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Design and international harmonization of pharmacopoeial standards ☆

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Abstract

As the global market for pharmaceuticals increases, the adverse consequences of different regulations and requirements are becoming more obvious. Discussions between the regulatory authorities for the European Community, United States and Japan under the International Conference on Harmonization (ICH) intended to remove some of these differences are mirrored by similar discussions between the corresponding pharmacopoeial authorities.

Moves towards harmonized requirements in pharmacopoeial monographs depend on a consensus view of the purpose and scope of their contents. Aspects of the construction of the four main elements (identification, characterization, control of impurities and assay) of a monograph for an active substance or excipient are considered. The choice of analytical methods is influenced by their availability, the level of control required and their transfer reproducibility between laboratories.

Some activities of the Pharmacopoeia Discussion Group, involving the European, United States and Japanese Pharmacopoeias, and their present status are surveyed.

Keywords: Pharmacopoeia; Monograph; Pharmacopoeial harmonization

1. Introduction

Regulatory requirements in major areas of the World have evolved in response to legal, technical, scientific and medical considerations. Not surprisingly, the requirements imposed vary. This presents an increasing problem to pharmaceutical companies seeking a global market for their products, has adverse consequences economically and technically, and can introduce delays in the approval of a product. Recognizing that some of the differences may have no scientific or technical justification, a tripartite International Conference on Harmonization (ICH) has been established by the regulatory authorities of the United States, European Community and Japan to examine ways of removing some of the differences. Discussions are proceeding in many areas including analytical validation and characterization of impurities.

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In parallel with these activities in the regulatory sphere, a similar tripartite Pharmacopoeial Discussion Group drawn from the Pharmacopoeias of the United States, Council of Europe and Japan began work in 1990 on a voluntary basis to reach a consensus on monograph requirements for active substances and excipients as a means of increasing trade in pharmaceutical products and to fulfil requests made by the industry and regulators [1]. In this paper, the purpose and scope of pharmacopoeial monographs is reviewed together with progress in, and obstacles to, international harmonization.

2. Discussion

2.1. Scope and purpose of a monograph

A pharmacopoeial monograph is a public statement of the appropriate quality of an active substance or excipient for use in the preparation of a formulation and for administration to a patient. For a bulk substance, the specification of the monograph defines the quality appropriate for incorporation in a product. For a dosage form, the specification defines the quality that applies throughout the shelf life of the product. A specification applies to all material defined in the monograph irrespective of source and, in the case of dosage forms, composition of the formulation. These monographs are of value to manufacturers, the purchasers and suppliers of bulk substances and dosage forms, to control authorities that may need to test products and samples taken from the market or during inspection, to regulatory authorities seeking to apply uniform criteria to materials of different origin, and to health professionals requiring knowledge of medicines in the pursuit of their duties.

However, the needs of these groups are not identical. The quality specification of the manufacturer at the time of manufacture and release may be more strict, since allowance has to be made for changes that may occur during storage but that are not sufficient to prevent use of the material. A purchaser of a bulk active may also wish to impose tighter requirements on a supplier in order to ensure that the material purchased remains suitable for use for some time or for a particular purpose or process. An independent analyst or control authority may be satisfied with the specification because the decision on compliance tests on the suitability of the sample for use. Regulatory authorities have full access to information about the synthetic route, formulation, manufacture, in-process controls and testing applicable to an active substance or dosage form from an individual source, and in the light of this knowledge may recognize deficiencies in the range of tests and limits imposed in a pharmacopoeial monograph written for all material available at the time. Health professionals may find the information in the monograph sufficient for their needs.

Pharmacopoeial authorities not only prepare specifications against a legal framework and regulatory background that is different in different regions, but also have different legal status and structures themselves. Perceptions of the purpose and the users of pharmacopoeias change and develop. There is legitimate debate about the state of scientific knowledge and its application in a field as sensitive as the control of drug quality and safety standards. It is, therefore, to be expected that achievement of harmonization will present challenges.

