VARIATION GUIDELINES FOR ALLOPATHIC MEDICINES

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Introduction

The FDA is mandated by section 148 of the Public Health Act of 2012, ACT 851to develop guidelines in pursuit of its legal mandate. Post approval changes to a registered medicinal product forms part of the product life cycle

The variation guidelines has been developed to bring it in line with the principles of the new FDA Guidelines for Registration of Allopathic drugs.

The guidelines[i] retain the basic structure and function of the previous variation guidelines, and has been developed technically and structurally in line with WHO technical report series (TRS) 981. It includes the classification of post-approval changes and establishes the level of risk inherent to each change. This guideline is developed to help the applicant to classify changes that may occur related to all the major sections of a quality dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

The change categories are organized according to the structure of the common technical document (CTD). The specific CTD sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold). Presentation corresponds to section 1.4 in Annex 4 of WHO Technical Report Series, No. 970.[ii]

Changes are classified as major only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the FDA with adequate time for an assessment of the supporting documentation. Particular circumstances are identified where lower reporting requirements (annual notification (AN), immediate notification (IN) or minor variation (Vmin)) are possible. In all cases where notification to FDA or acceptance by FDA is required prior to implementation, assessment timelines will be published in order to provide predictable and reasonable timeframes.

In addition, the guidelines assist in understanding the possible consequences of the listed changes, and may be useful as a risk management tool to promote or enhance best practices within organizations.

The Variation guidelines are not exhaustive, applicants are encouraged to contact the FDA for advice for variations not covered under this guidelines

1. Background

This guidance document is technically and structurally inspired by the WHO TRS 981 Guideline on Post Approval Changes that provides the various categories of variations to the terms of marketing authorizations for medicinal products for human use. It is intended to provide supportive information on how to present an application to implement a change to a product.

This guidance supersedes the guidance published in 2013.

An applicant is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the registered product. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by FDA prior to implementation.
Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by FDA and to ensure that variations to the medicinal product do not result in health concerns.
The guidelines provide requirements for submitting variations and are not intended to provide the procedure for submitting variations.

1.1 Objectives

These guidelines are intended to:

- Assist applicants with the classification of changes made to the quality part of a registered finished pharmaceutical product (FPP);
- Provide guidance on the technical and other general data requirements to support changes to the quality attributes of the active pharmaceutical ingredient (API) or FPP.

1.2 Scope and application

These guidelines apply to applicants intending to make changes to the quality sections of product dossiers for an API or an FPP. This guidance should be read in conjunction with the FDA Guidelines for registration of allopathic medicines as well as other related FDA guidelines.

This guidance document is applicable only to APIs and excipients manufactured by chemical synthesis or semi-synthetic processes and FPPs containing such APIs and excipients. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin are treated as special cases. The applicant is requested to contact FDA regarding planned variations to such products.

The notification requirements for API-related changes differ depending on the manner in which information on the API was submitted in the FPP application, namely, use of a active pharmaceutical ingredient master file (APIMF), WHO Prequalification of API or use of an European Pharmacopoeia Certificate of Suitability (CEP).

The conditions and documentation stipulated in this guidance for API related variations focus primarily on those FPPs that relied upon the provision of full APIMF for API information within the FPP dossier. When an FPP relies upon a CEP or WHO-API, FPP applicants are required to notify FDA only when the associated CEP and WHO-API has been revised.

When a variation leads to a revision of the summary of product characteristics (SmPC), the patient information leaflet (PIL), labelling and packaging leaflet and updated product information should be submitted as part of the application.

For variations that require generation of stability data on the API or FPP, the stability studies required, including commitment batches, should always be continued to cover the currently accepted retest or shelf-life period. FDA should be informed immediately if any problems with the stability of APIs or FPPs occur during storage, e.g. if found to be outside specifications or potentially outside specifications.

Applicants should be aware that some variations may require the submission of additional consequential variations. Therefore, for any given change the applicant should consider whether one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes 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 that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

All variations with the exception of annual notifications should be approved by the FDA prior to its implementation.

2. Guidance for implementation

2.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of quality-related changes. Specific examples of changes are provided in these guidelines. However, it should be noted that a change not covered by these guidelines, should be considered as a major change by default. Whenever the applicant is unclear about the classification of a particular change, FDA should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only under the following circumstances:

- 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, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notification.

For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified as a particular reporting type, classification within a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact FDA prior to submission of the variation application to obtain guidance on classifying such changes.

2.1.1 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Annual notification (AN) do not require prior acceptance, but must be notified to FDA within 12 months following implementation of the change. Immediate notification (IN), however require prior acceptance and must be notified to the FDA immediately upon implementation of the change.

It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request

or at the time of inspection. ANs should be submitted to FDA within 12 months of implementation of the changes. For convenience applicants may group several AN changes as a single submission.

Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by FDA within 90 calendar days of the date of acknowledgement of receipt of the application.

2.1.2 **Minor variation (Vmin)**

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Such variations can be implemented if no objection letter has been issued within a time period indicated on the FDA web site. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of approval from FDA.

2.1.3 **Major variation (Vmaj)**

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by FDA is required before the changes can be implemented. A letter of approval will be issued for all major variations if and when the variation is considered acceptable.

2.1.4 **New applications and extension applications**

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

2.1.5 **Labelling information**

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, FDA must be notified and submission of the revised labelling information is expected as per the guidance on the FDA web site in line with the respective SmPC, PIL and labelling template.

2.2 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Vmin) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a Vmaj.

In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the FPP.

2.3 Documentation required

Examples of variations are organized according to the structure of the CTD. For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation.

Where applicable, the following should be included in the application:

- a variation application form (a template can be downloaded from the web site). All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF, should be provided in addition to the printed version;
- an updated quality information summary (QIS) (if applicable);
- replacement of the relevant sections of the dossier as per CTD format;
- copies of SmPC, PIL and labels, if relevant.

