Annex 10

WHO general guidance on variations to multisource pharmaceutical products

1. Introduction

A marketing authorization (MA) holder or applicant is responsible for the quality, safety and efficacy (QSE) of a finished pharmaceutical product (FPP) that is placed on the market, throughout its life cycle. After the FPP has been authorized for marketing, the manufacturer will often wish to make changes (variations) for a number of reasons, for example, to respond to technical and scientific progress, to improve the quality of the FPP, to apply updates to the retest period for the active pharmaceutical ingredient (API) or shelf life of the FPP, to meet market requirements such as for scale-up or additional manufacturing sites, or to update product information (e.g. the information on adverse reactions). Such changes, regardless of their nature, are referred to as variations and may require the approval of the national medicines regulatory authority (NMRA) prior to implementation.

NMRAs and MA holders should recognize that:

- any change to the manufacture of the API or the FPP may impact the QSE of that FPP;
- any change to the information associated with the FPP (i.e. product labelling information) may have an impact on the safe and effective use of that FPP.

This document is intended to serve as a guide for establishing national requirements for the regulation of post-approval changes. The proposed categories of changes and reporting procedures are provided in these guidelines. It is possible that modification of these principles may be justified in light of risk–benefit and legal considerations specific to each NMRA.

2. Scope

This document provides guidance for NMRAs on the regulation of variations to the original MA dossier or MA for an authorized multisource pharmaceutical product on:

- procedures and criteria for the appropriate categorization and reporting of changes; and
- how NMRAs can establish regulatory procedures for the post-approval variations to an authorized FPP.

These guidelines can be used by NMRAs with respect to changes to the quality sections of product dossiers and should be read in conjunction with the

Guidelines on submission of documentation for a multisource (generic) finished product: quality part (*1*) as well as other related WHO guidelines or applicable national guidelines. These guidelines are intended to provide an overview of the principles that NMRAs should consider when establishing pharmaceutical product variation procedures. Specific guidance on data requirements or risk categorization of a particular change cannot be provided since the approach taken by a specific NMRA is intrinsically linked to the regulatory framework and resources available to that NMRA. Nonetheless, illustrative examples of the data required to enable NMRAs to evaluate the impact of the variation on QSE are provided in detail in the *Guidelines on variations to a prequalified product* (*2*) or other national guidelines.

These guidelines are applicable only to APIs manufactured by chemical synthesis or semisynthetic processes and FPPs containing such APIs. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin fall outside the scope of these guidelines. For vaccines, NMRAs may refer to the *WHO Guidelines for procedures and data requirements for changes to approved vaccines* (*3*).

3. Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

active pharmaceutical ingredient starting material. A raw material, intermediate or an active pharmaceutical ingredient (API) that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house.

biobatch. The batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or biowaiver studies, respectively.

finished pharmaceutical product. A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling.

in-process control. Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization holder. For the purposes of this document, the term marketing authorization holder refers to any person or entity that holds the legal responsibility for the product on the market by submission of the required documentation on a product that has been listed after evaluation as registered or approved.

multisource (generic) pharmaceutical product. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

officially recognized pharmacopoeia (or compendium). Those pharmacopoeias recognized by the national regulatory agencies (e.g. national pharmacopoeia (if applicable), the *British Pharmacopoeia*, the *European Pharmacopoeia*, *The International Pharmacopoeia*, the *Japanese Pharmacopoeia* and the *United States Pharmacopeia*).

pilot-scale batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

production batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

register. A list of all the pharmaceutical products authorized for marketing in a particular country. The medicines regulatory authority of the country in question maintains the register.

registered medicinal products. Pharmaceutical products that have a marketing authorization.

validation. The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity or system leads to the expected results.

variation. A change to any aspect of a pharmaceutical product, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

4. General considerations

For any change, the MA holder must consider the potential impact upon the QSE of the FPP. As part of this consideration the MA holder should decide if the information in the original MA needs to be supplemented and whether this requires an official submission to the responsible NMRA or a change in the application dossier, based on the recommendations in these guidelines. Prior to implementing the variation, the MA holder should assess the effects of the variation and demonstrate through appropriate studies the absence of a significant negative effect of the change on the QSE of the FPP. MA holders should be aware that some variations generate subsequent changes that might require the submission of additional consequential variations. Therefore, for any given variation, the MA holder should consider whether it is better to submit more than one variation. In general no variation should be implemented without the approval of the NMRA unless exempted in the national guidelines.

Even well-resourced agencies find it difficult to evaluate all the pharmaceutical changes that are made to all products. This has resulted in a shift towards increased self-assessment of changes by the MA holder. Therefore it is necessary to define those changes that can be made without the NMRA's prior approval (self-assessable changes) and those that require prior approval based on an understanding of the risk and how best to manage this risk. NMRAs may also establish an intermediate category of changes that do not require prior approval but must be notified ("notifiable" changes) and may or may not be subject to assessment.

