The Institute for Standardization and Control of Pharmaceuticals
Jerusalem

Effective date

4/7/2012

Standard Operating Procedure for Submitting an Application for a Variation for a Medicinal Product

SOP Number EX-009/01

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<th>Name</th>
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<tbody>
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<td>Dr. Vered Ben-Naim</td>
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Introduction

Under Regulation 13 of the Pharmacists Regulations (Preparations), 1986, the Marketing Authorization Holder (MAH) of a medicinal product is obliged to report on any variation in the terms of marketing authorization to the Ministry of Health.

With regard to changes in the aspects of quality, the European "Guideline on the details of the various categories of variations to the terms of marketing authorization for medicinal products for human use and veterinary medicinal product" has been adopted, apart from those cases where adaptation to legislation and registration conditions in the State of Israel was required.

Variation requests relating to the quality of registered medicinal products, are assessed by the assessment units within the Institute for Standardization and Control of Pharmaceuticals (hereinafter: "the Institute").

This SOP does not apply to variations relating to Clinical Information, Medical Device and the administrative variations addressed in the circular issued by the Pharmaceutical Administration of June 30th 2010.

1. Purpose

The purpose of this SOP is to describe the manner in which requests for variations to the terms of registered medicinal products should be submitted, and their processing by the Institute.

2. References

2.1 The Pharmacists Regulations (Preparations), 1986.

2.2 The European SOP for introducing variation entitled:

"Guideline on the details of the various categories of variations to the terms of marketing authorization for medicinal products for human use and veterinary medicinal product, Regulation (EC) No. 1234/2008"


2.3 The Institute's circular regarding the adoption of the SOP, issued 27th January 2010.
2.4 The Institute's announcement regarding postponement of the date for adopting the SOP, issued December 7th 2011.

2.5 The announcement by the Pharmaceutical Administration regarding variations submitted directly to the Pharmaceutical Administration, issued June 30th 2010.

2.6 The Institute's circular regarding submission of applications to the assessment units, issued September 19th 2011.

2.7 Circular to manufacturers/importers regarding applications to register biological products, issued May 27th 2007.

2.8 Stability SOP: "Submitting Stability Data Relating to Active Substances and Medicinal products when Filing for Registration, Registration Renewals and Variations" EX-007.

2.9 Renewal SOP: "SOP for Submitting an application to renew a Quality certificate for a Medicinal Product" EX-005.

2.10 SOP for submitting samples: "Submission of Samples and Reference Standards When Filing Applications with the Institute" EX-001.

2.11 ICH M4Q: "Common technical document for the registration of pharmaceuticals for human use - Quality".

3. **Definitions**

3.1 Variation: Any change from a quality aspect in the information which was filed with the Institute in the product's registration dossier, including changes in the Active Substance Master File and in the Plasma Master File.

3.2 Type IA variation: A variation which has little or no effect on the preparation's quality, safety and efficacy.

3.3 Type IAIN variation (IN - Immediate Notification): A modification which has little or no effect on the product's quality, safety and efficacy, however it does effect the continuous control over the product and/or results in a change in the details recorded in the registration certificate.

3.4 Type IB modification: A modification which has little effect but which does not meet the requirements of Type IA and Type IAIN variation.
3.4.1 Type 1B foreseen: A minor modification for which all the documents required under the European Variation guideline have been submitted.

3.4.2 Type 1B un-foreseen: A minor modification which does not satisfy the conditions and/or the documents required under the European Variation guideline.

3.5 Type II modification: A significant modification which is likely to affect the quality, safety and efficacy of the product.

3.6 Grouping: The submission of a number of variations in conjunction with one another.

3.7 The implementation date: The date on which the modification was actually implemented within the manufacturer's quality system.

3.8 The filing date: The date on which the variation application was received by the Institute.

4. Responsibility

The marketing authorization holder's appointed pharmacist shall be responsible for ensuring compliance with the requirements of the SOP.