It should be noted that FDA reserves the right to request further information not explicitly described in these guidelines.

The QIS provides a summary of the key quality information from the product dossier. For FPPs that have an agreed-upon QIS, the QIS should be revised and submitted (in Word format only) with every variation application. Any revised sections within the QIS should be highlighted. If there is no change to the QIS as a result of the variation, a statement should be made in the covering letter to this effect.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that FDA may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy and quality of an FPP.

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 (API) OR drug substance

A substance used in the FPP, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

active pharmaceutical ingredient (API) starting material

A raw material, intermediate, or an 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.

Applicant:

The product owner or licence holder. Representatives of licence holders may not hold themselves as applicants unless they own the product.

biobatch

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

final intermediate

The last reaction intermediate in the synthetic pathway that undergoes synthetic transformation to the API or the crude API. Purification is not considered to be a synthetic transformation.

finished pharmaceutical product (FPP)

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 re-labelling of pharmaceuticals.

officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized in schedule 4 of the Public Health Act of 2012, ACT 851 (i.e. *The International Pharmacopoeia* (Ph. Int.), the *European Pharmacopoeia* (Ph. Eur.), the *British*

Pharmacopoeia (BP), the *Japanese Pharmacopoeia* (JP), the *United States Pharmacopeia* (USP) or any other pharmacopoeia as recommended by the FDA .

pilot-scale batch
A batch of an API or FPP 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.[6]

production batch
A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

stringent regulatory authority (SRA) A stringent regulatory authority is:

- the medicines regulatory authority in a country which is: (a) a member of the International Council on Harmonisation (ICH) (European Union (EU), Japan and the United States of America); or
  (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);
- only in relation to good manufacturing practices (GMP) inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at http://www.picscheme.org

4. Administrative changes

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
Change in the name and/ or corporate address of the supplier of the FPP.	1	1	IN

Conditions

1. Confirmation that the supplier of the product remains the same legal entity

Documentation required

1. A formal document from a relevant official body (eg the national medicines regulatory authority (NMRA) in which the new name and/or address is mentioned

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2 Change in the name or address of a manufacturer of an API	1	1–2	IN

Conditions to be fulfilled

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

1. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.
2. An updated Letter of Access in case of change in the name of the holder of the APIMF.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3 Change in the name and/or address of a manufacturer of the FPP.	1	1	IN

Conditions to be fulfilled

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
4	Deletion of a manufacturing or manufacturer involving			
4a	production of the API starting material	1	1	AN
4b	production or testing of the API intermediate or API	1–2	1	IN
4c	production, packaging or testing of the intermediate or FPP	1–2	1	IN

Conditions to be fulfilled

1. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.
2. The deletion of the site is not a result of critical deficiencies in manufacturing.

Documentation required

1. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.

5. Changes to a CEP

	Description of change	Conditions to be fulfilled	documentation required	reporting type
5	Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API:			
5a.1	from a currently accepted manufacturer	1–5	1–5	AN
5a.2		1–4	1–6	IN
5a.3		1, 3–4	1–6	Vmin

5b.1 from a new manufacturer	1–4	1–6	IN
5b.2	1, 3– 4	1–6	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. Unchanged (excluding tightening) additional specification for any impurities including organic, inorganic and genotoxic impurities and residual solvents, with the exception of residual solvents when the limits stipulated comply with ICH requirements
3. The manufacturing process of the API, starting material or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data
4. For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
5. No revision of the FPP manufacturer's API specification is required.

Documentation required

1. Copy of the current (updated) CEP including any annexures and a declaration of access for the CEP to be duly filled up by the CEP holder on behalf of the FPP manufacturer or applicant to the FDA who refers to the CEP.
2. A written commitment that the applicant will inform FDA in the event that the CEP is withdrawn and an acknowledgement that withdrawal of the CEP will require additional consideration of the API data requirements to support the product dossier.
3. Replacement of the relevant pages of the dossier with the revised information for the CEP under 3.2.S of the FDA Guidelines for registration of allopathic medicines.
4. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation data.
5. (P.8.2) In the case of submission of a CEP for an API, if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot-scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to FDA.
6. (S.4.1) Copy of FPP manufacturer's revised API specifications.

Description of change		Conditions to required	Documentation type	Reporting be fulfilled
6	Submission of a new or updated confirmation of API- prequalification document			
6a.1	from a currently accepted	1–3	1–3, 5	AN
6a.2	manufacturer	1–2	1–5	Vmin
6b.1	from a new manufacturer	1–3	1–3, 5	IN
6b.2		1–2	1–5	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. For low solubility APIs the API polymorph is the same, and whenever particle size is critical (including low solubility APIs), there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
3. There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturers API specification

Documentation required

1. Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
2. Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option (*Option 1: confirmation of API Prequalification document*) stipulated under section 3.2.S. of the FDA *Guidelines on of submission of documentation for a finished pharmaceutical product: quality part*.
3. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation.
4. (S.4.1) Copy of FPP manufacturer's revised API specifications.
5. (P.82) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of at least pilot-scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to FDA.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
7 Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient or API (addition or replacement)	None	1	AN

Conditions to be fulfilled
None

Documentation required
1. Copy of the current (updated)TSE CEP

6. Quality changes
3.2. S Drug substance (or API)
3.2. S.2 Manufacture

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
8 Replacement or addition of a new manufacturing site or manufacturer of an API involving:			

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8a.1	API testing only	1, 2, 4	1, 3–4	IN
8a.2		2, 4	1, 3–4	Vmin
8b.1	production of API starting material	3–4	No variation is required; such changes are handled as amendments to the DMF by the DMF holder.	
8b.2		4–5	1–2, 12	IN