2.2. Structure and design of a monograph

Monographs for active substances and excipients generally have a common format. They open with the structural formula together with the empirical formula and molecular weight, followed by definition, tests for identification, tests for purity and an assay. The definition includes the systematic name of the substance and a statement of content or potency. Reliance for identification is placed on instrumental and on separation methods. The main part of the monograph consists of tests for purity. These include: tests with limits for physical properties, such as melting point, optical rotation and absorbance; tests usually employing separation and other methods to control related impurities, generally compiled to control any organic impurities that may be present but also

including specific tests for impurities that are particularly critical or toxic; tests for impurities not specific to a single monograph such as heavy metals, sulphated ash, water and residual solvents.

The assay selected in the past has often been non-specfic, e.g. a titration, on the grounds that such a method has high precision and impurities are limited to low levels by other tests in the specification, so that their inclusion in the assay figure obtained does not have sufficient impact to justify the use of a specific assay. Today, more reliance is placed on selective assay, often employing liquid chromatography, since the relatively lower precision is offset by the information gain in obtaining an assay value for the substance itself without a contribution from related substances. The monograph introduced into the European Pharmacopoeia in 1994 for alprenolol hydrochloride [2] illustrates the first of these approaches having a definition of content of 99.0–101.0% on the dried basis using a potentiometric titration, whereas that for ciprofloxacin hydrochloride [3] has a content of 98.0–102.0% on the anhydrous basis using LC. In both monographs, tests are included for overall control of related substances and for a named impurity. In the former, these are by TLC and LC, and by UV respectively, and in the latter by LC and by TLC respsectively. The choice of methods depends on a number of factors, including the techniques validated and used by the innovative manufacturer, the ability to reveal unexpected or novel impurities, and experimental evidence of reproducible transfer of methods between laboratories.

These two monographs illustrate other features of monographs in the European Pharmacopoeia: that for alprenolol contains two series of tests for identification, one employing IR and a test for chloride, the other using TLC, melting point and a test for chloride. The two series are necessary because of the requirement in some European countries for identification of samples of active substances under circumstances where access to instrumental methods is not possible. The monograph for ciprofloxacin contains a statement naming impurities controlled by the requirements of the monograph. Control may be exercised by tests other than separation methods for related substances, for example by UV, and the monograph has to be viewed in its entirety. These 'transparency' statements have been introduced in response to requests from regulatory authorities, in particular so that it is at once clear whether material from a new source will be controlled adequately by the existing tests or whether the monograph may be sufficient if a new synthetic route is involved.

Another development in the construction of monographs of the European Pharmacopoeia has been the introduction of a section on Production, particularly in monographs for materials of biological and biotechnological origin. In drafting a monograph for a substance obtainable in several ways, a pharmacopoeial authority can make no assumptions about the source of any one sample. Further, it may be recognized that some in-process controls are critical analytical parameters, but that appropriate tests cannot be carried out by an analyst independent of the manufacturer because reagents such as suitable monoclonal antibodies are unavailable. This is a consequence of the test having to be applied before the final material is isolated or of the test forming part of the process validation. Under these circumstances, it has been seen as helpful to set and publish requirements that form part of the controls exercised by the manufacturer, so that their role in the specfication is clear and regulatory authorities can ensure that such requirements are met. Introduction of the Production section has been especially valuable for recombinant products such as human insulin.

2.3. Physicochemical and (microbiological) methods

Differences in a consensus view of the state of scientific knowledge and its application to pharmacopoeial specifications can be seen most clearly in striking the balance between the adequacy of physicochemical tests and the need for additional (micro)biological methods. The structure of the monograph on human insulin [4] illustrates the European view that a molecule of this size, obtained by recombinant technology, and adequately purified to a defined content of

95.0–105.0% on the dried basis, can be controlled by a specification that does not require measurement of biological potency. The Production section imposes controls over manufacture and residual host-cell protein. The specification includes tests with limits on high molecular weight impurities and related substances by HPLC methods, pro-insulin by immunoassay, bacterial endotoxins and an assay by reversed-phase LC. It is known that material complying with this specification has a consistent, high, specific biological activity. For the convenience of users of insulin formulations that continue to be labelled in International Units, an equivalence between these and mass is stated.

