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Ph. Eur. / USP Prospective Harmonisation – API Pilot Project: Industry Perspective

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ABSTRACT

This article has been prepared to share information with interested stakeholders regarding recent efforts to develop prospectively harmonised monographs for Active Pharmaceutical Ingredients (APIs) in the European Pharmacopoeia (Ph. Eur.) and United States Pharmacopeia (USP). The current state of the work is presented from the perspective of the two pharmaceutical companies engaged in the Pilot Project.

INTRODUCTION

For more than a decade, the pharmaceutical industry has been monitoring and supporting the Pharmacopoeial Discussion Group (PDG) activities with excipient and general chapter harmonisation. The importance of the PDG efforts to develop global quality standards is emphasised in the following statement on International Harmonization from the European Directorate for the Quality of Medicines & HealthCare (EDQM) website [1].

> "Why We Need Harmonisation–Globalisation and expansions in international trade present further challenges as there is a growing need to develop global quality standards. Harmonisation among the world's three major pharmacopoeias, the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia, is currently an important and challenging task, as these standards are a vital instrument in the registration, market surveillance, and free movement and trade of medicines among as many countries as possible."

This critical work by PDG has resulted in numerous harmonised compendial standards. However, PDG's harmonisation activities do not include Active Pharmaceutical Ingredients (APIs), which represent another key category of monographs in each of the pharmacopoeias. During 2007 and 2008, industry initiated discussion with the PDG partners to assess interest in trying to harmonise new API monographs at the point of initial submission and development. As an outcome of these discussions, the EDQM (which establishes the European Pharmacopoeia – Ph. Eur.) and USPC (United States Pharmacopeial Convention, which establishes the United States Pharmacopeia – USP) agreed to participate in a pilot project to investigate the possibilities of prospective API monograph harmonisation. At the same time, the PMDA (Pharmaceutical and Medical Devices Agency, which establishes the Japanese Pharmacopoeia – JP) indicated their interest in observing the pilot project.

By now, stakeholders will have seen the release of four proposed monographs in Pharmeuropa and the Pharmacopeial Forum for public review and comment. These unique monographs (Montelukast Sodium [2] and Rizatriptan Benzoate [3] submitted by Merck; Celecoxib [4] and Sildenafil Citrate [5] submitted by Pfizer) represent the first prospectively harmonised API monographs jointly developed between EDQM, USPC, and industry.

This article provides background information for stakeholders interested in the prospective harmonisation pilot project. It is intended to also lay the foundation for future discussions to evaluate the ultimate success of the monographs developed by this process, as well as on-going maintenance for these monographs. The process for developing harmonised API monographs in the pilot project is neither finalised nor established as the only process that may be followed. Stakeholders are encouraged to continue identifying mutually beneficial approaches for innovative and more efficient means of establishing regional or global standards.

DEVELOPMENT OF MONOGRAPHS: CURRENT STATE

The guidelines for submitting new monographs for the Ph. Eur. and USP are referenced in the EDQM *Technical Guide for the Elaboration of Monographs* (4th Edition, 2005) [6] and the USPC *Guideline for Submitting Requests for Revision to USP-NF* (V 3.1, April 2007) [7], respectively. The information requested in both guidelines is similar and includes the list of appropriate tests, analytical procedures, and acceptance criteria for the material or product, as filed in the Marketing Authorisation Application or New Drug Application. Monograph submissions for the Ph. Eur. and USP typically include identification, assay (potency), related substances (impurities), residue on ignition, water, and any additional tests required to ensure appropriate quality of the API.

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Although the stated requirements in both technical guides are similar and industry sponsored submissions for the Ph. Eur. and USP are generally consistent, they invariably lead to official monographs that are not equivalent. There are many factors that contribute to this outcome. The USPC will generally adopt – without change – a given industry procedure, such as chromatographic assay and related substances, along with the acceptance criteria that have been filed and approved by the FDA for the US market. On the other hand, it is inherent to the EDQM elaboration process that all material sources included in marketing authorisations for medicinal products at the time of monograph development are taken into account for the creation of a public standard which will be mandatory for all future users. This requires an in-depth practical laboratory evaluation and selection process of proposed methods and verification of important aspects such as method robustness and selectivity regarding the different impurity profiles. Revised chromatographic procedures may be developed for related substances tests to help ensure unambiguous impurity peak identification and quantification, complemented by a precise titration method for assay. As an outcome, the resulting Ph. Eur. monograph may include changes in methods when compared to those in the USP monograph, or used by the individual manufacturers involved.