8b.3		None	1,2,5, 7–8,12, 13	Vmaj
8c.1	production of API intermediate	3–4	No variation is required; such changes are handled as amendments to the DMF by the DMF holder.	
8c.2		4, 6	1–2, 12	IN
8c.3		None	1, 2, 5, 7–8, 12, 13	Vmaj
8d.1	production of API (APIMF procedure)	3, 7–9	1, 2, 6, 8	IN
8d.2		3, 7, 9	1, 2, 6–8	Vmin
8e.1	production of API (DMF)	1, 9–11	1–2, 4, 8–9	IN
8e.2		None	1, 2, 4, 5, 7–8, 10–11, 13	Vmaj

Conditions to be fulfilled

1. The API is non-sterile.
2. The transfer of analytical methods has been successfully undertaken.
3. The new site is supported by an APIMF that is currently accepted through the APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
4. No change in the FPP manufacturer's API specifications.
5. The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does not require revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted.
6. Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require revision of the API manufacturer's API intermediate specifications.
7. No change in the FPP release and end-of-shelf-life specifications.
8. No difference in impurity profile of the proposed API to be supplied, including skip organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer’s specifications do not require revision of the FPP manufacturer’s API specification.
9. For low-solubility APIs the API polymorph is the same, and whenever particle size is critical (including low-solubility APIs), there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.

10. Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or a new contract manufacturing site with evidence of an acceptable and similar quality system to that of the main manufacturer).
11. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) *or equivalent guidelines of the ICH* region and associated countries.

Documentation required

1. (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid testing authorization or a certificate of GMP compliance, if applicable.
2. (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites and a tabulated summary of the differences.
3. (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence of analytical procedures to be used at the proposed testing site.
4. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.
5. Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the FDA Guidelines for registration of Allopathic medicines (CTD) *quality part.*
6. The open part of the new DMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of requirements for the DMF Section 3.2.S of the FDA Guidelines for registration of Allopathic medicines (CTD) *quality part.*
7. (P.8.2) if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to FDA.
8. (S.4.1) A copy of the FPP manufacturer's API specifications.
9. (S.2) A declaration from the supplier of the registered FPP that the route of synthesis, materials, quality control procedures and specifications of the API and key (ultimate)

intermediate " in the manufacturing process of the API (if applicable) are the same as those already accepted.

10. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
11. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility APIs) where there is a significant difference in particle distribution compared to the lot used in the biobatch, evidence that the difference do not impact quality and bioavailability of the FPP.
12. Certificates of analysis for at least one batch of API starting material or intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material or intermediate (as applicable) from the new source and from a previously accepted source. For an alternative source of plant-derived starting material, control of pesticide residues must be established. This can either be in the form of an attestation from the starting material supplier that no pesticides are used during the growth of the plant material, or by providing the results of pesticide screening from one batch of the starting material.
13. An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
9a	change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	1–5	No variation is required: such changes are handled as amendments to the APIMF by the APIMF holder. 1-4	
9b		1, 3–5	1–4	IN

Conditions to be fulfilled

1. The API is non-sterile.
2. The API manufacturing block or unit is currently accepted through the DMF procedure.
3. The same quality system covers currently accepted and proposed units or blocks.
4. For low-solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the biobatch.

5. No change in the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment are acceptable.

Documentation required

1.(S.2) A declaration from the supplier of the FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
2. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if applicable.
3. (S.4.4) Description of batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks.
4. (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
10a	change in the manufacturing process of the API	1–3, 9	1–2, 8	AN
10b.1		1–2, 4, 6–9	3–4, 11–12	IN
10b.2	change in the manufacturing process of the API	1–2, 4, 6–8, 10	3–4, 11–12	Vmin
10c		1–2, 4–7	3–4, 11–12	Vmin
10d		None	2–14	Vmaj

Conditions to be fulfilled

1. No change in the physical state (e.g. crystalline, amorphous) of the API.
2. For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to that of the API lot used in the preparation of the biobatch.
3. The API manufacturing site is currently accepted through the DMF procedure.

4. Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.
6. No change in qualitative and quantitative impurity profile or in physicochemical properties of API.
7. The change does not affect the sterilization procedures of a sterile API
8. The change involves only steps before the final intermediate.
9. The change does not require revision of the starting material, intermediate or API specification.
10. The change does not require revision of the API specifications.

Documentation required

1. A copy of the APIMF amendment acceptance letter.
2. (P.8.2) If the quality characteristics of the API are changed in a way that may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to FDA.
3. (S.2.2) A side-by-side comparison of the current process and the new process.
4. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
5. (S.2.3) Information on the quality and controls of the materials (e.g raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
6. (S.2.3) Either a TSE CEP for any new source of material or previously assessed and accepted by FDA or EMA *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www. Emea.europa.eu/EMA or equivalent guidelines of the ICH region and associated countries.
7. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
8. (S.2.5)Evidence of process validation and/or evaluation studies for sterilization if applicable.
9. (S.3.1) Evidence for elucidation of structure, where applicable.
10. (S.3.2) Information on impurities.
11. (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12. (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes.

13. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
14. For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.