MA holders are expected to evaluate the specific change that they are planning to make in the context of their particular circumstances to determine the impact on product QSE. In an application to vary the MA, the MA holder advises the NMRA of an intended change and submits appropriate supportive data. To encourage MA holders to give prior notice regarding such changes, submissions for variations should be processed as quickly as possible. The NMRA should consider publication of the timelines for processing the variations.

Implementation of these guidelines should not affect supply of and access to medicines. Therefore NMRAs are strongly encouraged to establish requirements that are commensurate with public health priorities and their own regulatory capacity and resources. Communication of proposed procedures and requirements to the pharmaceutical industry should also be ensured so that they can adequately plan for the implementation of any new guidance.

Regional NMRA associations or networks could serve as forums for sharing information and exchanging experience on technical issues and regulatory decisions. Use of such networks would expand the capacity of individual NMRAs through work sharing and recognition of the decisions

of other NMRAs in the network and convergence of regulatory requirements, thus avoiding unnecessary repetition of evaluations of the same variation by multiple NMRAs.

In these guidelines, descriptions of the reporting categories are discussed in section 5; proposed recommendations on the regulatory procedures for the reporting of changes to the NMRAs are discussed in section 8.

5. Reporting categories for quality changes

In order to enhance predictability, guidelines on the data requirements and conditions for the various categories of variations should be established and regularly updated in light of scientific and technical progress, taking into account the impact of the variation on the product QSE and how to manage this risk.

In addition to considering the impact of the change on a product's QSE, NMRAs may also modify the risk classification of a change through the introduction of prerequisites that must be met by the MA holder. In this way a change nominally identified as high-risk may be categorized across several risk categories depending on the conditions applied. Generally speaking the greater the number and specificity of the prerequisites the greater the possibility that the change can be self-assessed by the MA holder.

An additional consideration for NMRAs when designing their variation procedure is the determination of the default risk-category of changes not described in their variation guidance. For example, if an unspecified change defaults to a major variation, then effort should be focused on describing the conditions and data requirements for circumstances where the change might be considered as a lower risk category. In contrast, if a change defaults to a minor variation, then the conditions and data requirements of major changes and low-risk changes must be clearly defined.

The definitions outlined in the following reporting categories are intended to provide examples of change classification strategies that may be adopted by NMRAs for quality-related changes. Examples of specific variations data and conditions requirements can be found in the *WHO guidelines on variations to a prequalified product* (*2*) or other national regulatory guidelines that NMRAs may consult or reference; attention should be given to the default risk category underpinning the specific guidance.

NMRAs should also issue statements that whenever the MA holder is unclear about the categorization of a particular variation, the respective NMRA should be contacted.

Variations may be categorized into major variation, minor variation and notification. NMRAs may decide to have fewer categories or more categories depending on their national requirements.

5.1 Notifications

Notifications can be made for changes to the product that may have no potential or a minimal potential to have a negative impact on the QSE. The MA holder may implement such variations without prior approval by the NMRA. The NMRA may require the MA holder to submit these variations as immediate notifications (i.e. within a specific time frame after implementation) or as annual notifications.

5.2 Minor variations

Minor variations are changes to the product that may have a potential to have a moderate or negative impact on the QSE. Therefore such changes must be submitted to the NMRA with all required documentation prior to implementation. The MA holder may implement the change if no objection letter has been issued within a time period specified by the NMRA.

5.3 Major variations

Major variations are changes to the product that may have a significant potential to have a negative impact on the QSE. A major variation should be reviewed and approved by the NMRA prior to implementation of the change.

Individual changes normally require the submission of separate variations, but to increase efficiency NMRAs may accept grouping of variations under specific circumstances, for example:

- when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;
- when the same change affects multiple FPPs from the same MA holder, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notifications;
- when variations are related to a common technical topic, for example drug master file updates or changes to the analytical procedures and specifications to comply with pharmacopoeias.

MA holders and NMRAs should exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified in a particular category, classification within a higher-risk category may be warranted as a result of the composite effect of these changes. In all such cases, it is recommended that MA holders are able to contact the NMRA prior to submission of the variation application to obtain guidance on classifying such changes.

If changes to the dossier only concern editorial changes, such changes typically need not be submitted as a separate variation but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case a declaration should be provided indicating that the contents of the associated sections of the dossier have not been altered by the editorial changes beyond the substance of the variation submitted.

The "timeline" and "implementation of the variation" are subject to the NMRA's specific provisions and should be made publicly available.

6. New applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as variations. In these cases submission of a new dossier should be considered, in line with applicable national requirements for applications for MA.

Examples of such changes are:

- change of the API to a different API;
- inclusion of an additional API in a multicomponent product;
- removal of one API from a multicomponent product;
- change in the dose and/or strength of one or more APIs;
- change from an immediate-release product to an extended- or delayed-release dosage form or vice versa;
- change from a liquid to a powder for reconstitution or vice versa;
- changes in the route of administration.

7. Considerations for changes in product information and labelling

For any change to product information[1] (summary of product characteristics (SmPC), patient information leaflet (PIL) and/or labels) the NMRA should be notified and submission of the revised product information and/or labelling is expected as per country-specific requirements.

