Notice to applicant

Central Administration of Pharmaceutical Products
General Administration For Human Pharmaceutical Products

Guidance for human pharmaceutical type II variations

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1-Executive summary

This guidance will address the information required for common human pharmaceutical type II variations.

This guidance seeks to illustrate the data required for variations to active substances and/or finished products. It is not always necessary to comply with this guidance when there are scientifically justifiable reasons for using alternative approaches.

While the human variation guideline provides a general indication on the requirements for PAC N & PAC B variations, it allows sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the material being evaluated.

2-Scope

The purpose of this guidance is to outline the required studies which have to be generated in case of PAC II variations. It is applicable to chemical active substances and related finished products, related to human pharmaceutical products.

3. Type II variations

Type II variations could be defined as major variations which may have a significant impact on the quality, safety or efficacy of medicinal products. Type II variations are defined in the Guidelines on the details of the various categories of variations. However, data to be submitted with these variations are not defined in the majority of cases. The required data outlined below should to be part of the documentation at submission of the variation.

3.2.1 Active substance (3.2.1.1.) Change in the manufacturer of The Active Substance: (3.2.1.1.b.1) Addition or Replacement of a new manufacturer of active substance

In case of an introduction of a manufacturer of the active substance (Supported by DMF) the following recommendations should be fulfilled:

1. Batch analysis data of at least two batches of active substance manufactured from the current and proposed API manufacturer sites.

2. If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are changed in a way that stability may be compromised, stability data are recommended in long term and accelerated testing conditions on the active substance.

3. A commitment is given that a long-term stability study on first production batch will be conducted and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

4. If the quality characteristics of the active substance are changed in a way that may impact the dissolution profile of the finished product, Comparative in-vitro dissolution study at most suitable medium on first production batch of Finished Pharmaceutical product manufactured from the new API manufacturer against the innovator product is recommended. (Or may be changed to 3 different PH media in addition to the most suitable medium in case of modified release products or Bioequivalence study according to category of API & its criticality).

5. Amendment of the relevant section(s) of the dossier concerning the change

In case of an introduction of a manufacturer of the active substance the following recommendations should be <u>fulfilled:</u>

1. Batch Analysis for two production batch at CADC labs (At administration of post approval control **with detailed report** and if the product doesn't have CADC COA before, analysis at Administration of evaluation and approval is required for first production batch)

2. Result of stability testing generated on at least two pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing on Finished Product. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. Comparative in-vitro dissolution study at most suitable medium on first production batch of Finished Pharmaceutical product manufactured from the new API manufacturer against the innovator product. (Or may be changed to 3 different PH media in addition to the most suitable medium in case of modified release products or Bioequivalence study according to category of API & its criticality).

4. Amendment of the relevant section(s) of the dossier concerning the change.

<u>3.2.1.2. Changes in the manufacturing process of the active substance: (3.2.1.2.b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product</u>

In variations to the manufacturing process of the active substance, the following approaches may be considered as acceptable:

1. Batch analysis data of at least two batches of the active substance, manufactured according to the currently approved and proposed process.

2. If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are changed in a way that stability may be compromised, comparative stability data are

recommended in long term and accelerated testing conditions, on the active substance before and after the change:

• for active substances known to be stable: three months data on at least one batch of at least pilot scale batch size.

• for active substances known to be unstable: six months data on at least three batches of at least pilot scale batch size.

If the quality characteristics of the active substance are changed in a way that may impact the stability of the finished product, additional stability data on the finished product, in long term and accelerated testing conditions, six months data on at least two batches of at least pilot scale batch size are recommended.

