid sessions, and introduces the changes necessary to enhance participation, improve efficiency and allow objectives to be reached. These analyses and reflections will be entrusted to the ROP WP, which will present specific proposals to the EPC.

1.3. Stakeholder engagement

One of the innovations of the 11th Ed. Conference was an increase in sessions that enhance participation of attendees in discussions, notably the open debates and round tables. Participants highly appreciated being given the opportunity to share ideas, experiences, needs and concerns, as well as their proposals for action, improvements or solutions during these sessions.

Collaboration of users, interested parties and stakeholders through the experts network, the comments on the texts published in *Pharmeuropa*, public enquiries, symposia,

workshops, webinars and the HelpDesk, etc. is crucial for the continuous improvement of the Ph. Eur. Any action enhancing this collaboration will be supported by the Presidium.

In this framework, **communication** is a key factor: not only can it advertise the innovations, improvements and achievements of the Ph. Eur. but it can also be used to attract the interest and commitment of industry and new experts. It is important to reflect on the communication channels, formats and materials through which we can reach the desired target audience with the most suitable and adapted information. At the same time, this reflection must take into account and achieve a balance between needs, objectives and expected outcomes and resources that can reasonably be allocated for the possible actions.

National Pharmacopoeia Authorities (NPAs) also play an important role in the Ph. Eur., as was highlighted during the 11th Ed. Conference. In particular, they are the link between the Ph. Eur. and the national pharmaceutical networks, including competent authorities, industry, users, experts, and institutions that are able to provide expertise. For this reason, NPA engagement in the communication network of the Ph. Eur. has a synergistic effect and must be encouraged.

The experience of **industry**, providing methods, data and experts to the Ph. Eur., is to be encouraged and protected. This collaboration relies heavily on achieving the right balance between transparency and confidentiality. The aforementioned *Guide on the declassification of documents pertaining to the work of the European Pharmacopoeia* is a first step, but the reflection initiated on transparency inside the ROP WP will continue in order to identify any possible gap and propose the corresponding actions.

The Ph. Eur. is nourished by the contributions of a highly qualified network of around 900 **experts** with a background in fundamental and/or applied sciences, their institutions and companies and the staff of the EDQM. The equilibrium between experts from academia, industry and regulatory bodies is fundamental for ensuring the rich and fruitful discussions that lead to a state-of-the-art and relevant Ph. Eur. It is essential to maintain this equilibrium and ensure that new young experts are recruited to the Ph. Eur. and the Presidium will fully support the actions undertaken by the EDQM to attract the interest of potential candidates. Universities and research centres provide around 15 per cent of the experts of the Ph. Eur., but the increasing pressure for high impact research outcomes in these institutions could make it difficult to attract new young experts from them: a reflection on how this situation can be overcome is necessary.

1.4. Harmonisation and international collaboration

International collaboration is in the DNA of the Ph. Eur.: decisions are taken by consensus by the EPC, which represents the 39 states and the European Union that form the current Ph. Eur. membership, and the texts adopted are enforced in all of them. The Ph. Eur. also means collaboration with experts from beyond the frontiers of the member states, from observer and other countries.

Collaboration with other pharmacopoeias is also important. In this context, it is worth mentioning the Pharmacopoeial Discussion Group (PDG), which brings together the US Pharmacopeia (USP), the Japanese Pharmacopoeia and the Ph. Eur., with the recent addition of the Indian Pharmacopoeia as part of a pilot expansion programme, together with the WHO as observer. The aim of the PDG is to harmonise pharmacopoeial standards while maintaining a constant level of science with the shared goal of protecting public health. The PDG's recent plan to expand membership to pharmacopoeias currently not

yet represented will be further supported to enlarge its global footprint. In addition, bilateral initiatives with the USP, and the International Pharmacopoeia (WHO), as well as more global discussions in the framework of the International Meeting of World Pharmacopoeias (IMWP) are ongoing to enhance pharmacopoeial co-operation and harmonisation.

The Ph. Eur. and the EDQM also collaborate with a number of institutions, such as – to name but a few – the EMA, HMA, the EU Commission and ICH, to ensure that Ph. Eur. texts are aligned with current regulations and to provide input for guidelines and future regulatory requirements.

All this international activity is highly relevant for harmonisation, but it also ensures that the Ph. Eur. remains current and pertinent, aligned with the constantly changing regulatory landscape and influential in countries beyond its member states.

