



IRISH MEDICINES BOARD
**GUIDE TO SUBMISSION OF A VARIATION APPLICATION
FOR A MANUFACTURING/IMPORTATION
AUTHORISATION OR A WHOLESALE'S
AUTHORISATION**

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

1. SCOPE

The purpose of this document is to provide guidance on documentation requirements which should be provided to the IMB when making a submission to vary a manufacturing / importation authorisation (relating to human, veterinary or investigational medicinal products) or a wholesaler's authorisation.

This guide contains minimum documentation requirements which will facilitate the approval of such variation applications; however, the list of requirements is not exhaustive.

2. INTRODUCTION

Manufacturing/importation authorisations (MIAs) and wholesaler's authorisations are issued to facilities following successful inspections in line with national and EU legislation and guidelines. It is the responsibility of holders of these authorisations to ensure that the details described in them are accurate and are maintained throughout the life cycle of the authorisation.

There are certain changes to authorised facilities which can impact on the detail described in the authorisation and as such, require prior approval by the IMB before the implementation of the change. Therefore, it is the responsibility of the holder of these authorisations to maintain a system to assess the impact of the proposed change on the authorisation and to request approval from the IMB accordingly.

Changes to authorisations are made by submission of a variation application. The application is categorised as either 'Admin' (Administrative) or 'Technical' depending upon the nature of the proposed change and is assessed and reviewed on receipt by the IMB. In order to facilitate the expedited approval of variation applications, applicants are encouraged to provide, at a minimum, the documentation listed below and any additional documentation which may support the proposed variation application.

If the proposed change at the facility is believed to impact on the details of the authorisation but is not described within this guide, please contact a member of the Compliance Department at compliance@imb.ie.

3. MANUFACTURING / IMPORTATION AUTHORISATION

Variation type	Procedure type	Supporting documentation
1. General information		
1.1 Minor corrections / typographical errors to authorisation	Admin	Submit a signed variation application form outlining the nature of the typographical error.
1.2 Change in the name of authorisation holder	Admin	Submit a Certificate of Incorporation. Submit a statement from a Qualified Person (QP) named on the authorisation outlining any implications that this change may have on the quality management system or its operation at the site. The IMB reserves the right to perform an inspection at the site if considered necessary.
1.3 Change in the legally registered address of the authorisation holder	Admin	Submit a Certificate of Incorporation.
1.4 Change in the main address of the manufacturing site	Technical	Submit a proposed revision of the Site Master File including the new manufacturing address. It should be noted that an inspection may also take place as part of the assessment of such a variation.
2. Schedule 2, Annex 1 (Scope of authorisation), Part 1 – Manufacturing operations		
2.1 Addition to the currently approved manufacturing operations (this refers to operations which are managed directly by the authorisation holder)	Technical	Specify the proposed manufacturing operation(s), using the terms below and the address(es) where each operation is carried out: (a) manufacture (of the dosage form or intermediate product e.g. granulate) (b) primary packing (c) secondary packing (d) batch certification (e) importation (of partially manufactured or finished medicinal products – see Schedule 2, Annex 1, Part 3) (f) storage (g) distribution (h) quality control testing microbiological (sterility) microbiological (non-sterility) physical/chemical biological Submit a proposed revision of the Site Master File including the proposed additional manufacturing operations.

Variation type	Procedure type	Supporting documentation
		It should be noted that an inspection may also take place as part of the assessment of such a variation.
2.2 Deletion of currently approved manufacturing operations	Admin	None required.
2.3 Change in the address at which manufacturing operations are carried out.	Technical	<p>Specify the new address and where the relevant manufacturing operations will be carried out.</p> <p>Submit a proposed revision of the Site Master File including the new address(es).</p> <p>It should be noted that an inspection may also take place as part of the assessment of such a variation.</p>
3. Schedule 2, Annex 1 (Scope of authorisation), Part 2 – Production activities		
3.1 Addition to the currently approved manufacturing operations in relation to a product type	Technical	<p>Specify the general product class and dosage form using the list provided in Appendix 1</p> <p>Specify the manufacturing operations carried out in relation to the dosage form where these include manufacture of the dosage form (or intermediate), primary packing or batch release.</p> <p>Include a statement ‘Exempt Medicines Only’ where manufacturing operations carried out in relation to a particular dosage form only relate to Exempt Medicines as defined in the Medicinal Products (Control of Placing on the Market) Regulations 2007.</p> <p>Include a statement ‘Herbal Medicines Only’ where manufacturing operations carried out in relation to a particular dosage form only relate to herbal medicines.</p> <p>Include a statement ‘Homeopathic Medicines Only’ where manufacturing operations carried out in relation to a particular dosage form only relate to homeopathic medicines.</p> <p>Submit a proposed revision of the Site Master File including the proposed additional manufacturing operation(s) and the product type to which these relate.</p> <p>Submit a summary of training provided to QPs responsible for batch certification, where the proposed general product class / dosage form is new to the manufacturing site.</p> <p>It should be noted that an inspection may also take place as part of the assessment of such a variation.</p>