3. Amendment of the relevant section(s) of the dossier concerning the change.

*** An active substance is considered as stable if it is within the initial specifications when stored at 25°C/ 60 % RH or 30°C/65% RH, respectively, (2 years) and 40°C/75 %RH (6 months).**

3.2.1.4. Change to in-process tests or limits applied during the manufacture of the active substance: (3.2.1.4.d) Widening of the approved in-process control limits, which may have a significant effect on the overall quality of the active substance / (3.2.1.4.e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance

In variations to in-process tests or limits applied during the manufacture of the active substance; the following approaches may be considered as acceptable:

1. Batch analysis data on two batches of the active substance for all specification parameters from API Supplier.

2. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.1.5. Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance : (3.2.1.5.d)Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product / (3.2.1.5.e) Change outside the approved specifications limits range for the active substance /(3.2.1.5.f) change outside the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product

In variations to specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance, the following approaches may be considered as acceptable:

1. Batch analysis data on two batches of the active substance for all specification parameters from API Supplier.

2. If the quality characteristics of the active substance are changed in a way that may impact the stability of the finished product, additional stability data on the finished product, in long term and accelerated testing conditions, six months data on at least two batches of at least pilot scale batch size are recommended.

3. If the quality characteristics of the active substance are changed in a way that may impact the dissolution profile of the finished product, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification.

4. Amendment of the relevant section(s) of the dossier concerning the change.

(3.2.1.7) Change in the immediate packaging of the active substance: (3.2.1.7.b.) Change in immediate packaging of sterile liquid active substances

In variations to immediate packaging of the active substance, the following approaches may be considered as acceptable:

1. Batch analysis data on two batches of the active substance for all specification parameters from API Supplier.
2. Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 6 months of accelerated of existing active substances from the API manufacturer should be submitted.
3. Amendment of the relevant section(s) of the dossier concerning the change.

B. Finished Product:

3.2.2.3. Changes in the composition (excipients) of the Finished Pharmaceutical product : (3.2.2.3.b.2.)Change in components of other excipients as Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product / (3.2.2.3.b.3.)Any new excipient that includes the use of materials of animal origin for which assessment is required of viral safety data or TSE risk.

In variations to the composition (excipients) of the Finished Pharmaceutical product, the following approaches may be considered as acceptable:

1. Batch Analysis for two production batch at CADC labs (First production batch at Administration of evaluation and approval & Second batch at Administration of post approval control **with detailed report**).
2. For Conventional dosage forms (e.g conventional release solid dosage form, Solutions) Result of stability testing generated on at least two pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing are recommended.

For critical dosage forms (e.g modified release form) Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing are recommended.

A commitment is given that these long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. Comparative in-vitro dissolution study at 3 different PH media (1.2,4.5,6.8) & most suitable medium (D3/4) on one production batch against the innovator product. (Or Bioequivalence study according to of API criticality).
4. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.4 Change in coating weight of oral dosage forms or change in weight of capsule shell: (3.2.2.4.c) modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism

In variations to coating weight of oral dosage forms or change in weight of capsule shell, the following approaches may be considered as acceptable:

1. Batch Analysis for two production batch at CADC labs (First production batch at Administration of evaluation and approval & Second batch at Administration of post approval control **with detailed report**).
2. Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
3. Comparative in-vitro dissolution study at 3 different PH media (1.2,4.5,6.8) and most suitable medium (D3/4) on one production batch against the innovator product. (Or Bioequivalence study according to category of API).
4. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.5 Change in the manufacturing site for part or all of the manufacturing process of the Finished Product:

(3.2.2.5.b) Addition or replacement of a Site responsible for any manufacturing operation(s) of finished product:

In variations to manufacturing site for part or all of the manufacturing process of the Finished Product, the following approaches may be considered as acceptable:

1. Batch analysis for the first three consecutive production batches manufactured/packed at the proposed site at CADC labs (At administration of post approval control **with detailed report** and if the product doesn't have CADC COA before, analysis at Administration of evaluation and approval is required for first production batch) or at Company labs according to Updated Regulations of Addition/ Change of manufacturing site published on 3/8/2025 (Except For Imported Finished Products).
2. Results of stability testing generated with a minimum of 6 months Accelerated testing, of the first three production batches of Finished Pharmaceutical product manufactured/packed at the proposed site. A commitment is given that long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
3. Comparative in-vitro dissolution tests at 3 different PH media (1.2, 4.5, 6.8) & most suitable medium on the first production batch manufactured/packed at the proposed site against a batch manufactured/packed at the old site (must be previously validated if not available, tests must be done against the innovator product). (Or Bioequivalence study according to category of API).
4. Process validation reports for the first three production batches manufactured/packed at the proposed site.
5. Amendment of the relevant section(s) of the dossier concerning the change.