Description of change		Conditions to required	Documentation type	Reporting be fulfilled
11	Change in the in-process tests or limits applied during the manufacture of the API:			
11a	any change in the manufacturing process controls	1	No variation is required; such changes are handled as amendments to the DMF by the DMF holder	
11b	tightening of in-process limits	2–4	1	AN
11c	addition of a new in-process test and limit	2, 5	1–5	AN

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
11d	addition or replacement of an in-process test as a result of a safety or quality issue	None	1–5, 7, 8–10	Vmin
11e.1	deletion of an in-process test	2, 6–7	1–3, 6	AN
11e.2		None	1–3, 7–10	Vmaj
11f	relaxation of the in-process test limits	None	1–3, 5, 7–10	Vmaj

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by unexpected events arising during manufacture e.g a new unqualified impurity or a change in total impurity limits.
3. The change is within the range of currently accepted limits.
4. The analytical procedure remains the same, or changes to the analytical procedure are minor.
5. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The affected parameter is non-significant.
7. The change does not affect the sterilization procedures of a sterile API

Documentation required

1. A comparison of the currently accepted and the proposed in-process tests.
2. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
3. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.
4. Details of any new non-pharmacopoeial analytical method and validation where relevant.
5. Justification for the new in-process test and/or limits.
6. Justification and/or risk-assessment showing that the parameter is non-significant.
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization where applicable.
8. (S.3.2) Information on impurities, if applicable.
9. (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable).

10. (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results in a comparative tabular format, for at least two batches (minimum pilot-scale) for all specification parameters.

Description of change		Conditions to required	Documentation be fulfilled	Reporting type
12	Change in batch size of the API or intermediate involving:			
12a	up to 10-fold compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	AN
12b.1	downscaling	1–4	1, 3–4	AN
12b.2		1–3	1–4	IN
12c	any change in scale (DMF procedure)	5	1–2, 4–5	AN
12d	more than 10-fold increase compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	Vmin

Conditions to be fulfilled

1. No changes to the manufacturing process other than those necessitated by changes in scale (e.g use of a different size of equipment).
2. The change does not affect the reproducibility of the process.
3. The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.
4. The change does not concern a sterile API.
5. The API manufacturing site and batch size is currently accepted through the DMF procedure.
6. The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through subsequent major or minor variation.

Documentation required

1. (S2.2) A brief narrative description of the manufacturing process.
2. (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.
3. (S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).
4. (S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5. A copy of the APIMF amendment acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
13	Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving:			
13a	any change	1	No variation is required; such changes are handled as amendments to the DMF by the DMF holder	
13b	tightening of the specification limits	2–4	1–3	AN
13c	minor change to an analytical procedure	5–7	2–3	AN
13d	addition of a new specification parameter and a corresponding analytical procedure where necessary	2, 7–9	1–3	AN
13e	deletion of a specification parameter or deletion of an analytical procedure	2, 10	1–4	AN

13f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–3, 5	Vmin
13g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	4, 7, 9–10	1, 3–4	IN
13h	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1–3, 5	Vmaj

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any change is within the range of currently accepted limits.
4. The analytical procedure remains the same.
5. The method of analysis is based on the same analytical technique or principle (e.g changes to the analytical procedure are within allowable adjustments, to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method.
6. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7. No change to the total impurity limits; no new impurities are detected.
8. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The change does not concern a genotoxic impurity.
10. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation required

1. Comparative table of currently accepted and proposed specifications.
2. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
3. (S.2.4) Information on intermediates, where applicable.
4. Justification and/or risk assessment showing that the parameter is non-significant.
5. (S.3.2) Information on impurities, where applicable.

	Description of change	Conditions to required	Documentation be fulfilled	Reporting type
14	Change to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturers API specifications involving			
14a	a. API supported through the APIMF procedure	1–2	No variation is required; such changes are handled as amendments to the associated APIMF	
14b	b. API not supported through the APIMF procedure	2	1–4	IN

Conditions to be fulfilled

1. The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated DMF and accepted.
2. The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer’s API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API’s is maintained

Documentation required

1. (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4. Justification as to why the change does not affect the FPP manufacturer's specifications.

3.2. S.4 Control of the API by the FPP manufacturer

Description of change	Conditions to be fulfilled		Documentation required	Reporting type
15	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
15a	11	1-5		AN
updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.				

15b.1		1–2	1, 6	AN
	deletion of a test parameter			
15b.2		10	1, 6, 8	IN
15b.3		None	1, 6	Vmaj
15c.1		1, 4–8	1–6	AN
	addition of a test parameter			
15c.2		1, 5–6, 10	1–6, 8	IN
15c.3		1, 5–6	1–6	Vmin
15c.4		None	1–7	Vmaj
15d.1		1, 5–8	1–6	IN
	replacement of a test parameter			
15d.2		5, 7, 10	1–6, 8	Vmin
15d.3		None	1–7	Vmaj
15e.1	tightening of an acceptance criterion	1, 3, 9	1, 6	AN
15f.1	relaxation of an acceptance criterion	1, 5–9	1, 6	IN
15f.2		5, 7, 10	1, 6, 8	Vmin
15f.3		None	1, 6–7	Vmaj

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
2. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3. The change is within the range of currently accepted acceptance criteria.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low-solubility APIs) there is no change in particle size distribution acceptance criteria.
6. No additional impurity found over the ICH identification threshold.
7. The change does not concern sterility testing.

8. The change does not involve the control of a genotoxic impurity.
9. The associated analytical procedure remains the same.
10. The change has resulted from a revision of the API manufacturer’s specifications and is accepted as part of DMF amendment.
11. No change is required in FPP release and shelf-life specifications.

Documentation required

1. (S.4.1) A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used.
4. (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.
6. (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
7. (P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact FPP for advice. For changes to the polymorph of an insoluble API the applicant should contact FPP for advice before embarking upon any investigation.
8. Copy of the APIMF amendment acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
16	Change to the analytical procedures used to control the API by the FPP manufacturer involving:			
16a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	1–3	AN
16b	change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another official recognized pharmacopoeia	None	1–4	IN
16c.1	addition of an analytical procedure	1–3	1–3	AN
16c.2		3, 8	1–3, 5	AN
16c.3		8	1–3, 5	Vmin
16c.4		None	1–3	Vmaj
16d.1	modification or replacement of an	1–6	1–4	AN
16d.2		2–3, 5–6, 8	1–5	AN

16d.3	analytical procedure	1–3, 5–6	1–4	Vmin
16d.4		5–6, 8	1–5	Vmin
16d.5		None	1–4	Vmaj
16e.1	deletion of an analytical procedure	6–7	1, 6	AN
16e.2		6, 8	1, 5, 6	IN
16e.3		None	1, 6	Vmaj

Conditions to be fulfilled

1. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. No new impurities have been detected as a result of the use of the new analytical method.
4. The method of analysis is based on the same analytical technique or principles (e.g changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities detected.
5. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted method.
6. The change does not concern sterility testing.
7. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
8. The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.