Variation type	Procedure type	Supporting documentation
3.2 Deletion of currently approved manufacturing operations in relation to a dosage form or deletion of a general product class / dosage form and the associated manufacturing operations from this section.	Admin	None required.
4. Schedule 2, Annex 1 (Scope of authorisation), Part 3 – List of product dosage forms		
4.1 Addition to the list of imported products where the proposed product is either (i) sourced from a new contract manufacturer or (ii) a new dosage form sourced from a contract manufacturer which is already approved on the authorisation,(e.g. tablets already listed but sterile small volume liquids to be added from the same contract manufacturer)	Technical	<p>Specify the proposed new dosage form(s) to be imported including the general product class, description of the dosage form, active ingredient and strength. (Use the product classification / dosage forms listed in Appendix 1.)</p> <p>Imported products should be sequentially numbered and this number used to cross reference the product to the relevant contract manufacturing site(s) involved in manufacture of the product and listed in Schedule 2, Annex 2 (see below).</p> <p>Where the change in this section involves new activities for the relevant contract manufacturer please refer to section 5.4. (Note: the addition to the list of imported products and any associated changes to the authorisation, e.g. to the section on contract manufacturers, which are a consequence of this addition, will be charged as a single technical variation.)</p> <p>Specify whether the site to which the manufacturer's authorisation applies is acting as site of physical importation and/or is the named site of 'batch release' with respect to the imported products. Where the latter applies then all sites involved in the manufacture of the product (as would appear in the application for the marketing authorisation) must be named as contract manufacturers on the authorisation (refer to section 5.1). Where the authorisation holder is solely acting as site of physical importation then only the site where the product is sourced need be named on the authorisation.</p> <p>Where the importation activity relates to IMPs then only the general product class and description of the dosage form (e.g. non-sterile products; tablets) needs to be included in this section of the authorisation. Descriptions of individual products (active ingredient and strengths) need not be included. The associated third country manufacturing site(s) should be named (see section 5.1).</p>

Variation type	Procedure type	Supporting documentation
		Include the statement 'Importation of Exempt Medicinal Products' where the importation activity relates to exempt medicines as defined in the Medicinal Product (Control of Placing on the Market) Regulations 2007. It is not necessary to specify the dosage forms or the associated sites from which the exempt medicinal products will be imported.
4.2 Addition to the list of imported products where the contract manufacturer is already approved on authorisation for manufacture of the same product type (e.g. addition of another tablet product sourced from a contract manufacturer which has already been authorised for supply of tablets)	Admin	Specify the proposed product to be imported, including general product category, description of the dosage form (e.g. tablets), active ingredient and strength. (Use the product categories / dosage forms listed in Appendix 1.) Specify the contract manufacturing site from which the product is sourced.
4.3 Deletion of an imported product	Admin	None required.
5. Schedule 2, Annex 2 – Contract manufacturing site / contract storage site		
5.1 Addition of contract manufacturing site	Technical	Where the site, to which the manufacturer's authorisation applies, is the named site of batch release in relation to a marketing authorisation or a clinical trial application, then all sites involved in manufacture of the product should be named as contract manufacturers on the authorisation. See section 4.1 of this table for guidance on which contract sites should be included on the manufacturer's authorisation in relation to imported medicinal products and IMPs. For each contract manufacturer listed clearly specify the proposed manufacturing activity which will be undertaken in relation to the relevant dosage forms. The applicable operations are manufacture, primary packing, secondary packing, storage. For sites which are engaged in storage or secondary packing it is not necessary to specify the particular product types to which these activities apply. Submit a current GMP certificate issued following an inspection within the last three years by a Competent Authority in the EEA or an MRA partner, where