5. Implementation

5.1 The marketing authorization holder shall report through the appointed pharmacist on any variation to the quality of any medicinal product which is recorded in the medicinal products register.

5.2 This SOP is based on the European Variation Guideline in which the various types of variations are defined and categorized according to their effect on the quality, safety and efficacy of the medicinal product.

5.3 A variation application must be submitted in the following way:

5.3.1 An application for a variation to a chemical medicinal product must be submitted to the Chemistry Assessment Unit Coordinator.

5.3.2 An application for a variation to a biological product must be submitted to the Biological Assessment Unit Coordinator.
5.3.3 The application shall include the following documents:

5.3.3.1 An accompanying letter, in duplicate, detailing the variations, the attached documents and the number of files that were submitted. On the letter, at the top of the page, the variation classification must be indicated in accentuated, font size 18 lettering.

5.3.3.2 A checklist (Appendix 1).

5.3.3.3 The variation application form in duplicate (Appendix 2).

5.3.3.4 A copy of the relevant page relating to the variation taken from the European Variation Guidelines, on which the conditions and documentation to be attached to the request have been marked.

5.3.3.5 In the case of imported products: For Type II variations, a certificate of approval from the authority of a recognized country (according to the Pharmacists Regulations). The certificate may be submitted either together with the variation application or during its assessment by the Institute. Type II requests shall not be approved before receiving a certificate from the authorities. The assessor may, in his discretion, request a certificate of approval for an IB Type variation.

5.3.3.6 Relevant administrative documents, such as: CPP, Appendix 6 (questionnaire), GMP certificate and a receipt for payment of the fee.

5.3.3.7 For site change and composition modification requests, two copies of the quality certificate application form and appendix must be sent.

5.3.3.8 Material supporting the variation request: The material shall be submitted in CTD format. Where the Institute's file is not in CTD format the material may be submitted in whatever format the file was submitted in.

5.3.4 As a rule, samples may not be submitted with variation applications.

5.4 A number of variation applications may be submitted simultaneously (grouping) with one accompanying letter and a separate variation request form for each of the changes.
5.4.1 Grouping may be carried out in the following cases:

5.4.1.1 Where a number of Type IA, IAIn and IB variations are being requested for the same product. The application shall be processed on the basis of the most significant modification type amongst them.

5.4.1.2 An identical variation application submitted for different dosages of the same product.

5.4.1.3 The variations are attributable to one another. That is, where a particular variation is the result of another variation, and not for the simultaneous implementation of different variations.

5.4.1.4 Other requests shall be judged on a case by case basis.

5.4.2 The submission of applications for variations which are likely to affect the quality, safety or efficacy of the medicinal product shall not be delayed because of a desire to submit a number of variation applications simultaneously (grouping).

5.4.3 It shall not be possible to submit group variation applications where some of the requests are intended for the Pharmaceutical Department and some for the Institute.

5.5 Minor Type IA variations may be reported within up to one year from the implementation date.

5.6 Type IAIn, IB and II variations must be reported before being implemented.

5.7 Because of their effect on the contents of the registration certificate, the following variations, which are classified under the European Variation Guidelines as Type IA, are classified by the Institute as Type IAIn:

5.7.1 A BIIa.3.a.2 variation - a change in the composition of the finished product's flavorings and colorings.

5.7.2 A BIIa.3.b.1 variation - a change in the composition of the finished product's inactive ingredients.

5.7.3 A BIIa.4.a variation - an change to the weight of tablet coating.
5.7.4 A BIIb.2.a variation - a change to the finished product's release site.

5.7.5 A BIIe.1.a.1 variation - a change to the primary packaging.

5.8 The assessor responsible for examining the application may reclassify the variation.

5.9 No variation application for a new product shall be submitted before it has been registered.

5.10 Applications for renewal of registration may only be accompanied by Type IA variation requests.

5.11 Enquiries and questions with respect to Type IA variations applications should be forwarded by electronic mail to the Chemistry Assessment Unit Coordinator and the Biological products Assessor, respectively (the e-mail addresses of who are listed in Appendix 3).