In addition to modifications made by the USPC and EDQM, there may be unique regional regulatory requirements and specifications that may lead to differences in monograph proposals. Among these unique regional requirements are differences in assay and impurity limits. When the proposed monographs are published in the public forum, comments received by the EDQM and USPC from industry may result in even further differences in the final monographs. In order to provide a suitable public standard, the USPC and EDQM may be required to modify the sponsor's monograph to be inclusive of all manufacturers. Modifications made in one pharmacopoeia may not be consistent with the modifications made by the other. Tests included in one pharmacopoeia may be eliminated in the other, such as the case of multiple identification tests.

DEVELOPMENT OF THE PROSPECTIVE HARMONISATION CONCEPT

The current pharmacopoeial process most often results in non-harmonised monographs. Industry saw a clear need for a new and improved approach to monograph development in order to achieve the desired goal of harmonised quality standards. The concept of the "Ideal Pharmacopoeia" had recently been published by industry, with the objective being a single, unified, global compendial standard to ensure the same, high-quality medicines for patients around the world [8]. Much of the groundwork for harmonisation was already in place, including the significant efforts by the pharmacopoeias through PDG. Additional activity by regulatory agencies along with industry was also underway through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), e.g. the Q4B Guideline: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions [9]. However, the majority of this activity was aimed at retrospective harmonisation of standards which had been developed separately in the various regions of the world.

The activity of PDG and ICH to resolve existing historical and regional differences has been, and will continue to be an important part of global harmonisation for drug standards. The question becomes whether it is possible to develop new harmonised standards at the outset, making retrospective harmonisation unnecessary. To some extent, this has already been achieved through the collaboration between the PDG partners which resulted in the creation of six new general chapters in the Ph. Eur., USP, and JP, which provide methods for biotechnology products [10]. Extending this success to the creation of prospectively harmonised API monographs introduced the industry sponsor of the monograph as an additional collaborator.

The possibility of developing prospectively harmonised API monographs arose in 2006 during pharmaceutical industry discussions regarding the "Ideal Pharmacopoeia". The prospective harmonisation model which emerged (Figure 1) was simple in theory, but potentially difficult in practice. As previously discussed, an industry sponsor would typically submit the same monograph to the separate pharmacopoeias and then sit back to watch the developing monographs diverge due to differences in the pharmacopoeial processes, expectations, preferences, timing, and regional regulatory practices. The novel concept was to proactively "complete the connection" between the industry sponsor and the pharmacopoeias, engaging all partners through open and transparent communication leading to a harmonised monograph at the end of the effort.