Variation type	Procedure type	Supporting documentation
		<p>appropriate. The scope of the certificate should include the proposed manufacturing operations for the relevant product type which will be manufactured at the site.</p> <p>For this type of variation to an IMP manufacturing authorisation, submit a declaration by a QP named on the authorisation stating that he/she is satisfied that the contracted site operates in accordance with EU GMP in relation to the activities concerned. The IMB reserves the right to perform its own inspection of the contracted site.</p>
5.2 Change in the name of a contract manufacturing site	Admin	<p>Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce) in which the new name is mentioned.</p> <p>Submit a statement from a QP named on the manufacturer's authorisation regarding any implications that this change may have on the quality management system or its operation at the contracted site. Alternatively a revised GMP certificate (as described in 5.1) which includes the new name may be provided.</p>
5.3 Change in the address of a contract manufacturing site	Technical	<p>Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce) in which the new address is mentioned.</p> <p>Submit a current GMP certificate in relation to manufacture of human or veterinary medicines or a QP declaration for IMPs, as described in 5.1.</p> <p>For this type of variation to an IMP authorisation, submit a declaration by a QP named on the authorisation (as per section 5.1) regarding GMP compliance of the contracted site in relation to the activities concerned at the new address. The IMB reserves the right to perform an inspection of the contracted site or request another relevant authority to inspect where appropriate.</p>
5.4 Addition of production activities at approved contract manufacturing site	Technical	<p>Specify the proposed new manufacturing operation(s) which will be undertaken in relation to the relevant dosage form.</p> <p>The applicable operations are manufacture, primary packing, secondary packing, and storage. In the case of storage or secondary packing, it is not necessary to specify the particular product types to which these activities apply.</p> <p>Submit a current GMP certificate which includes the</p>

Variation type	Procedure type	Supporting documentation
		proposed manufacturing operation(s) where the variation relates to a manufacturer's authorisation for human or veterinary medicines. For an IMP manufacturing authorisation, submit a QP declaration s, as described in section 5.1 of this table.
5.5 Deletion of operations carried out at a contract manufacturing site or deletion of a contract manufacturer	Admin	None required.
6. Schedule 2, Annex 3 – Contract laboratories		
<p>6.1 Addition of a new contract laboratory</p> <p>Note: contract laboratories performing the following testing should be named on the Manufacturer's Authorisation:</p> <p>(i) in-process tests or finished product tests which are described in a Marketing Authorisation</p> <p>(ii) identity testing of micro-organisms associated with the manufacture of sterile medicinal products</p> <p>(iii) identity testing of starting materials</p>	Technical	<p>Specify the proposed testing activity to be carried out at the contract laboratory. The testing activities should be described as:</p> <ul style="list-style-type: none"> - Microbiological (sterility) - Microbiological (non-sterility) - Physical/chemical - Biological <p>Submit a current GMP certificate issued following an inspection within the last three years by a Competent Authority in the EEA or an MRA partner, where appropriate. The scope of the certificate should include the proposed testing activity.</p> <p>Where the laboratory will only be used for testing in relation to IMPs or stability testing of medicinal products, submit a declaration of GMP compliance from a QP named on the authorisation. The IMB does reserve the right to perform its own inspection if deemed necessary or request another relevant authority to inspect where appropriate.</p>
6.2 Change in the name of a contract laboratory	Admin	<p>Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce) in which the new name is mentioned.</p> <p>Submit a statement from a QP named on the manufacturer's authorisation regarding any implications that this change may have on the quality management system or its operation at the contracted site. Alternatively, submit a revised GMP certificate (as per 6.1) including the new name of the contract laboratory.</p>
6.3 Change in the address of a contract laboratory	Technical	Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce) in which the new address is

Variation type	Procedure type	Supporting documentation
		mentioned. Submit a current GMP certificate in relation to sites performing testing on human or veterinary medicines or a QP declaration in the case of laboratories performing stability testing only or testing on IMPs (see section 6.1.) The IMB reserves the right to perform an inspection or request another relevant authority to inspect where appropriate.
6.4 Addition of activities at an approved contract laboratory	Technical	Submit either a GMP Certificate or a QP declaration to cover the additional testing activities (see section 6.1). The IMB reserves the right to perform an inspection or request another relevant authority to inspect where appropriate.
6.5 Deletion of testing activities carried out at a contract laboratory or deletion of a contract laboratory.	Admin	None required.
7. Schedule 2 – Annex 4 – Qualified Person(s)		
7.1 Addition of Qualified Person (primary or deputy)	Technical	Submit a copy of relevant qualifications as issued by relevant third level institution to support educational requirements for a QP. Submit a copy of the proposed QP's CV. Submit a summary of training relevant to the duties of a QP which has been provided at the manufacturing site. This should be signed by the proposed QP and his/her relevant superior.
7.2 Removal of Qualified Person	Admin	None required.
7.3 Change Deputy Qualified Person named on authorisation or licence to Primary QP (or vice versa)	Admin	None required.
8. Schedule 2, Annex 5 – Key personnel		
8.1 Addition of a person responsible for production (or deputy)	Technical	Submit a copy of the person's CV.
8.2 Addition of a person responsible for quality control (or deputy)	Technical	Submit a copy of the person's CV.
8.3 Addition of a person responsible for biological	Technical	Submit a copy of the person's CV.

