Regulation concerning the examination of variations to the terms of marketing authorization for biological medicinal products for human use

Article (1)
Definitions:

For the purpose of this regulation, the following definitions shall apply:

A- Biological medicinal product
- A biological medicinal product is a product, the active substance of which is a biological substance.

A biological substance is a substance that is produced by or extracted from a biological source and for which a combination of physico-chemical-biological testing and the production process and its control is needed for its characterization and the determination of its quality.

As a result, the following shall be considered as biological medicinal products:

1- Immunological medicinal products
Any medicinal product consisting of vaccines, toxins, sera or allergen products:
(a) Vaccines, toxins and sera shall cover in particular:
- Agents used to produce active immunity
- Agents used to diagnose the state of immunity, including e.g. tuberculins
- Agents used to produce passive immunity
(b) ‘Allergen product’ shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

2- Medicinal products derived from human blood and human plasma

3- Medicinal products developed by means of one of the following biotechnological processes:
- Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells
- Hybridoma and monoclonal antibody methods.

4- Advanced therapy medicinal products:
Bio-molecules intended for gene transfer, and/or modified cells as active substances or part of active substances:
- Gene therapy medicinal products (human & xenogeneic)
A product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.

- Somatic cell therapy medicinal products (human & xenogeneic)
Autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).

B- Variation to the terms of marketing authorization
Amendment to the contents of the documentation on which the original decision on the marketing authorization was based.

C-A Consequential variation
A consequential variation is regarded as a change, which is an unavoidable and direct result of another change (i.e. the main change) and not simply a change which occurs at the same time.

D- Technical commission:
A commission constituted by Ministerial decree that identifies its members according to the law No. 127/1955 concerning the practice of the pharmaceutical profession, article 60

Article (2)
Scope of the regulation

This regulation applies to applications submitted for variations concerning registered biological medicinal products.

Article (3)
Types of variations

Variations are classified in order to determine the procedure to follow in each case

1-Minor (Type I) variation:-
- A minor variation is a variation which has only a minimal impact or no impact at all on the quality, safety or efficacy of the biological medicinal product. Such a variation is classified as a type I variation.

- Minor variations are listed in annex I.

Applications for minor variations require the submission of the information specified further in this regulation but do not require the submission of a new application.

2-Major (Type II) variation:

- A major variation is a variation which may have a significant impact on the quality, safety, efficacy of the biological medicinal product. Such a variation is classified as a type II variation.

- Examples are listed in annex II

Applications for major variations require the submission of the information specified further in this regulation but do not require submission of a new application.

3-A variation that requires the submission of a new application:

- A variation which is so fundamental that it alters the terms of the dossier & consequently cannot be considered as a change.

- Examples are listed in annex III.

Article (4)
Procedure for minor (Type I) variations

1-The MAH shall submit to the Biological product registration department in CAPA the variation file containing the following documents (as minimum for receiving the file):

- Covering letter explaining the background for the proposed change and any consequential variations if applicable (on the company header, signed and stamped)
- Copy of the registration license of the product.
- Variation application (published on the web site) signed and stamped on each page.
- Documents listed in annex I.

2- A separate application shall be submitted for each Type I variation.
3- Where a variation leads to consequential variations; a single application may cover all such variations.

4- If the application & documents submitted fulfill the previous requirements, the competent authority shall start the following procedure:

Within 30 days from receiving application, the competent authority will advise the MA holder of the decision taken

- This decision may consist of an acceptance of the variation or a request for complementary information.

- The applicant submits the complementary information within maximum 30 working days or the application will be cancelled

- If applicable, within 30 days from receiving complementary information the competent authority will notify the MA holder of its opinion, which may consist of an acceptance or rejection of the variation.

- In case of a rejection the competent authority will inform the holder the grounds on which this is based.

- Within 30 days of receipt of the rejection, the holder may request an appeal. If no such request is received by the authorities, the variation is cancelled.

- Within 30 days from receiving a request for appeal, the competent authority shall submit the appeal to the Technical Commission for reassessment.

