Guideline for Post-Marketing Authorization Variations

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Message from the Director General, Directorate General of Drug Administration

The Guideline for Post-Marketing Authorization Variations is a very important and timely step to control and maintain the quality, safety and efficacy of registered medicine.

This is to clearly spell out the various activities and their sequence in the handling of these vital products as a means of assuring the quality of products and services in the national health and pharmaceutical sectors and securing the supply chain from falsified or substandard medical products.

This guideline is directed primarily at manufacturers and importers of medical products. These guidelines are intended to assist applicants with the classification of changes made to the quality part of a registered API & finished pharmaceutical product (FPP) and 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.

This guideline will assist DGDA concern official to review the application dossier addressing the intended changes by the applicant.

Major General Md. Mustafizur Rahman
Directorate General
Directorate General of Drug Administration & Licensing Authority of Drugs

Members of "Post-Markrting Authorization Variations" guideline Core Working Committee

SL	Name	Designation	Portfolio
1.	Md. Ruhul Amin	Director, DGDA	Convener
2.	Md. Aziulla	Superintendent of Drugs	Member
3.	Md. Monir Uddin Ahmed	Superintendent of Drugs	Member
4.	Romel Mullick	Inspector of Drugs	Member
5.	Mr. Faruk Ahmad	Regulatory Affairs Specialist, USP-PQM	Member
6.	Mr. Mohamed Ramzy Ismail	Technical Officer – Essential Drugs and Medicines, DGDA	Member

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1. Introduction

The guidelines retain the basic structure and function of the variation guidelines and have been expanded to include the classification of additional post-marketing authorization changes and to establish the level of risk inherent to each change.[2]

The change categories are organized according to the structure of the DGDA registration application checklist. The specific sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold).

Changes are classified as major only in those instances where the level of risk is high.

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.

A companion Question and Answer document is in preparation to assist in interpretation of the guidelines. This document will address many of the questions raised during the guidelines circulation process.

2. Objectives

These guidelines are intended to:

- assist applicants with the classification of changes made to the quality part of a registered API & 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.

3. 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 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.

This document is applicable to all manufacturers/importers of Medical Products those are granted license for manufacturing/importing of Medical Products as per existing drug law.

4. 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 DGDA web site. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from DGDA.

5. 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 DGDA is required before the changes can be implemented. A letter of acceptance will be issued for all major variations if and when the variation is considered acceptable.

6. Documentation required

Examples of variations are organized according to the structure of the registration dossier. For each variation, certain documents have been identified as supporting data and are organized according to dossier 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;
- replacement of the relevant sections of the dossier as per dossier format;
- copies of SmPC, PIL and labels, if relevant.

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

7. Part-A: Administrative Information

7.1 Change in the name and/ or corporate address of the Manufacturer/MA holder

Conditions to be fulfilled

i. Confirmation that the supplier of the product remains the same legal entity.
ii. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

i. A formal document from a relevant official body in which the new name and/or address is mentioned.

7.2 Change in the name or address of a manufacturer of an API

Conditions to be fulfilled

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

Documentation required

i. A formal document from a relevant official body in which the new name and/or address is mentioned.
ii. An updated Letter of Access in case of change in the name of the holder of the APIMF.

8. Part-B: Quality Information

8.1 For API Manufacturer

8.1.1 Replacement or addition of a new manufacturing site or manufacturer of an API

Conditions to be fulfilled

1. The transfer of analytical methods has been successfully undertaken.
2. API specifications will remain unchanged.
3. The impurity profile of the API starting material is essentially the same as other accepted sources.
4. 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.
5. No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents.
6. 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.

Documentation required

1. Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid authorization (License) or a certificate of GMP certificate, if applicable.
2. Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence of analytical procedures to be used at the proposed testing site.
3. Description of the batches, copies of certificates of analysis and batch analysis data for at least two (minimum pilot- scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.
4. 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.
5. A copy of the FPP manufacturer's API specifications.
6. 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 size distribution, evidence that the differences do not impact the quality and bioavailability of the FPP.