Documentation required

1. (S.4.1) Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (S.4.2) Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.
3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used.

4. (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.
5. A copy of the APIMF acceptance letter.
6. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
17a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	3, 4	1–2, 4	AN
17b		1–2, 4	2–3	IN
17c		4	1–3	Vmin

Conditions to be fulfilled

1. Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, and moisture permeability among others).
2. The change does not concern a sterile API.
3. The change has previously been accepted through the APIMF procedure.
4. The change is not the result of stability issues.

Documentation required

1. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from current process.
2. (S.6) Information on the proposed primary packaging (e.g. description and specifications) and data in fulfillment of condition 1.
3. (S.7.1) Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type.
4. A copy of the APIMF amendment acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
18	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
18a	tightening of specification limits	1–2	1	AN
18b	addition of a test parameter	2–3	1–3	AN
18c	deletion of a non-critical parameter	2	1, 4	AN
18d	any change (APIMF procedure)	4	No variation is required: such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way
4. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (S.4.2) Details of method and summary of validation of new analytical procedure
3. (S.6) Certificate of analysis for one batch.
4. Justification to demonstrate that the parameter is not critical.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
19	Change to an analytical procedure on the immediate packaging of the API involving:			
19a	minor change to an analytical procedure	1–3	1	AN
19b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
19c	deletion of an analytical procedure	5	2	AN
19d	any change (APIMF procedure)	6	No variation is required: such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1.The method of analysis is based on the same analytical technique or principle (e.g changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).

2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.

3. Comparative studies indicate the new analytical procedure to be at least equivalent to the currently accepted procedure.

4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.

6. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.

2. Justification for deletion of the analytical procedure.

3.2. S.7 Stability

Description of change		Conditions to be fulfilled	Documentation	Reporting type
20	Change in the retest period or shelf-life of the API involving:			
20a	any change (APIMF procedure)	4	4	IN
20b	reduction	3	1–2	IN
20c	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging in direct contact with the API or to the recommended condition of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. The revised retest period has previously been accepted through the APIMF procedure.

Documentation required

1. (S.7.1) Proposed retest period or shelf-life, summary of stability testing according to currently accepted protocol and test results.
2. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.
3. (S.7.3) Stability data to support the change
4. A copy of the APIMF acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
21	Change in the labelled storage conditions of the API involving:			

21a	any change in storage conditions (APIMF procedure)	1	1	IN
21b	Any change in storage conditions	2	2	Vmin

Conditions to be fulfilled

1. The revised storage conditions have been previously accepted through the APIMF procedure
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

1. A copy of the APIMF acceptance letter.
2. (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions.

3.2. P Drug product (or FPP)
3.2. P.1 Description and composition of the FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
22a	Change in the composition		2, 4, 7, 9–10	IN

	1–6		1–10	Vmaj
22b	of a solution dosage form	None		

Conditions to be fulfilled

1.The affected excipient (s) does/do not function to affect the solubility and/or the absorption of the API.
2. The affected excipient (s) does/do not function as a preservative or preservative enhancer.
3. No change in the specification of the affected excipient (s) or the FPP.
4. No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).
5. The change does not concern a sterile FPP.
6. The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within ±10% of the amount (or concentration) of each excipient in the originally registered product

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the FDA Guidelines in Bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, suitability studies on the packaging system for the changed product).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5. (P.4) Control of excipients, if new excipients are proposed.
6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk material has been previously assessed and accepted by the FDA or previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability

programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).

10. (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to required	Documentation type	Reporting be fulfilled
23	Change in the colouring system or the flavouring system currently used in the FPP involving:			
23a	reduction or increase of one or more components of the colouring or the flavouring system	1–3, 6	1, 4, 6–7	AN
23b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	1–6	1–7	IN

Conditions to be fulfilled

1. No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Specifications for the FPP are updated only with respect to appearance, odour and/or taste or if relevant, deletion or addition of a test for identification.
4. Any new component must comply with section 3.2.P.4 of the FDA *Guidelines on Registration of allopathic medicines: quality part*.
5. Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required, or is in compliance with the current *WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (www.who.int/biologicals) or EMA Note for guidance on minimizing*

the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (www.emea.europa.eu/ema) or an equivalent guide from the ICH region and associated countries.

6. Where applicable, the change does not affect the differentiation between strengths and for paediatric formulations it does not require submission of results of taste acceptability studies.

Documentation required

1. Sample of the FPP.
2. (P.2) Discussion on the components of the FPP (e.g compatibility of API and qualitative composition of the colouring or flavouring system if purchased as a mixture, with specifications, if relevant).
3. (P.4.5) Either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
4. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches.
5. (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
6. (P.8.1) Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
24	Change in weight of tablet coatings or capsule shells involving:			
24a	immediate-release oral FPPs	1–3	2–5	AN
24b	gastro-resistant, modified or prolonged release FPPs	None	1–5	Vmaj

Conditions to be fulfilled

1. Multipoint in vitro dissolution profiles of the proposed version of the product (determined in the routine release medium on at least two batches of pilot- or production-scale), are similar to the dissolution profiles of the biobatch.
2. Coating is not a critical factor for the release mechanism.
3. Specifications for the FPP are updated only with respect to weight and dimensions, if applicable.