5.12 Urgent requests may only be submitted in the following cases:

5.12.1 A danger exists to public health.

5.12.2 The variation resulting from a deviation.

5.12.3 Variation of strains in seasonal flu vaccinations.

5.13 Urgent variation applications should be sent by post to the biological and chemical variation coordinators, respectively. It should be indicated on both the variation application form and the accompanying letter that the variation is urgently required. A notice should be sent simultaneously by electronic mail to the addresses of the departmental modification coordinators as set out in Appendix 3.

5.14 The e-mail notice must include the full application and a justification as to why it is being filed as urgent.

5.15 Urgent requests for site change for chemical medicinal products which meet the criteria contained in paragraph 5.12.1 should be referred to the site changes coordinator.

5.16 The timetables for the various types of variation applications are as follows:

5.16.1 Type IA variations applications must be submitted to the Institute within one year of the implementation date. Confirmation of receipt shall be given within
40 calendar days.

5.16.2 Type IAIN variation applications must be submitted to the Institute before implementation and shall be examined within 40 calendar days. No variation may be implemented without receiving the Institute's approval.

5.16.3 Type IB variation applications must be submitted to the Institute before implementation and shall be examined within 120 calendar days. Should the Institute's response not be received within 120 calendar days from the date on which the application was submitted, the variation may be implemented, provided that they do not affect the registration certificate. Where necessary, a letter requesting missing details shall be sent which shall stop the counting of days for processing and implementation. The marketing authorization holder shall reply to the missing details letter within 60 calendar days. A final answer shall be given within 30 calendar days from the date on which the marketing authorization holder's answer to the missing details letter was received. Should the Institute fail to issue a response letter within this time the variation may be implemented, provided that it does not affect the registration certificate.

5.16.4 Type II variation applications must be submitted to the Institute before implementation and shall be examined within 120 calendar days. A missing details letter shall be dispatched where necessary. The marketing authorization holder shall respond to the missing details letter within 60 calendar days. A final answer shall be received within 30 calendar days from the date on which the marketing authorization holder's response to the missing details letter was received. The variation shall not be implemented without receiving the Institute's approval.

5.16.5 The marketing authorization holder's answers to the Institute's missing details letters shall be sent directly to the assessor who examined the application and who wrote the letter. The application number must be clearly written on the reply.

5.16.6 Other than those relating to variations of strains in seasonal flu vaccinations, urgent variation applications (as defined in paragraph 5.12) shall be examined within 15 working days from the day on which they were received by the Institute by post.

5.16.7 Should the marketing authorization holder's answers not be received within the requisite period of time, then the application shall be denied and closed. The marketing authorization holder may resubmit the application which shall then be processed as a new variation application.

6. **Date on which the SOP comes into effect: 10/10/2012**
### Distribution:
- Director of the Pharmaceutical Administration
- Director of the Registration Department
- Importers/Manufacturers
- District Pharmacists
- The Institute's website
Appendix 1 - Checklist

CHECKLIST FOR SUBMITTING A VARIATION APPLICATION TO THE CHEMICAL AND THE BIOLOGICAL ASSESSMENT UNITS

NAME OF MEDICINAL PRODUCT: ____________ REGISTRATION NUMBER: ____

☐ VARIATION APPLICATION FORM (IN DUPLICATE)

☐ ACCOMPANYING LETTER DESCRIBING THE NATURE OF THE VARIATION

☐ CERTIFICATE OF APPROVAL FROM A RECOGNIZED COUNTRY

☐ RELEVANT SUPPORTING INFORMATION

☐ RELEVANT DOCUMENTS. E.G.: QUALITY CERTIFICATE, CPP

☐ RECEIPT FOR PAYMENT OF FEE

Signature of Appointed Pharmacist ______________ Date ______________

1 This may be submitted while the application is being processed
Appendix 2 - Variation Application Form

APPLICATION FOR A VARIATION TO THE TERMS OF REGISTRATION OF A MEDICINAL PRODUCT REGARDING ITS' QUALITY (TO BE SUBMITTED IN DUPLICATE)