Article (5)
Procedure for Major (Type II) variations

1- The marketing authorization holder shall submit to the competent authority an application for variation accompanied by:-

- Covering letter explaining the background for the proposed change and any consequential variations if applicable (on the company header, signed and stamped)
- Copy of the registration license of the product.
- Variation application (published on the web site) signed and stamped on each page
- The supporting data relating to the variation applied for;
- All the parts of the MA amended as a result of the application.

2- A separate application shall be submitted for each type II variation.
3- Where a type II variation leads to consequential variations, a single application may cover all such variations.

4- If the application & documents submitted fulfill the previous requirements, the competent authority starts the following procedure:-

- Within 20 days from receiving application, the competent authority will send an assessment report and notification to applicant to the MA holder requesting for the complementary documents and any clarifications required
- The applicant should respond within 30 working days from receiving the assessment report and the notification to applicant or the application is cancelled
- Within 60 from fulfilling all the requirements mentioned in the AR, the competent authority will inform the MA holder the decision taken by the Technical committee.
- The technical Committee’s decision may consist of an acceptance of the variation or a request for complementary information.
- The technical Committee’s decision may consist of an acceptance or rejection of the variation.
- In case of a rejection the competent authority will inform the holder the grounds on which this is based.
- Within 30 days of receipt of the rejection, the holder may request an appeal. If no such request is received by the authorities, the variation is rejected.
- Within 30 days from receiving a request for appeal, the competent authority shall submit the appeal to the Technical Commission for reassessment.

If the variation is accepted, the holder shall - wherever necessary - update and submit the parts of the MA that have been modified as a result of the final outcome of the variation application.

Article (6)
Final provisions

- This regulation shall enter into force on the next day following its publication.

Annex (I)
Minor (Type I) variations

- It means a variation which has only a minimal impact or no impact at all on the quality, safety or efficacy of the medicinal product.

- List & conditions for minor variations:-
<table>
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<tr>
<th>Type of variation</th>
<th>Conditions to be considered</th>
<th>Documentation</th>
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<tr>
<td>Variations of administrative nature</td>
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<tr>
<td>1- Change in the name and/or address of the marketing authorization holder</td>
<td>The marketing authorization holder shall remain the same legal entity.</td>
<td>A formal document from a relevant official body in which the new name or new address is mentioned.</td>
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<tr>
<td>2- Change in the name of the medicinal product</td>
<td>No confusion with the names of existing medicinal products or with the international non-proprietary name (INN).</td>
<td>A formal document from a relevant official body in which the new name is approved.</td>
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<td>3- Change in name of the active substance</td>
<td>The active substance shall remain the same.</td>
<td>A formal document from a relevant official body in which the new name is approved.</td>
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<tr>
<td>4- Change in the name and/or address of a manufacturer of the finished product</td>
<td>The manufacturing site shall remain the same.</td>
<td>Copy of the modified manufacturing authorization, if available; or a formal document from a relevant official body in which the new name and/or address is mentioned.</td>
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Variations related to tightening of specification limits

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Tel.: +202 – 23684288 +202 – 23648769 +202 – 23640368    Ext.:1330    Fax: +202 - 23684194
Website: [www.eda.mohp.gov.eg](http://www.eda.mohp.gov.eg)    Version: 01    Email: biologicals@eda.mohp.gov.eg
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<thead>
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<th>Type of variation</th>
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<tr>
<td>5- Tightening of in-process tests applied during the manufacture of the product</td>
<td>1-The change is not a consequence of any commitment from previous assessments 2-The change should not be the result of unexpected events arising during manufacture 3-Any change should be within the range of currently approved limits.</td>
<td>1-Amendment to the relevant section in the technical file. 2-Comparative table of current and proposed specifications.</td>
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<tr>
<td>6- Tightening of the specification limit of the finished product/immediate packaging of finished product.</td>
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<tr>
<td>7- Tightening of the specification limit of an active substance or a starting material/intermediate /reagent/ used in the manufacturing process of the active substance or excipient.</td>
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Variations related to changes to physicochemical test procedures