Documentation required

1. Justification for not submitting a new bioequivalence study according to the current FDA Guidelines on bioequivalence (*Proposal for a biowaiver*).
2. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.
3. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch.
4. (P.8.1) Results of stability testing generated on at least one pilot- or production scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
5. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
25	Change in the composition of an intermediate-release solid oral dosage form involving:			
25a.1	Replacement of a single excipient with a comparable excipient at similar concentration	1–5	1–10	Vmin
25a.2		None	1-10	Vmaj
25b.1	Quantitative changes in excipients	1–4	1–4, 7-10	Vmin

25b.2	Quantitative changes in excipients	None	1–4, 7-10	Vmaj

Conditions to be fulfilled

1. No change in functional characteristics of the pharmaceutical form.
2. Only minor adjustments (see appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Stability studies have been started under conditions according to FDA Guidelines on registration of allopathic medicines*: quality part*[10] (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 3 months are at the disposal of the applicant, and the stability profile is similar to that of the currently accepted product.
4. The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.
5. The change is not the result of stability issues and/or does not result in potential safety concerns, i.e differentiation between strengths.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current FDA Guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP
3. (P.2) Discussion on the components of the proposed product (e.g choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained on at least two batches of pilot- or production-scale of the proposed product and the biobatch (depending on the solubility and permeability of the drug, dissolution in the routine release medium or in multiple media covering the physiological pH range).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5. (P.4) Control of excipients, if new excipients are proposed.
6. (P.4.5) If applicable, either a CEP for any component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE material has

been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use.

7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch**,** and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to required	Documentation type	Reporting be fulfilled
26	Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:			
26a	changes in imprints, markings	1–3 embossing or other	1–2, 5–6	IN
26b	deletion of a scoreline	2–5	1, 5–6	IN
26c.1	addition of a scoreline	2–4	1, 3, 5–6	Vmin
26c.2		None	1, 3–6	Vmaj

Conditions to be fulfilled

1. Any ink complies with section 3.2.P.4 of the FDA *Guidelines on registration of allopathic medicines: quality part*.

2. The change does not affect the stability or performance characteristics (e.g release rate) of the FPP.
3. Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.
4. Addition or deletion of a score line from a generic product is consistent with a similar change in comparator or was requested by the FDA
5. The scoring is not intended to divide the FPP into equal doses.

Documentation required

1. Sample of the FPP.
2. (P.1.) Qualitative composition of the ink, if purchased as a mixture.
3. (P.2) Demonstration of the uniformity of the dosage units of the tablet portions for gastro-resistant, modified or prolonged release products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change	Conditions to required	Documentation be fulfilled	Reporting type
27 Change in dimensions without change in qualitative or quantitative and mean mass of:			
27a tablets, capsules, suppositories and pessaries other than those stated in change no. 27b	1–2	2–6	IN
27b gastro-resistant, modified or prolonged-release FPPs and scored tablets	1–2	1–6	Vmin

Conditions to be fulfilled

1. Specifications for the FPP are updated only with respect to dimensions of the FPP.

2. Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the routine release medium, on at least one batch of pilot- or production-scale), are comparable.

Documentation required

1. For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according the current FDA Guidelines on bioequivalence. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions.
2. Sample of the FPP.
3. (P.2) Discussion on the differences in manufacturing process (es) between the currently accepted and proposed products and the potential impact on product performance.
4. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

3.2. P.3 Manufacture

Description of change		Conditions to be fulfilled	Documentation required type	Reporting
28	Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:			
28a	secondary packaging of all types of FPPs	2–3	1	IN
28b	primary packaging site of:			
28b.1	solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs	2–4	1, 8	IN
28b.2	Other liquid FPPs (suspensions, emulsions)	2–5	1, 5, 8	IN
28c	all other manufacturing operations except batch control and/or release testing	1–3, 5	1–9	Vmin

Conditions to be fulfilled

1. No change in the batch formula, description of manufacturing process and process and process controls, equipment class and process controls, control of critical steps and intermediates, or FPP specifications.
2. Satisfactory inspection in the last three years either by FDA or an SRA.
3. Site appropriately authorized by an NMRA (to manufacture the pharmaceutical form and the product concerned).
4. The change does not concern a sterile FPP.
5. Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol.

Documentation required

1. Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned;

    - A copy of the current manufacturing authorization, a GMP certificate or equivalent issued by the NMRA
    - A GMP statement or equivalent issued by FDA or an SRA
    - Date of last satisfactory inspection concerning the packaging facilities by FDA or an SRA in the last three years.

2. Date and scope (with indication as to whether scope was e.g. product specific or related to a specific pharmaceutical form) of the last satisfactory inspection.
3. (P.2) Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
4. (P.2) For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.
5. (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary.
6. (P.5.1) Copies of release and shelf-life specifications.
7. (P.5.4) Batch analysis data on one production-scale batch from the proposed site and comparative data on the last three batches from the previous site.
8. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the FPP produced at the new site into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9. (R.1) Executed production documents for one batch of the FPP manufactured at the new site.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
29 Replacement or addition of a site involving batch control testing	1–2	1–3	AN

Conditions to be fulfilled

1. Site is appropriately authorized by the NMRA and satisfactorily inspected either by FDA or an SRA.
2. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation required

1. Clear indication of the currently accepted and proposed quality control sites on the letter accompanying the application.
2. Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected either by FDA or an SRA.
3. (P.5.3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
30 Change in the batch size of the FPP involving:			
30a up to and including a factor of 10 compared to the biobatch	1–7	2, 5–6	IN
30b downscaling	1–5	2, 6	AN
30c other situations	1–7	1–7	Vmin

Conditions to be fulfilled

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3. Changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g use of different-sized equipments.