Variation type	Procedure type	Supporting documentation
testing (or deputy)		
8.4 Removal of a person responsible for production (or deputy)	Admin	None required.
8.5 Removal of a person responsible for quality control (or deputy)	Admin	None required.
8.6 Removal of a person responsible for biological testing (or deputy)	Admin	None required.

4. WHOLESALER'S AUTHORISATION

Variation type	Procedure type	Supporting documentation
1. General information		
1.1 Minor corrections/typographical errors to authorisation	Admin	Submit a signed variation application form outlining the nature of the typographical error.
1.2 Change in the name of authorisation holder	Admin	Submit a Certificate of Incorporation. Submit a statement from a Responsible Person (RP) named on the authorisation outlining any implications that this change may have on the quality management system or its operation at the site.
1.3 Change in the legally registered address of the authorisation holder	Admin	Submit a Certificate of Incorporation.
1.4 Change in the name of the wholesale site	Admin	Submit a formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name is mentioned.
2. Premises		
2.1 Change in address of wholesaling premises	Technical	None required. Approval of this variation on the basis of a satisfactory GDP inspection.
3. Classification of medicinal products		
3.1 Addition of a category of medicinal product	Technical	Submit details of proposed category of medicinal product. Approval of this variation may include an inspection.
3.2 Removal of a category of medicinal product	Admin	None required.

Variation type	Procedure type	Supporting documentation
4. Responsible Person		
4.1 Change of Responsible Person	Technical	Submit the following documents: <ul style="list-style-type: none"> - Copy of applicant's CV. - Training plan for proposed applicant (covering GDP and procedural training) along with confirmation upon completion of training signed by the proposed RP. - Role profile/job description signed by the proposed RP.
4.2 Change/addition/removal of a deputy Responsible Person	Technical	Submit the following documents: <ul style="list-style-type: none"> - Copy of applicant's CV. - Training plan for proposed applicant (covering GDP and procedural training) along with confirmation upon completion of training signed by the proposed RP. - Role profile/job description signed by the proposed RP.
4.2 Removal of a Responsible Person	Admin	None required.
5. Annex		
5.1 Addition of a new marketing authorisation holder	Admin	Submit the following documents: <ul style="list-style-type: none"> - List of marketing authorisation holders and corresponding MA number to be included in annex. - Letter of confirmation from the MAH. - Confirmation from the RP that there no changes to the QMS resulting from the addition.
	Technical	Submit the following documents: <ul style="list-style-type: none"> - As above - List of QMS updates resulting from the addition, including an overview of the changes
5.2 Removal of a marketing authorisation holder	Admin	None required.
5.3 Change of name of marketing authorisation holder	Admin	Submit a letter of confirmation from the MAH.
5.4 Addition of marketing authorisation number	Admin	Submit a letter of confirmation from the MAH.

5. CONTACT DETAILS

For further information or guidance, please contact:

Compliance Department
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APPENDIX 1: CATEGORIES OF MEDICINAL PRODUCTS / INVESTIGATIONAL MEDICINAL PRODUCTS

Sterile Products

Aseptically prepared (list of dosage forms)

Large volume liquids

Lyophilisates

Semi-solids

Small volume liquids

Solids and implants

Other aseptically prepared products <free text>

Terminally sterilised (list of dosage forms)

Large volume liquids

Semi-solids

Small volume liquids

Solids and implants

Other terminally sterilised prepared products <free text>

Non-sterile products

Non-sterile products (list of dosage forms)

Capsules, hard shell

Capsules, soft shell

Chewing gums

Impregnated matrices

Liquids for external use

Liquids for internal use

Medicinal gases

Other solid dosage forms <free text>

Pressurised preparations

Radionuclide generators

Semi-solids

Suppositories

Tablets

Transdermal patches

Intraruminal devices

Veterinary premixes

Other non-sterile medicinal product <free text>

Biological medicinal products

Blood products

Immunological products

Cell therapy products

Gene therapy products

Biotechnology products

Human or animal extracted products

Other biological medicinal products <free text>

Other products or manufacturing activity (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when manufacturing, etc). required by national legislation), herbal or homeopathic products, bulk or total

Manufacture of:

Herbal products

Homoeopathic products

Biological active starting materials

Other <free text >

Sterilisation of active substances/excipients/finished product:

Filtration

Dry heat

Moist heat

Chemical

Gamma irradiation

Electron beam