When a variation leads to a revision of the SmPC, the PIL and/or labelling, the updated information should be submitted as part of the variation. NMRAs may request the MA holder to submit a side-by-side tabular comparison of the current and proposed changes.

[1] Different regions and countries use different terminology for product information. In this document, package insert, the PIL and label are used to refer to product information.

Note that a change in the recommendations for use for a multisource product, such as indications or patient population would result in the product no longer being interchangeable with the comparator product. Therefore the NMRAs may need to take this into consideration prior to approval of such changes.

8. Procedures

8.1 General

NMRAs should establish procedures and criteria for adequate oversight of variations to authorized products. These should include written instructions regarding the submission procedures and timelines with action dates, to be consulted by MA holders when they prepare applications for variations. Depending on the category of the variation, different timelines may be applicable.

Regulation of post-approval variations is part of the whole regulatory framework, which includes among other aspects, MA, good manufacturing practices (GMP) inspection and post-marketing surveillance. Different branches of the NMRA often perform these activities. It is essential that these different branches interact and exchange information effectively and that the roles and responsibilities of each branch are clearly defined, particularly when they operate as separate entities. When multiple branches are involved in the evaluation of a variation a formal decision-making process should be in place to discuss, for instance, whether a change may require a GMP inspection or may be reviewed during the next routine inspection. Procedures should also be established so that the outcomes of inspections are verified or taken into account prior to the approval of variations. Good coordination and communication are pivotal.

8.2 Presubmission meetings

NMRAs should establish procedures to allow MA holders the opportunity to obtain advice prior to submitting variations. MA holders should be encouraged to contact the NMRA regarding plans for future changes and proposed filing dates for changes to authorized products to aid NMRAs in the planning and allocation of review resources.

8.3 Proposed documentation for minor variations

Where applicable the following basic information may be included as part of the description of the variation in the immediate notification, or the annual notification where prior approval is not required:

- a covering letter (including a list of changes, describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);

- an application form;
- a list of subsections of the current dossier affected by the change(s);
- a list and description of each change, reason for change(s) and the date each change was implemented (each change should be described in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);
- the relevant summary of data from studies and tests performed to assess the effects of each variation on product quality, including (where applicable) a list of cross- references to the change control and change validation protocols and standard operating procedures (SOPs) that were used to assess or demonstrate the effect of the variation;
- copies of the updated subsections of the original dossier.

The description should also include:

- the name(s) of one or more FPP(s) affected or involved in the change (e.g. different label strengths/product presentations);
- reference to any previously approved variations, if the change affected multiple products.

Executed batch records, SOPs and data from studies and tests performed to assess the effects of each change should be kept on file and made available to the NMRA upon request (e.g. during an inspection).

In the case of annual notifications, which represents the lowest risk category, it may be permissible not to request any summary data if the acceptability of the change can be determined without them.

8.4 Proposed documentation for variations requiring prior approval

Where applicable the following basic information may be included in the application for variations requiring prior approval:

- a covering letter (including a list of changes describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);
- an application form;
- a list of subsections of the original dossier affected by the change(s);
- a document summarizing the current and proposed condition(s) and the reason(s) for the change(s);

- where relevant, a side-by-side comparison of the currently approved and the proposed information;
- replacement of the relevant subsections of the dossier in accordance with the acceptable dossier format for the NMRAs concerned, with the proposed changes clearly annotated;
- copies of the SmPC, PIL and labels, if relevant;
- the relevant summary of data from studies and tests performed to assess the effects of each variation on product quality, including (where applicable) a list of cross-references to change control and change validation protocols and SOPs that were used to assess or demonstrate the effect of the variation;
- registration status and date of the proposed change(s) in other countries and/or agencies that have already approved the variation(s), especially the country of origin and the reference agencies.

8.5 Review procedures

Taking into account the national situation, the capacity of the NMRA and regional harmonization initiatives, the NMRA should adopt a risk-based review strategy for assessment, concentrating most effort on those changes considered to carry the greatest risk. A key factor in reducing workload is to ensure that the variation documentation requirements permit rapid assessment of changes. Moreover, the NMRA may consider whether it will:

- rely on decisions made by other national authorities;
- rely on assessment reports prepared by other national authorities;
- prepare its own full assessment reports;
- use some combination of these approaches.

If the decision of another NMRA is adopted, it is nevertheless essential for certain minimum information to be available. Where the NMRA has granted MA based on a reference NMRA or WHO prequalification it is recommended that any post-approval variations of such products should have prior approval from the initial reference NMRA or WHO prequalification (*4*, *5*), as appropriate.

References

1. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 6 (WHO Technical Report Series, No. 986).

2. Guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981).
3. Guidelines for procedures and data requirements for changes to approved vaccines. In: WHO Expert Committee on Biological Standardization: sixty-fifth report. Geneva: World Health Organization; 2015: Annex 4 (Technical Report Series, No. 993).
4. Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 5 (WHO Technical Report Series, No. 986).
5. Collaborative procedure between the World Health Organization Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996).