2. Technical priorities

2.1. Modernisation of analytical procedures and integration of new technologies

Modernisation of analytical procedures is a permanent challenge that has the continuous attention of the Ph. Eur. When updating these procedures, it is essential to maintain an equilibrium between the possibilities offered by new and sophisticated technologies and the real need for data for quality assessment purposes, while bearing in mind the associated industrial constraints. Fitness for purpose is essential. A number of general texts and individual monographs have been recently revised in this context, including general chapter *2.2.46. Chromatographic separation techniques* that now allows adjustments to be able to switch from HPLC to UHPLC. However, there is still room for improvement and the expert groups constantly endeavour to replace old analytical strategies by more appropriate state-of-the-art approaches. For example, the classical spectrophotometric assay of hydroxyanthracene glycosides is being replaced by an HPLC assay in a number of texts on herbal drugs and herbal preparations (see **section 2.5**). In the field of biologicals, the development of **horizontal standards** for monoclonal antibodies – which have an obvious added value since they can be applied to a number of individual monographs – together with the work for the implementation of the **new sequencing technologies** will be prioritised (see **section 2.2**).

Predicting future needs with regard to the application of **new analytical technologies** is also important in order to commence, as soon as possible, reflections and discussions on possibilities and potential difficulties. As highlighted in the 11th Ed. Conference, this is *investing in the future*, it is preparing the Ph. Eur. to integrate new analytical procedures. It is not always easy to incorporate new technologies into the Ph. Eur., since it must be borne in mind that they will be applied in a regulatory environment, in routine analysis and in a broad range of laboratories and processes. The Presidium will encourage such discussions and the elaboration of texts that will help the Ph. Eur. face the future.

Over the past years, a number of general texts have already moved in this direction, such as the already published and constantly kept up-to-date *5.21. Chemometric methods applied to analytical data*, *5.25. Process analytical technology* and *5.28. Multivariate statistical process control*. A new general chapter, *5.33. Design of experiments*, is under public consultation. In addition, the newly formed **Analytical quality by design** WP (aQbD) will assess the feasibility and impact of incorporating analytical procedures

developed using these concepts in Ph. Eur. monographs and will advise the EPC and expert groups on the strategies required to achieve this goal.

Flexibility is important to fulfil the needs of users and is an added value for the Ph. Eur. It is therefore important to consider this aspect during both elaboration and revision of texts, while safeguarding the robustness expected from a pharmacopoeial standard. On the one hand, flexibility is not given by a specific Ph. Eur. text, but is essentially the sum of small contributions allowed in different texts. On the other hand, one part of this flexibility is to allow the use of alternative procedures, but it is important to clarify the conditions under which these procedures can be compared and used instead of the official ones: a new general chapter on *5.27. Comparability of alternative analytical procedures* is under discussion and will significantly contribute to this clarification.

2.2. Biologicals

Biologicals is a fast moving field and the expectations from the Ph. Eur. are increasing. Fulfilling these expectations and being prepared for the future is a priority for the Presidium. A number of significant projects are in the pipeline, including several new general texts, such as those related to the **new approach to gene therapy medicinal products for human use**, and the information chapters on **cell-based preparations**, on the quality of **phage therapy** active substances and medicinal products for human and veterinary use, and on the quality of **mRNA vaccines** and their components. Regarding the latter, the newly created **mRNAVAC WP** will be in charge of developing quality standards supporting this emerging field.

The development of **horizontal standards** in the field of **monoclonal antibodies** led to the publication of the chapter on *Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26)* including different assay procedures that are suitable for more than one TNF-alpha antagonist. Furthermore, two new **general methods** are being prepared, one on *Size-exclusion chromatography for recombinant therapeutic monoclonal antibodies (2.5.43)* and one on *Capillary isoelectric focusing for recombinant therapeutic monoclonal antibodies (2.5.44)*. These developments are highly appreciated and encouraged by the Presidium.

As part of the implementation of **new sequencing technologies**, a general chapter on *High throughput sequencing for the detection of extraneous agents (2.6.41)* is being prepared. It will include a description of the technology and guidelines for method validation and will be of particular interest in the fields of vaccines and viral vectors used as gene therapy products. This text will be a significant step towards further modernising the Ph. Eur. and will contribute to the replacement of *in vivo* tests.

2.3. Alternatives to animal testing

Great and pioneering work has been done since 2013 by the Ph. Eur. in the field of Replacing, Reducing and Refining animal tests (3Rs), particularly in the field of vaccines, both for human and for veterinary use. Nevertheless, as highlighted in the 11th Ed. Conference, the Ph. Eur. must continue to compromise on this topic. It is proposed to maintain it as a priority for the coming years, in particular, among other actions, developing the **new pyrogenicity strategy**, which should lead to the future deletion of the rabbit pyrogen test from 60 Ph. Eur. monographs and the corresponding general chapter (*Pyrogens*, *2.6.8*).