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<th>Type of variation</th>
<th>Conditions to be considered</th>
<th>Documentation</th>
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<tr>
<td>8- Replacement or addition of a test procedure of the immediate packaging of the finished product</td>
<td>1-Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. 2-Results of method validation show new test procedure to be at least equivalent to the former procedure. 3-Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way</td>
<td>1-Amendment to the relevant section in the technical file which includes a description of the analytical methodology, validation data, revised specifications for impurities (if applicable) 2-Comparative validation results showing that the current test and the proposed one are equivalent.</td>
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<tr>
<td>Type of variation</td>
<td>Conditions to be considered</td>
<td>Documentation</td>
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| **9- Minor changes to an approved test procedure of the immediate packaging of the finished product** | 1- The method of analysis should remain the same  
2- Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.  
3- Results of method validation show new test procedure to be at least equivalent to the former procedure. | 1- Amendment to the relevant section in the technical file which includes a description of the analytical methodology, validation data, revised specifications for impurities (if applicable); |
| **10- Addition of new in-process tests & limits applied during the manufacture of the product** | 1- The change should not be the result of unexpected events arising during manufacture  
2- Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way | 1- Amendment to the relevant section in the technical file.  
2- Comparative table of current and proposed specifications.  
3- Details of any new analytical method and validation data.  
4- Batch analysis data on three production batches of the relevant substance for all tests in the new specification manufactured to both prequalified & proposed specification |
| **11- Addition of new test parameter in specification of a starting material/intermediate/reagent/ used in the manufacturing process of the active substance** | 1- The method of analysis should remain the same  
2- Appropriate re-validation studies have been performed in accordance with relevant guidelines.  
3- Results of method validation show new test procedure to be at least equivalent to the former procedure.  
4- Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way | 1- Amendment to the relevant section in the technical file.  
2- Comparative validation results showing that the current test and the proposed one are equivalent. |
| **12- Minor change to an approved test procedure of the finished product for biological excipient or biological active substance.** | 1- The method of analysis should remain the same  
2- Appropriate re-validation studies have been performed in accordance with relevant guidelines.  
3- Results of method validation show new test procedure to be at least equivalent to the former procedure.  
4- Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way | 1- Amendment to the relevant section in the technical file.  
2- Comparative validation results showing that the current test and the proposed one are equivalent. |

Variations related to changes to manufacturing site
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<tr>
<th>Type of variation</th>
<th>Conditions to be considered</th>
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</table>
| 13 - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the Secondary packaging of finished product | 1-Satisfactory inspection in the last three years by an inspection service of relevant authority. 2-Site appropriately authorized | 1-Proof that the proposed site is appropriately authorized:  
  * GMP certificate or equivalent document from relevant authority should be issued.  
  2-Date of the last satisfactory inspection concerning (the packaging facilities) by an inspection service (one of the of relevant authorities), in the last three years.  
  3-The variation application form should clearly outline the “present” and “proposed” finished product manufacturers.  
  N.B.(The national DRA has the right to inspect the manufacturing site if necessary)                                                                 |
| 14- Replacement or addition of a manufacturer responsible for batch release (Not including batch control /testing) | I- The site is appropriately authorized.                                                                                           | 1- A copy of the current manufacturing authorization or formal accreditation as test laboratory or GMP certificate.  
  2- The variation application form should clearly outline the “present” and “proposed” finished product manufacturers.  
  3-A declaration by the qualified person that the manufacturer operates in compliance with GMP.                                                                 |
| 15- Change in source of an excipient or reagent used in the manufacture of biological active substance from a TSE risk to a vegetable or synthetic material | Excipient and finished product release and end of shelf life specifications remain the same.                             | 1-Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin  
  2-Study of equivalence of the materials and the impact on production of the final material.                                                                 |