(3.2.2.5.c) Addition or replacement of a site for Imported finished products and /or sites which requires initial GMP inspection.

In variations to Addition or replacement of a site which requires initial GMP inspection, the following approaches may be considered as acceptable:

1. Batch analysis for the first shipment manufactured/packed at the proposed site at CADC labs (At administration of post approval control **with detailed report** and if the product doesn't have CADC COA before, analysis at Administration of evaluation and approval is required)
2. Results of stability testing generated with a minimum of 6 months Accelerated testing, of three production batches of Finished Pharmaceutical product manufactured/packed at the proposed site.

3. Comparative in-vitro dissolution tests at 3 different PH media (1.2, 4.5, 6.8) & most suitable medium on one production batch manufactured/packed at the proposed site against a batch manufactured/packed at the old site (must be previously validated if not available, tests must be done against the innovator product). (Or Bioequivalence study according to category of API).
4. Process validation reports for three production batches manufactured/packed at the proposed site.
5. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.6. Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product (3.2.2.6.b) Major changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product / (3.2.2.6.c) Introduction of a non-standard terminal sterilization method / (3.2.2.6.d) Introduction or increase in the overage that is used for the active substance

In variations to the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product, the following approaches may be considered as acceptable:

1. Batch analysis data of at least two batches of the Finished Product (At administration of post approval control **with detailed report)**, manufactured according to the currently approved and proposed process.
2. For Conventional dosage forms (e.g conventional release solid dosage form, Solutions) Result of stability testing generated on at least two pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing are recommended.

For critical dosage forms (e.g modified release form) Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing are recommended.

A commitment is given that these long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.7. Change in the batch size of the finished product: (3.2.2.7.b.) Scaling up/down to and including a factor of 10 folds for pharmaceutical forms manufactured by complex manufacturing process e.g Gastro-resistant, modified or prolonged release pharmaceutical forms, etc.

In variations to Change in the batch size (Scaling up/down to and including a factor of 10 folds) for pharmaceutical forms, the following approaches may be considered as acceptable:

1. Comparative in-vitro dissolution study at 3 different PH media (1.2, 4.5, 6.8) and most suitable medium on one production batch manufactured with the proposed batch size against a batch manufactured with the current batch size or against the innovator product. (Or Bioequivalence study according to category of API).
2. Process validation reports for first three production batches of the proposed batch size.
3. If the batch size of the Finished Pharmaceutical product is changed in a way that may impact the stability of the finished product, result of stability testing generated on at least two pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing are recommended. A commitment is given that these long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
4. Amendment of the relevant section(s) of the dossier concerning the change.

(3.2.2.7.d.) Scaling up more than a factor of 10 folds for pharmaceutical forms manufactured by complex manufacturing process e.g Gastro-resistant, modified or prolonged release pharmaceutical forms, etc./(3.2.2.7.e.) The change requires assessment of the comparability or the change in batch size requires a new bioequivalence study.

In variations to Change in the batch size (Scaling up more than a factor of 10 folds) for pharmaceutical forms or requires assessment of the comparability or the change in batch size requires a new bioequivalence study, the following approaches may be considered as acceptable:

1. Batch analysis for first three consecutive production batches manufactured with the proposed batch size at CADC labs. (At administration of post approval control **with detailed report** and if the product doesn't have CADC COA before, analysis at Administration of evaluation and approval is required for first production batch).
2. Results of stability testing generated with a minimum of 6 months Accelerated testing, of the first three production batches of Finished Pharmaceutical product manufactured with the proposed batch size. A commitment is given that these long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
3. Comparative in-vitro dissolution study at 3 different PH media (1.2, 4.5, 6.8) and most suitable medium on one production batch manufactured with the proposed batch size against a batch manufactured with the current batch size or against the innovator product. (Or Bioequivalence study according to category of API).
4. Process validation reports for first three production batches of the proposed batch size.
5.Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.8. Change to in-process tests or limits applied during the manufacture of the finished product: (3.2.2.8.d.) Deletion of an in-process test which may have a significant effect on the overall quality of the finished product / (3.2.2.8.e.) Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product