Application Number (to be filled in by the Institute): ________________

1. Product classification:
   □ chemical    □ biological    □ veterinary
   □ urgent request    □ Grouped request

2. Type of request:
   □ Type IA    □ Type IAIN    □ Type IB    □ Type IB (unforeseen)    □ Type IB (foreseen)    □ Type II

3. Serial number of variation (as defined in the European Guideline):
   ______

   Mark the applicable paragraphs on the relevant page of the European Guideline.

   □ The relevant marked page is attached
   □ Supporting data and appropriate documents are attached
   □ A certificate of approval from competent authorities is attached

4. A fee in the amount of NIS ______ has been paid    Receipt number ______

5. Details of the product (to be written in English)
### Name of preparation and strength: Registration certificate number:

### Name and address of the finished product manufacturer: Dosage form:

### Name and address of marketing authorization holder in Israel: Name, telephone number and e-mail address of appointed pharmacist:

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6. **Nature of the variation (give a concise description of the variation including justification):**

   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

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7. **Details of the variation:**

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<th>Current Registration</th>
<th>Proposed Registration</th>
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8. **List of pending applications (renewals and variations) for this product and the date on which they were submitted:**

   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
9. List of products for which an identical application was submitted
(name of product, registration number and date of the application):
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

10. List of variations which were submitted to the Institute related to
and/or resulting from the current variation:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

11. Planned implementation date: ________________

12. Declaration - I hereby declare that:

☐ No variations are being made other than those indicated in
  this request (paragraph 7).

☐ In the case of Type IA, IAIN variations: All the conditions in the request as
  set out in the European Variation Guideline have been satisfied.

☐ All the necessary documents as specified in the European Variation
  Guideline have been filed.

  In the case of imported products -

☐ The documents which have been filed with respect to the variation are
  identical to those which were filed in a recognized state (specify the name of
  the state ________). Any addition which shall be submitted in the
  context of this variation shall be forwarded immediately to the Institute.
In the case of Type IA, IA\textsubscript{IN} variations:

13. Your variation application, number ______________ is valid/is invalid, based on your declarations in paragraph 12.

Date: ______________ Name: ____________ Signature: ____________

In the case of Type II, IB modifications:

14. After examining all the data which was attached to your application, we have no objection/object to implementation of the variation number ________.

15. Remarks:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

Date: _______ Name: _______________ Signature: _______
Appendix 3 - Electronic mail addresses

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Electronic mail</th>
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<tbody>
<tr>
<td>Simona Barak</td>
<td>Registration Coordinator</td>
<td><a href="mailto:Simona.Barak@eliav.health.gov.il">Simona.Barak@eliav.health.gov.il</a></td>
</tr>
<tr>
<td></td>
<td>Chemical Preparations</td>
<td></td>
</tr>
<tr>
<td>Ayala Tamar</td>
<td>Registration Coordinator</td>
<td><a href="mailto:Ayala.Tamar@eliav.health.gov.il">Ayala.Tamar@eliav.health.gov.il</a></td>
</tr>
<tr>
<td></td>
<td>Biological Preparations</td>
<td></td>
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<tr>
<td>Carmela Wajntraub</td>
<td>Variation Coordinator</td>
<td><a href="mailto:Carmela.wajntraub@eliav.health.gov.il">Carmela.wajntraub@eliav.health.gov.il</a></td>
</tr>
<tr>
<td></td>
<td>File Assessor Chemistry</td>
<td></td>
</tr>
<tr>
<td>Vered Ben-Naim</td>
<td>File Assessor, Biology</td>
<td><a href="mailto:Vered.ben-naim@moh.health.gov.il">Vered.ben-naim@moh.health.gov.il</a></td>
</tr>
<tr>
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<td>Site Changes Coordinator</td>
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