4. A validation protocol is available or validation of the manufacture of three production-scale batches has been successfully undertaken in accordance with the current validation protocol.
5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6. The change does not require supporting in vivo data.
7. The biobatch size was at least 100 000 units in the case of solid oral dosage forms.

Documentation required

1. (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet dissolution profile similarity (f2) requirements. For semisolid dosage forms (e.g. lotions, gels, creams and ointment containing the API in the dissolved or non-dissolved form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request.
2. (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3. (P.5.1) Copies of release and shelf-life specifications.
4. (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial).
5. (P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production-scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production document for one batch (if manufactured as required by documentation 4) (above) and confirmation that there are no changes to the production documents other than those highlighted.
7. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current FDA guidelines on bioequivalence

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
31a Change in the manufacturing process of the FPP	1–9	1–4, 6–7	AN
31b	1–3, 5–9	1–7	Vmin

Conditions to be fulfilled

1. The change does not require in vivo data.
2. No change in qualitative and quantitative impurity profile or in physicochemical properties dissolution profiles are similar to those of the biobatch.
3. The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet or dry granulation or vice versa would be considered a change in manufacturing principle), the same processing intermediates and there are no changes to any manufacturing solvent used in the process.
4. The same classes of equipment, operating procedures, in-process controls (with no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5. No change in the specifications of the intermediates or the FPP.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function.
8. The change does not concern a gastro-resistant, modified or prolonged-release FPP.
9. The change does not affect the sterilization parameters of a sterile FPP

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current FDA guidelines on bioequivalence.

2.(P.2) Discussion on the development of the manufacturing process; where applicable

- Comparative in vitro testing, e.g multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);
- Comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or nondissolved form

(one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);

- Microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the APIs present in non-dissolved form.

3. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
4. (P.5) Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process.
5. (P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products, one pilot batch; the other one can be smaller) with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
32	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
32a	tightening of in-process limits	1–2, 5	1	AN
32b	deletion of a test	2, 4	1, 6	AN
32c	addition of new tests and limits	2–3	1–6	AN
32d	revision or replacement of a test	2–3	1–6	IN

Conditions to be fulfilled

1. The change is within the range of acceptance limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).
5. No change in the analytical procedure.

Documentation required

1. (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.
6. (P.5.6) Justification for the addition or deletion of the tests and limits.

3.2.P.4 Control of excipients

	Description of change	Conditions to required	Documentation type	Reporting be fulfilled
33	Change in the source of an excipient from TSE risk to a material of vegetable or synthetic origin:	1	1	AN

Conditions to be fulfilled

1. No change in the excipient and FPP release and shelf-life specifications

Documentation required

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthethic origin

Description of change		Conditions to be fulfilled required	Documentation type	Reporting
34	Change in the specifications or analytical procedures for an excipient involving:			
34a	deletion of a non-significant in-house parameter	2	1–3	AN
34b	addition of a new test parameter or analytical procedure	2–3	1–2	AN
34c	tightening of specification limits	1–2, 4	1–2	AN
34d	change or replacement of an analytical procedure	2–3	1–2	Vmin

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard or a standard technique used in a novel way
4. No change in the analytical procedure.

Documentation required

1. Justification for the change.

2. (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable).
3. Justification to demonstrate that the parameter is not critical.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
35	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	1	AN

Conditions to be fulfilled

1. No change to the specification other than those required to comply with the pharmacopoeia (e.g. no change in particle size distribution).

Documentation required

1. Comparative table of currently accepted and proposed specifications for the excipient.

3.2. P.5 Control of FPP

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
36a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	1–3	1–5	AN
36b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the FPP is controlled	None	1, 3, 5	AN

Conditions to be fulfilled

1. The change is made exclusively to comply with the officially recognized pharmacopoeia.
2. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test).
3. No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
3. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.
4. (P.5.6) Justification for the proposed FPP specifications.
5. (P.5.3) Demonstration of the suitability of the monograph to control the FPP

Description of change		Conditions to required	Documentation type	Reporting be fulfilled
37	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
37a	deletion of a test parameter	5	1, 6	AN
37b	addition of a test parameter	2–4, 7	1–6	AN
37c	tightening of an acceptance criterion	1–2	1, 6	AN
37d	relaxation of an acceptance criterion	2, 4, 6–7	1, 5–6	IN
37e	replacement of a test parameter	2–4, 6-7	1–6	IN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way
4. No additional impurity found over the ICH identification threshold.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The change to the specifications does not affect the stability and the performance of the product.
7. The change does not concern sterility testing.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5.(P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.
6. (P.5.6) Justification for the proposed FPP specifications.

Description of change		Conditions to required	Documentation be fulfilled	Reporting type
38	Change in the analytical procedures for the FPP involving:			
38a	deletion of an analytical procedure	5	1, 6	AN
38b	addition of an analytical proceduref	3–4, 6–7	1–5	AN
38c.1	modification or	1–4, 6–7	1–5	AN
38c.2	replacement of an analytical procedure	2–4, 6–7	1–5	Vmin
38d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	1–5	AN

38e	change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from the analytical procedure in one officially recognized pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	2, 7	1–3, 5	IN

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
2. Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not concern sterility testing.
5. The deleted analytical procedure is an alternative method and is equivalent to the currently accepted analytical procedure.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. No new impurities have been detected.

Documentation required

1. (P.5.1) A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4)Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures.
6. Justification for the deletion of the analytical procedure, with supporting data.