The Ph. Eur. could further promote the 3Rs on the international scene by publicising the work done by the EPC and by inviting or even encouraging other pharmacopoeias or

authorities outside Europe to follow its example. Indeed, European stakeholders wishing to apply the 3Rs usually play a role on a global scene and report that without such an international perspective, the use of animals will continue.

2.4. Impurities

After carcinogenic ***N*-nitrosamine impurities** were detected in a series of sartans in 2018, the great work done by the OMCLs and then by the Ph. Eur. led to the publication of the general chapter *2.5.42. N-nitrosamines in active substances* in June 2021 and to several revisions of the "sartans" monographs. Since they were first detected, it has been discovered that these impurities can be found in other classes of APIs, and the risk has shifted to the medicinal product level. Regulatory requirements have continuously evolved, making it difficult for the Ph. Eur. to give a valid framework for *N*-nitrosamines in line with the relevant guidelines and regulations, which may be different among the Ph. Eur. member states. The approaches have now been clarified and the revision of the general monographs on *Substances for pharmaceutical use (2034)* and *Pharmaceutical preparations (2619)* is a priority for the Presidium. After the revision of these two general monographs, additional reflections and actions will still be needed to define a framework addressing N-nitrosamine and more generally DNA-reactive impurities in relation to individual monographs. The possible contribution of excipients, mainly due to their nitrites content, will also be taken into account by the new **Excipients Strategy** WP (EXS).

Similarly, general monograph *2619* will have to be revised to address the issue of **contaminant pyrrolizidine alkaloids**.

Another current challenge in this field is setting standards for impurities in complex matrixes, for instance **antibiotics** obtained by fermentation. These standards require the development of highly demanding analytical procedures and complex CRS mixtures.

2.5. Herbal drugs and herbal drug preparations

The draft of the monograph on *Cannabis flower (3028),* elaborated in response to high stakeholder demand, has recently been published in *Pharmeuropa 34.4*. The finalisation of this monograph and the preparation of those on the corresponding extracts are considered priorities.

The Ph. Eur. contains 13 monographs on herbal drugs or herbal drug preparations for which an **assay of hydroxyanthracene glycosides** is prescribed. More than half of these monographs have already been revised to replace the classical spectrophotometric assay by a more modern one relying on HPLC. Since such hydroxyanthracene glycosides are considered to be compounds with known therapeutic activity, this work and its outcome is very relevant for industries and assessors. Therefore, we propose to give priority to the development of new HPLC assays for the remaining monographs.

Finally, in the field of the **essential oils**, there is important work to be done in relation to the use of the *essential oil CRS* for the update of the qualification of gas chromatography systems used to establish their chromatographic profile.

2.6. Excipients

In relation to excipients, we propose to give priority to reviewing the current approach of the Ph. Eur. when setting standards in this area, with the establishment of a **new strategy for excipients**, that takes into account the work done and the challenges identified in the different groups involved in the field. A new Excipients Strategy WP (EXS) was

approved during the 173rd session of the EPC in June 2022 and entrusted with exploring and proposing specific recommendations to the EPC.

Involvement of stakeholders in this process of elaborating recommendations is key to establishing a future-proof approach that takes into account the specificities of excipients compared to active substances, such as setting impurity specifications – including mutagenic impurities – and matrix effects, but also different routes of administration, to name some of the challenges.

2.7. Nanomedicines

Although the reflection on nanomedicines will be launched in the field of mRNA vaccines (see **section 2.2**) it should be extended to other types of nanomedicines, to prepare for a more comprehensive incorporation of these medicines in the Ph. Eur. A number of them have reached the market in the last two decades and it is also important to support them, for example liposomal formulations, by setting standards in the Ph. Eur. The Presidium supports further reflections and preliminary work on standards for formulations and specific components (e.g. lipids) not yet covered by the Ph. Eur.

2.8. Medicinal product monographs for chemically defined APIs

The concept of medicinal product monographs (MPMs) for chemically defined APIs is now well established in the Ph. Eur., with an increasing number of monographs published. In recent times, there have been discussions on how to tackle **widening specifications for impurities** in MPMs in circumstances where this is considered necessary. This is one of the challenges that the Ph. Eur. will have to deal with in the coming years for the elaboration of MPMs, that will require reflection and, in some cases, flexibility. Challenging issues include the elaboration of monographs for **complex formulations** that include more than one active substance and setting specifications for **multisource medicinal products.**

2.9. European Paediatric Formulary

The European Paedriatic Formulary is an excellent tool that provides clinicians and pharmacists with appropriate formulations for use when no licensed product is available. It is elaborated by the PaedForm WP under the auspices of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the EPC. The Presidium fully supports its development and encourages the preparation of new monographs to add to the formulary to ensure that it is a useful tool throughout Europe and beyond.

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