The corresponding USP monograph [5] includes a definition in USP units per mg, similar tests for impurities, but with conventional gel filtration specified for control of high molecular weight impurities, and a test for biological potency. The definition is based on the result of an LC assay and thus assumes a specific activity in order to convert the chromatographic response of the weighed samples into a potency. Since measurement of the biological potency forms an integral part of the specification, a definition depending on the result from this would seem more logical. The specification also includes a test for nitrogen, included in earlier monographs for insulin as a measure of the peptide, which appears superfluous given the range and specificity of the other tests now employed.

A difference in approach is also evident in monographs for erythromycin. The current USP monograph [6] is essentially the same as that adopted by the European Pharmacopoeia in 1991 [7]. The defintion is in 'micrograms' of activity and International Units respectively, determined by microbiological assay. Neither monograph controls related substances other than through tests for specific rotation and pH. With the availability of LC procedures to separate and measure the individual erythromycins present, the revised European Pharmacopoeia monograph published in 1994 [8] now includes control of related substances by LC and employs LC for assay. The definition sets a requirement of 93.0–100.5% on an anhydrous basis for the sum of the erythromycins A, B and C present. This is considered to represent the microbiological activity of the sample. Since erythromycin preparations have been labelled by weight, the change in definition of content has not required any educational programme.

2.4. International harmonization

With the establishment of the informal Pharmaceutical Discussion Group bewteen representatives of the United States, Japanese and European Pharmacopoeias, a procedure has been developed for production and implementation of harmonized monographs [1]. The first stages involve identification of important items widely used in preparations, and in international trade and saelection of one Pharmacopoeia as the lead body. The available monographs are examined, and a draft is prepared from them and published by the lead pharmacopoeia for initial comment. The draft is modified on the basis of comments received and this version is published by all three Pharmacopoeias for a general enquiry. From the responses at this stage, a consensus monograph is prepared for adoption by the USP Committee of Revision and by the Commissions of the European and Japanese Pharmacopoeias. The monograph is then brought into force by the appropriate body: the USP, the Japanese Ministry of Health and Welfare, and the Council of Europe and member countries of the European Pharmacopoeia.

After a somewhat slow start to devising and implementing the system, and allowing sufficient time for full consultation, the first harmonized monograph, for lactose monohydrate, came into effect in 1993 [9]. Although most of the requirements are identical, the USP systematically includes a test for organic volatile impurities for products used in large amounts that might be contaminated during transport and storage. Such a requirement is not imposed by the other Pharmacopoeias. By the beginning of 1996, a further ten monographs are expected to be implemented, including microcrystalline and powdered cellulose and two cellulose derivatives, citric acid, sodium chloride, sucrose and polyvidone. More than 40

other monographs for substances and for general methods such as endotoxins/pyrogens, preservative efficacy, heavy metals and residue on ignition/sulphated ash, are now included in the process [10].

Barriers to harmonization still remain. The need to modify and extend the requirements and information in the monograph to aid a wide range of users is a matter for lively debate. Under pressure from the regulatory authorities and especially from the desire for closer integration of the Pharmacopoeia into the regulatory process in Europe, the European Pharmacopoeia has probably moved further towards extending the scope of its monographs than the other two participants in the harmonization process. The introduction of production and transparency sections, and greater emphasis on discriminating related substances tests are examples.

Another barrier may prove to be differences in the practice of medicine in different countries. Parenteral use of calcium sodium edetate is not permitted in Japan, although this is the main use of the substance in Europe and America. Thus, the draft monograph does not contain tests for bacterial endotoxins and iron, but these may be added by the individual Pharmacopoeias that consider them necessary [11].

The examples given above also illustrate the differences in opinion on the expression of content and potency, and the appropriate balance between physicochemical and (micro)biological testing. These will continue to be issues for discussion before an international consensus in reached.

3. Conclusion

The need for harmonization of pharmacopoeial monographs to take account of the reality of international marketing and distribution of medicines is now recognized. A voluntary process has been started in order to prepare, adopt and implement agreed requirements for the United States, Japan and Europe. The first fruits of this process are now appearing. As more experience is gained, it may be expected that the pace of harmonization will increase.

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