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<tr>
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<tr>
<td><strong>Variations related to changes made to specifications</strong></td>
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<tr>
<td><strong>16- Change to comply with an international pharmacopoeia</strong></td>
<td>1-The change is made exclusively to comply with the pharmacopoeia 2-Unchanged specifications (additional to the pharmacopoeia) for product specific properties</td>
<td>1- Amendment to the relevant section in the technical file. 2- Comparative table of current and proposed specifications. 3- Batch analysis data on two production batches of the relevant substance for all tests in the new specification. 4- Data to demonstrate the suitability of the monograph to control the substance 5- Batch analysis data on two production batches of the finished product containing the substance complying with the current and proposed specification &amp; where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch 6- Demonstration that consistency of quality &amp; of the production process is maintained</td>
</tr>
<tr>
<td><strong>17- Change to comply with an update of relevant monograph of an international pharmacopoeia</strong></td>
<td>1-The change is made exclusively to comply with the pharmacopoeia 2-Unchanged specifications (additional to the pharmacopoeia) for product specific properties.</td>
<td>1- Amendment to the relevant section in the technical file. 2- Comparative table of current and proposed specifications.</td>
</tr>
<tr>
<td><strong>Variations related to packaging</strong></td>
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<tr>
<td><strong>18- Change in shape or dimensions of the container or closure</strong></td>
<td>1-No change in the qualitative or quantitative composition of the container. 2-The change does not concern a fundamental part of the packaging material which affect delivery, use, stability of finished product</td>
<td>1-Amendment to the relevant section in the technical file including description, composition of the container or closure material. 2-The batch numbers of the batches used in the stability study</td>
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Tel.: +202 – 23684288 +202 – 23648769 +202 – 23640368 Ext.:1330 Fax: +202 - 23684194
Website: www.eda.mohp.gov.eg Version: 01 Email: biologicals@eda.mohp.gov.eg
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<tr>
<td>3- Change in any part of the product surface/volume ratio, stability studies have been started with at (least three pilot scale) or industrial scale batches &amp; at least (six months) stability data are at the disposal of the applicant.</td>
<td></td>
<td>1-Amendment to the relevant section in the technical file.</td>
</tr>
<tr>
<td>19- Change in any part of the (primary) packaging material (such as color code rings on ampoules, change of needle shield (different plastic used).</td>
<td>The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.</td>
<td>1-Amendment to the relevant section in the technical file.</td>
</tr>
<tr>
<td>20-Deletion of a supplier of packaging components or devices (when mentioned in the dossier)</td>
<td>No deletion of packaging component or device.</td>
<td>1-Amendment to the relevant section in the technical file.</td>
</tr>
<tr>
<td>21-Replacement or addition of a supplier of packaging components or devices (when mentioned in the dossier)</td>
<td>1-No deletion of packaging component or device. 2-The qualitative and quantitative composition of the packaging components/device remain the same. 3-The specifications and quality control method are at least equivalent. 4-The sterilization method and conditions remain the same, if applicable.</td>
<td>1-Amendment to the relevant section in the technical file. 2-For devices for medicinal products for human use, proof of CE marking. 3-Comparative table of current and proposed specifications, if applicable.</td>
</tr>
<tr>
<td>Type of variation</td>
<td>Conditions to be considered</td>
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<tr>
<td>22- <strong>Change in pack size of the finished product:</strong></td>
<td>1-New pack size should be consistent with the posology and treatment duration</td>
<td>1-Amendments to the relevant section in the technical file.</td>
</tr>
<tr>
<td>- Change in the number of units(e.g. ampoules) within the range of the currently approved pack sizes</td>
<td>2-The primary packaging material remains the same.</td>
<td>2-Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected.</td>
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<td>3-Justification for the new pack size, showing that the new size is consistent with the dosage regimen &amp; duration of use.</td>
</tr>
<tr>
<td>23- <strong>Change in pack size of the finished product:</strong></td>
<td>1-New pack size should be consistent with the posology and treatment duration</td>
<td>1-Amendments to the relevant section in the technical file.</td>
</tr>
<tr>
<td>- Change in the number of units outside the range of the currently approved pack sizes</td>
<td>2-The primary packaging material remains the same.</td>
<td>2-Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected.</td>
</tr>
<tr>
<td>- Change in the fill weight/fill volume of non-parenteral multi-dose products</td>
<td></td>
<td>3-Justification for the new pack size, showing that the new size is consistent with the dosage regimen &amp; duration of use.</td>
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<tr>
<td>24- <strong>Change in the shelf life of the finished product as packaged for sale</strong></td>
<td>1-Stability studies have been done to the currently approved protocol showing that the agreed relevant specification are still met</td>
<td>1-Amendment to the relevant section in the technical file must contain results of real time stability studies on at least two batches of the finished product and/or first opening or reconstitution, result of microbiological testing should be included (Pilot scale batches can be accepted with a commitment to verify the shelf life of production scale batches.).</td>
</tr>
<tr>
<td></td>
<td>2-The change should not be the result of unexpected events arising during manufacture or because of stability concerns</td>
<td>2-Copy of approved end of shelf life finished product specification.</td>
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<td>3-The shelf life does not exceed five years.</td>
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<td>Type of variation</td>
<td>Conditions to be considered</td>
<td>Documentation</td>
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<tr>
<td><strong>25- Change in the shelf life of the finished product after dilution or reconstitution</strong></td>
<td>1-Stability studies have been done to the currently approved protocol 2-The change should not be the result of unexpected events arising during manufacture.</td>
<td>1-Amendment to the relevant section in the technical file must contain results of real time stability studies on at least two batches of the finished product and/or first opening or reconstitution, result of microbiological testing should be included (Pilot scale batches can be accepted with a commitment to verify the shelf life of production scale batches.) 2-Copy of approved end of shelf life finished product specification.</td>
</tr>
<tr>
<td><strong>26- Submission of a new or updated TSE certificate for an active substances or starting material/reagent/intermediate/excipient for a currently approved manufacturer &amp; currently approved manufacturing process</strong></td>
<td>None</td>
<td>1-Copy of the current (updated) TSE certificate of suitability. 2-Amendment to the relevant section in the technical file. 3- A document providing information of any materials Minimizing the Risk of TSE, it should include name of manufacturer, species, tissues from which the material is derivative, country of origin of the source animals &amp; its use</td>
</tr>
<tr>
<td><strong>27- Change in the storage conditions for the active substance</strong></td>
<td>1-Stability studies have been done to the currently approved protocol 2-The change should not be the result of unexpected events arising during manufacture or because of stability concerns.</td>
<td>1-Amendment to the relevant section in the technical file must contain results of appropriate real time stability studies &amp; guidelines on at least two or three pilot or production scale batches of the active substance covering the duration of the requested storage condition. 2-Copy of approved specifications of the active substance.</td>
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</table>
Annex (II)