3.2. P.7 Container-closure system

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
39a Replacement or addition of a primary packaging type	1	1–2, 4–6	Vmin
39b	None	1–6	Vmaj

Conditions to be fulfilled

1. The change does not concern a sterile FPP.

Documentation required

1. Samples of the product as packaged in the new container-closure system.
2. (P.2) Data on suitability of the container-closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.
3. (P.3.5) For sterile FPPs, process validation and/or evaluation studies.
4. (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate).
5. (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
40	Change in the package size involving:			
40a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	1–2	1–2	IN
40b.1	change in the fill weight	1–3	1–2	IN
40b.2	or fill volume of non-parenteral multidose products	1-2	1–2	Vmin

Conditions to be fulfilled

1. The change is consistent with the posology and treatment duration accepted in the SmPC.
2. No change in the primary packaging material.
3. No increase in the headspace or surface/volume ratio.

Documentation required

1. Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC.
2. (P.8.2) A written commitment that stability studies will be conducted in accordance with the FDA guideline for products where stability parameters could be affected.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
41	Change in the shape or dimensions of the container or closure for:			
41a	non-sterile FPPs	1–2	1–3	AN

41b	sterile FPPs	1–2	1–4	Vmin

Conditions to be fulfilled

1. No change in the qualitative or quantitative composition of the container and/or closure.
2. The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP.

Documentation required

1. Samples of the product packaged in the new container-closure system.
2. (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).
3. (P.8.1) In case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated and 3 months of long-term testing and, where applicable results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ration for non-sterile FPPs, a commitment for the above studies.
4. (P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
42 Change in qualitative and/or quantitative composition of the immediate packaging material for:			
42a solid FPPs	1–3	1–3	IN
42b Semisolid and liquid FPP	1–3	1–3	Vmin

Conditions to be fulfilled

1. The change does not concern a sterile FPP.
2. No change in the packaging type and material (an example of an allowable change is blister to blister).
3. The relevant properties of the proposed packaging material are at least equivalent to those of the currently accepted material.

Documentation required

1. (P.2) Data demonstrating the suitability of the proposed packaging materials (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, and moisture).
2. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
3. (P.8.1) Stability summary and conclusions, results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 3 months of accelerated and 3 months of long-term testing and, where applicable, results of photostability studies.

Description of change		Conditions to required	Documentation be fulfilled	Reporting type
43	Change in the specifications of the immediate packaging involving:			
43a	tightening of specification limits	1–2	1	AN
43b	addition of a test parameter	2–3	1–2	AN
43c	deletion of a non-critical parameter	2	1, 3	AN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. A new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way

Documentation required

1. (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure.
3. Documentation to demonstrate that the parameter is not critical

Description of change		Conditions to required	Documentation type	Reporting be fulfilled
44	Change to an analytical procedure on the immediate packaging involving:			
44a	minor change to an analytical procedure	1–3	1	AN
44b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
44c	deletion of an analytical procedure	5	2	AN

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principles (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method)
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies to indicate the new analytical procedure to be at least equivalent to the former procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.

Documentation required

1. (P.7) Description of the method and comparative validation studies demonstrating that the currently accepted and proposed methods are at least equivalent.
2. Documentation to demonstrate the equivalence of the deleted method and a currently accepted method.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
45	Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, or change of needle shield).	1	1–2	IN

Conditions to be fulfilled

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the FPP.

Documentation required

1. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
2. Sample of the FPP.

	Description of change	Conditions to required	Documentation type	Reporting be fulfilled
46	Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:			
46a	addition or replacement	1, 2	1–2	IN
46b	deletion	3	3	IN

Conditions to be fulfilled

1. The proposed measuring device is designed to accurately deliver the required dose for the product concerned in line with the posology, and results of such studies are available.

2. The proposed device is compatible with the FPP.
3. The FPP can be accurately delivered in the absence of the device.

Documentation required

1. (P.2) Data to demonstrate accuracy, precision and compatibility of the device.
2. Sample of the device.
3. Justification for the deletion of the device.

3.2. P.8 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
47	Change in the shelf-life of the FPP (as packaged for sale) involving:			
47a	reduction	3	1–3	IN
47b	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

1. (P.5.1) Copy of the currently accepted shelf-life specifications.
2. (P 8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot- or production-scale batches for a period sufficient to support the proposed shelf-life.
3. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

Description of change		Conditions to required	Documentation be fulfilled	Reporting type
48	Change in the in-use period of the reconstitution or dilution):	FPP (after first opening or after		
48a	reduction	1	1	IN
48b	extension	None	1–2	Vmin

Conditions to be fulfilled

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

1. (P 8) Proposed in-use period, test results and justification of change.
2. (P 5.1) Copy of currently accepted end of shelf-life FPP specifications and, where applicable, specifications after dilution or reconstitution.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
49	Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	1	1–2	Vmin

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

1. (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions.
2. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

Appendix 1 Examples of changes that make a new application or extension application necessary

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1. Change of the API to a different API 2. Inclusion of an additional API in a multicomponent product 3. Removal of one API from a multicomponent product 4. Change in the dose and/or strength of one or more APIs 5. Change from an immediate release product to an extended or delayed-release dosage form or vice versa. 6. Change from a liquid to a powder for reconstitution or vice versa 7. Changes in the route of administration	None	1	New application/ extension application

Conditions to be fulfilled

None

Documentation required

1. Documents in fulfilment of the requirements outlined in in the FDA *Guidelines on registration of allopathic medicines*

Appendix 2 Changes to excipients

Excipient	Percentage excipient (w/w) out of total target dosage form core weight
Filler	± 5.0
Disintegrant • starch • other	 ± 3.0 ± 1.0
Binder	± 0.5
Lubricant • Ca or Mg Stearate • other	 ± 0.25 ± 1.0
Glidant • talc • other	 ± 1.0 ± 0.1

- These percentages are based on the assumption that the active pharmaceutical ingredient (API) in the finished pharmaceutical product (FPP) is formulated to 100.0% of label/potency declaration. The total additive effect of all changes to excipients should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of API, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).
- If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

[i] Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 943), Annex 6.

[ii] Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4.