8.1.2 Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture

Conditions to be fulfilled

1. The API manufacturing block or unit is currently accepted through the DGDA.
2. The same quality system covers currently accepted and proposed units or blocks.
3. 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.
4. 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. 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. 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 available.
3. 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 units or blocks.
4. A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

8.1.3 Change in the manufacturing process of the API

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 APIMF 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 the 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 specifications.
10. The change does not require revision of the API specifications.

Documentation required

1. 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 DGDA.
2. A side-by-side comparison of the current process and the new process.
3. A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
4. 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.

5. Either a TSE CEP for any new source of material or, where applicabe.
6. Information on controls of critical steps and intermediates, where applicable.
7. Evidence of process validation and/or evaluation studies for sterilization, if applicable.
8. Evidence for elucidation of structure, where applicable.
9. Information on impurities.
10. A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
11. 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.
12. 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.
13. 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.

8.1.4 Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:

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.

Documentation required

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. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used.
4. 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. 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. Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
7. 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 DGDA for advice. For changes to the polymorph of an insoluble API the applicant should contact DGDA for advice before embarking upon any investigation.

8.1.5 Change to the analytical procedures used to control the API by the FPP manufacturer involving:

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. No new impurities have been detected as a result of the use of the new analytical method.
3. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
4. The change does not concern sterility testing.

Documentation required

1. Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.
3. Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used.
4. Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.
5. Justification for the deletion of the analytical procedure, with supporting data.

8.2 For Finished Product Manufacturer

8.2.1 Change in the composition of FPP:

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 DGDA *Guidelines*.
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 bio-batch.
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 DGDA guidelines on bioequivalence.
2. Description and composition of the FPP.

3. 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. Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5. Control of excipients, if new excipients are proposed.
6. If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk 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. 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. 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. 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. 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.

8.2.2 Change in the batch size of the FPP

Conditions to be fulfilled

1. The change does not affect the reproducibility and/or consistency of the product.
2. 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 equipment.
3. 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.
4. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
5. The change does not require supporting in vivo data.
6. The bio-batch size was at least 100 000 units in the case of solid oral dosage forms.

Documentation required

1. 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.

2. Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3. Copies of release and shelf-life specifications.
4. 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).

8.2.3 Change in the manufacturing process of the FPP

Conditions to be fulfilled

1. The change does not require supporting 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. No change in the specifications of the intermediates or the FPP.
5. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
6. The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function.
7. The change does not concern a gastro-resistant, modified or prolonged-release FPP.
8. 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 DGDA guidelines on bioequivalence.
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 non-dissolved 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 submitted or be available on request);
   - microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form.
3. Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
4. 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. 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. 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. 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.

8.2.4 Change in the standard claimed for the FPP from an in-house to an officially recognized Pharmacopoeial Standard

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.

Documentation required

1. Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. 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. 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.

8.2.5 Change in the specifications of the FPP involving test parameters and acceptance criteria:

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. No additional impurity found over the ICH identification threshold.
4. The change to the specifications does not affect the stability and the performance of the product.
5. The change does not concern sterility testing.

Documentation required

1. Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used.
4. 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. 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 procedures, if new analytical procedures are implemented.

8.2.6 Change in the analytical procedures for the FPP

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. The change does not concern sterility testing.
4. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted analytical procedure.
5. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
6. No new impurities have been detected.

Documentation required

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. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
4. 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. 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.

8.2.7 Replacement or addition of a primary packaging type

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. Data on the 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. For sterile FPPs, process validation and/or evaluation studies.
4. 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. 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.

8.2.8 Change in the package size involving

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. A written commitment that stability studies will be conducted in accordance with the DGDA guidelines for products where stability parameters could be affected.

8.2.9 Change in the shelf-life of the FPP (as packaged for sale) involving:

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. Copy of the currently accepted shelf-life specifications.
2. 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. Updated post-acceptance stability protocol and stability commitment and justification of change.