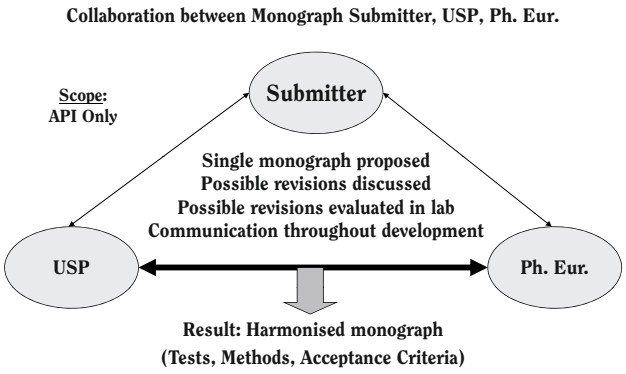

Figure 1 – *Prospective Harmonisation Concept*

Subsequently, discussions were held between industry, EDQM, and USPC to determine whether the vision of prospectively harmonised monographs was shared by the potential partners. In addition, the EDQM and USPC brought this bilateral initiative to the attention of PDG, with an invitation for PMDA to participate. The positive responses from the pharmacopoeias were a critical factor toward reaching the current milestone achieved in the four monograph proposals appearing in Pharmeuropa and Pharmacopeial Forum. As shown in Figure 1, a few additional considerations also emerged from the industry discussions with the pharmacopoeias. First, the scope of the activity would be initially limited to development of API monographs, since the Ph. Eur., in line with the current European regulatory framework, does not contain specific monographs for pharmaceutical products. The focus on APIs can also be understood since harmonised specifications for pure substances may be more readily applied to materials from multiple sources than would be possible for drug products from multiple sources due to formulation differences (excipients/processes). Second, the initial partnership for development of the monographs would include the industry sponsors, the EDQM and the USPC. While ultimately within the scope of creating global drug standards, the PMDA indicated that they would remain an interested observer at this early point in the new process.

But the stage was set to elaborate the specific process steps that would lead to the development of prospectively harmonised API monographs in the Ph. Eur. and USP.

DEVELOPMENT OF THE API PROSPECTIVE HARMONISATION PILOT PROCESS

During the development of the pilot process, it was important to share procedural information between all parties while maintaining confidentiality for specific company information. The goal was to share pharmacopoeial resources and release harmonised proposals, harmonised official monographs and harmonised reference standards as close to simultaneously as possible. Industry proposed using the EDQM Procedure 4 (P4 for elaboration of Ph. Eur. monographs) [11] as a basis for a prospective harmonisation process which could be put in place for a trial phase. In mid-2008, the parties involved discussed the individual monograph development processes and determined where activities could be combined, where activities would remain separate, and where industry should be involved in the pharmacopoeial discussions. From these meetings, the following monograph development process was drafted:

A. Submission and initial review
   1. Identical submission packages are provided by the monograph sponsor to EDQM and USPC.
   2. EDQM and USPC appoint leaders for the monograph development.
   3. Following a paper review by each organisation, a joint list of questions is submitted to the individual company.
   4. Once initial questions have been resolved, the first draft monograph is prepared and shared with a joint expert group from EDQM and USPC.

B. Laboratory evaluation
   5. Individual company coordinates material submissions for EDQM and USPC laboratory testing.
   6. Experimental testing of the draft monograph to be conducted by at least two laboratories: EDQM, EDQM network, USPC, USPC external resource, or FDA.
   7. When necessary, confirmatory testing to be conducted by additional laboratories not involved in Step 6 (including individual company laboratories).
   8. All laboratory reports are exchanged and discussed between EDQM and USPC.
   9. The EDQM and USPC discuss any necessary changes to the first draft with the sponsor company.
   10. A consensus draft is prepared and published (simultaneously if possible) in Pharmeuropa and Pharmacopeial Forum.
   11. Individual company submits material to support the EDQM CRS and USP RS programs.

C. Public Review
   12. All comments sent to EDQM and USPC are collated and reviewed by the joint expert group.
   13. Revised draft prepared in close collaboration between EDQM, USPC and the individual company to resolve any outstanding issues. All parties will discuss and address any concerns and agree to a common version of the consensus draft.

D. Official Harmonised Monograph
   14. Final consensus draft submitted to Ph. Eur. Commission and USP Council of Experts for adoption.
   15. If any significant changes from the consensus draft occur due to the final approval process, all parties should be notified to assess the revision.
   16. Publication and implementation dates for the official harmonised monograph in the Ph. Eur. and USP should be as close as practical, with an identical implementation date as target.

DEVELOPMENT OF DRAFT MONOGRAPHS: API PROSPECTIVE HARMONISATION PILOT PROJECT

Draft monographs for the four APIs in the pilot project were prepared by the two participating companies for submission to the EDQM and USPC by reviewing approved tests and acceptance criteria. As previously stated, appropriate methods were chosen for inclusion based on typical monograph requirements as stated in the EDQM *Technical Guide for the Elaboration of Monographs* and the USPC *Guideline for Submitting Requests for Revision to USP-NF: Small Molecule Drug Substances and Products*. In addition to tests for identity, related substances, heavy metals, water and assay, tests based on the physical characteristics of the material and/or other approved quality specifications not previously mentioned were included.