Major (type II) variations

- A major (type II) variation is a variation which may have a significant impact on the quality, safety, efficacy of the biological medicinal product.

- All variations that do not comply with the conditions to be fulfilled along with the variations listed in Annex I.

The following is a non-exhaustive list of variations that shall be classified as major variations of Type II:-

1. Change in the manufacturing process or sites of the active ingredients
2. Change in the composition of the finished product.
3. Change of immediate packaging of the product.
4. Addition or modification in the therapeutic indication.
5. Change in the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings.
6. Substantial changes to the formulation, specification or impurity profile of the active ingredient or finished medicinal product which may have significant impact on the quality, safety or efficacy of the product.
7. Variations related to changes outside the range of approved specifications, limits or acceptance criteria.
8. Replacement or addition of Primary packaging site.
9. Replacement or addition of a site or a manufacturer responsible for batch release where batch control/testing takes place.
10. Change in the manufacturing process of the active substance or finished product.
11. Change in batch size of active substance, intermediate or finished product.
12. Addition of a new test parameter to the specification of an active substance, excipient or finished product.
13. Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance.
14. Change in the manufacturer (replacement or addition) of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance.
15. Change in the re-test period of the active substance.
16. Replacement of an excipient with a comparable excipient.
17. Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure.
18. Change in synthesis or recovery of a non-pharmacopoeial excipient.
19. Change in the qualitative and/or quantitative composition of the immediate packaging material.
20. Change in the storage conditions of the finished product or the diluted/reconstituted product.

N.B. It remains the applicant’s responsibility to provide the relevant documentation (relevant parts of the dossier) expected to prove that the intended major change will not have an impact on the quality, safety or efficacy of the authorized product.

**Annex (III)**

**Changes leading to submission of a new of application**

N.B. The name of the medicinal product will be the same for the new application as it is for the existing marketing authorization of the medicinal product.

1. Changes to the active substance(s):

   (i) Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure.

   (ii) Modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not significantly different.

2. Changes to strength, pharmaceutical form and route of administration:

   (i) Change of bio-availability
   (ii) Change of pharmaco-kinetics e.g. change in rate of release
   (iii) Change or addition of a new strength/potency
   (iv) Change or addition of a new pharmaceutical form
   (v) Change or addition of a new route of administration

   - In general, all possible changes that are not listed in Annex I or III or which do not fulfill the conditions of Annex I are defined as major (type II) variations.