In variations to in-process tests or limits applied during the manufacture of the finished product; the following approaches may be considered as acceptable:

1. Batch analysis data on two production batches of the finished product for all specification parameters.
2. If the in-process tests are changed in a way that may impact the dissolution profile of the finished product, Comparative in-vitro dissolution study at 3 different PH media (1.2, 4.5, 6.8); most suitable medium on one production batch manufactured with the proposed in process tests against a batch manufactured with the current in process tests or against the innovator product. (Or Bioequivalence study according to category of API) is required.
3. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.9. Change in the specification parameters and/or limits of an excipient: (3.2.2.9.d.) Change outside the approved specifications limits range /(3.2.2.9.e.) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product

In variations to specification parameters and/or limits of an excipient of the finished product, the following approaches may be considered as acceptable:

1. Batch analysis data on two batches of the excipient for all specification parameters from excipient Supplier.
2. Batch analysis data on two production batches of the finished product for all specification parameters.
3. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.10. Change in the specification parameters and/or limits of the Finished Pharmaceutical product: (3.2.2.10.e.) Change outside the approved specifications limits range / (3.2.2.10.f.) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product

In variations to specification parameters and/or limits of the Finished Pharmaceutical product, the following approaches may be considered as acceptable:

1. Batch Analysis for two production batches at CADC labs (First production batch at Administration of evaluation and approval & Second batch at Administration of post approval control **with detailed report**).
2. If the specification parameters and/or limits of the Finished Pharmaceutical product are changed in a way that may impact the stability of the finished product, result of stability testing generated on at least two pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing are recommended. A commitment is given that these long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. If the specification parameters and/or limits of the Finished Pharmaceutical product are changed in a way that may impact the dissolution profile of the finished product, Comparative in-vitro dissolution study at 3 different PH media (1.2,4.5,6.8) & most suitable medium (D3/4) on one production batch against the innovator product. (Or Bioequivalence study according to API category) is required.

4. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.12. Change in immediate packaging of the Finished Pharmaceutical product
(3.2.2.12.a.3.) Qualitative and quantitative composition of an approved container for Sterile medicinal products.

In variations related to Change in immediate packaging of the Finished Pharmaceutical product (Qualitative and quantitative composition of an approved container for Sterile medicinal products.), the following approaches may be considered as acceptable:

1. Batch Analysis for first production batch at CADC labs (At administration of post approval control **with detailed report).**

2. Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing. A commitment is given

that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. Amendment of the relevant section(s) of the dossier concerning the change.

(3.2.2.12.a.4.) The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.

In variations related to Change in immediate packaging of the Finished Pharmaceutical product (The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life), the following approaches may be considered as acceptable:

1. Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

2. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.12. Change in Primary packaging of the Finished Pharmaceutical product
(3.2.2.12.b.2.) Change in type of container or addition of a new container for Sterile medicinal products

In variations to Primary packaging of the Finished Pharmaceutical product (Change in type of container or addition of a new container for Sterile medicinal products), the following approaches may be considered as acceptable:

1. Batch Analysis for first production batch at CADC labs (At administration of post approval control **with detailed report).**

2. Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing. A commitment is given

that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. Amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.16. Change in pack size of the Finished Pharmaceutical product: (3.2.2.16.c.) Change/Addition in the fill weight/fill volume of sterile multidose medicinal products.

In variations to pack size of the Finished Pharmaceutical product (Change/Addition in the fill weight/fill volume of sterile multidose medicinal products), the following approaches may be considered as acceptable:

1. Batch Analysis for first production batch at CADC labs (At administration of post approval control **with detailed report).**

2. Result of stability testing generated on at least three pilot- or production-scale batches with a minimum of 6 months of accelerated and 6 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3. Amendment of the relevant section(s) of the dossier concerning the change.

4. Amendment of Product Information (i.e., Inner leaflet and/or mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.

5. Re-pricing.

4-References:

1-Guidelines On Human Pharmaceuticals Variations (Sixth Edition) 6/2025
2-Guidelines on Stability testing for applications for Variations to a marketing Authorization dated on December 2025
3- EMA Guidelines by European commission in Official Journal of the European Union volume 56 dated on September 2025.