After the monographs were submitted, a list of consolidated EDQM and USPC questions was received by the monograph sponsor, including consideration of whether the materials show polymorphism. Answers were submitted and manufacturing sites were contacted to send samples for testing. Reference standards necessary to support the evaluation of specific tests in the monograph were identified and small quantities of these materials were sent to EDQM and USPC for use in laboratory evaluations. Where possible, samples of isolated, individual impurities were also sent.

Testing was performed by the laboratories of the EDQM, the European OMCL network, USPC, and/or FDA. Results were incorporated into laboratory reports that were provided to the sponsor, along with a draft monograph proposal. The draft monograph included some changes to the originally submitted methods, such as determining impurity limits by comparison with a diluted sample. The draft monographs have either been published in Pharmeuropa and Pharmacopeial Forum for public review and comment, or will be published soon.

There are several open issues that are still being discussed between the sponsors, EDQM, and USPC regarding the monographs developed in the pilot program. Among these challenging issues are the following:

- A harmonised approach is needed for the related substances and assay tests in the Ph. Eur. and USP monographs for these substances.
- Practical issues related to general chapter references in the monographs must be addressed. Non-harmonised general chapters may result in non-harmonised monographs, despite the activities of the pilot project. This is especially true where the monographs may reference a general chapter such as heavy metals or specific rotation where the USP and Ph. Eur. tests are not the same.
- A process to ensure the establishment of harmonised reference standards for assay and impurities is also necessary to ensure consistent results in the application of the harmonised monographs. As part of the pilot project, single lots of reference standards were submitted to the EDQM and USPC to support the harmonised monograph process. Characterisation of these reference standards must be handled in a manner that will enable use of the materials to support the harmonised monographs. It is particularly important that reference

standards used to determine assay (potency) for the APIs be assigned identical purity values by USPC and EDQM.

- Additional considerations for overall success include extending the applicability of the harmonised monographs through incorporation into the Japanese Pharmacopoeia and other pharmacopoeias. The JP was aware of this project but was not an active participant in the development of the monographs. In order to achieve full harmonisation, involvement with all compendia represented by PDG and other compendial organisations will be required.
- Additional revisions are being discussed by the EDQM, USPC, and monograph sponsors, even following publication in the pharmacopoeial forums. As indicated above, discussion is on-going as to how the public comments will be addressed by the USPC and EDQM in order to maintain a harmonised monograph. Possible revisions to the monographs once additional material sources become available through regulatory approval must also be considered to ensure the harmonised standards are maintained. Subsequent revision of the prospectively harmonised monographs, after they become official, will need to be addressed in a collaborative manner to ensure that the monographs continue to provide appropriate compendial standards for all approved manufacturers of the APIs. This change control aspect represents one of the most challenging and complex aspects for maintaining the harmonised monographs, and cannot be fully addressed until revision requests begin to be received by the pharmacopoeias.

CONCLUSION

At this point, it is still too early to measure the success of the API pilot project for Prospective Harmonisation. In practical terms, the project should be considered successful upon publication of harmonised official monographs for Montelukast Sodium, Rizatriptan Benzoate, Celecoxib, and Sildenafil Citrate in the Ph. Eur. and USP to provide a single standard in Europe and the US for these important drug substances. If the benefits realised through the development of prospectively harmonised monographs exceed the effort required to reach that goal, then the project will have proven valuable.

Among the anticipated benefits for industry is reduced testing in quality control laboratories based on the harmonised pharmacopoeial monograph. This outcome would represent an improvement over the current situation in which different standards are often developed in the USP and Ph. Eur. An additional benefit would be the ability to refer to the harmonised USP and Ph. Eur. monograph standard in product registrations in the US and Europe. It is industry's hope that the harmonised API standard could also be acceptable in product registrations outside the US and Europe. Given these potential benefits, the development of this new approach to monograph development through prospective harmonisation may provide a valuable tool for the future.

There may be other possible approaches which could lead to a single, unified, global compendial standard. In order to reach the ultimate goal of providing consistent global standards for high-quality drug products, efforts toward prospective harmonisation, PDG and ICH activities, and other harmonisation approaches not yet discussed should be pursued by all stakeholders to the ultimate benefit of patients around the world.

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