HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Pre-submission Scientific and Regulatory Advice for GXP Activities

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

CONTENTS

1 INTRODUCTION

In the context of this guideline, 'GXP' refers broadly to good practice activities which apply to a number of health product areas regulated by the Health Products Regulatory Authority (HPRA). These include:

- manufacture, importation and distribution of active substances used in the manufacture of human and veterinary medicines
- manufacture of human medicines and veterinary medicines
- distribution and brokering of human medicines
- laboratories involved in the contract testing of active substances and finished medicines
- Good Clinical Practice (GCP) in the conduct of clinical trials on medicines in humans
- Good Vigilance Practice (GVP) in the post marketing monitoring of medicines
- advertising of medicines for human use
- export certification for medicines, medical devices and cosmetics
- prescribed activities in relation to blood for transfusion, tissues and cells for human application and organs for transplantation in humans
- manufacture and distribution of cosmetics and requirements around the preparation and maintenance of technical files
- prescribed control and security activities relating to the manufacture, import, export or distribution of precursor chemicals

Important notes:

(i) Pre-submission advice is required for all potential applications for a manufacturer's/importer's authorisation (MIA) for the manufacture of human and veterinary medicines and investigational medicinal products.

(ii) Stakeholders should, in the first instance, consult available EU and HPRA guidance and it is expected that GXP advice will be sought only where the specific questions are not addressed in the relevant guidance.

The aim of providing pre-submission scientific or regulatory advice relating to GXP activities is to:

(i) Assist potential applicants for GXP authorisations/registrations to understand the requirements that must be fulfilled to be compliant. This can include review of plans for new manufacturing or wholesale facilities.

(ii) Assist existing authorisation holders, registrants and stakeholders to understand the requirements that must be fulfilled to be compliant. Advice will also be provided, on request, to existing authorisation holders that are, for example, considering expansion or alteration of premises, installation of new or revised processes, etc.

Discussion of the appropriate regulatory requirements and existing guidelines may form part of the advice. The advice is intended as a guide to the applicant, authorisation or registration holder but does not substitute for the applicant's responsibilities to ensure compliance.

Advice is generally given during face-to-face meetings. Advice can, for example, include

review of plans for area classifications, facility layout, equipment and utilities and personnel flows.

In general, the advice given is based on the information and documentation provided by the applicant in light of current relevant scientific knowledge and without prejudice to evolving developments in the scientific field. Advice will be given in good faith. However, if circumstances change over time, an alternative approach to that previously advised may become more appropriate. Therefore, any advice provided is not binding on the applicant or stakeholder or on the HPRA.

In all cases where the facility, process or modification are subject to inspection prior to approval, the applicant will be advised that the formal assessment of compliance will be based on the inspection findings.

2 OVERVIEW

Pre-submission scientific and regulatory advice meetings are organised to provide responses to specific questions pertaining to facilities, processes and other GXP activities.

The range of areas on which advice can be given includes, but is not limited to:

2.1 A company considering establishment of operations in Ireland

Introductory meetings with companies may be arranged at the request of IDA Ireland or Enterprise Ireland. The normal purpose of such briefings is to obtain an understanding of the regulatory framework and the company's proposed activities.

2.2 A company intending to apply for a manufacturer's/importer's authorisation (MIA) to include manufacturing activities in the scope

A request for a pre-submission meeting should be made and any requested information submitted in advance. The purpose of the meeting is to discuss the proposed manufacturing activities, and the approximate timeline for commencement of operations and steps involved in applying for an MIA authorisation.

2.3 Review of plans for construction or modification of GMP facilities already authorised

Holders of MIAs are encouraged to request a pre-submission meeting to facilitate review of the plans by inspectors. The plans should be at a reasonably advanced stage and presented as engineering drawings.

A pre-submission regulatory review for Good Manufacturing Practice (GMP) facility design includes qualification and validation activities, prior to formal inspection related to an application for an MIA.

The pre-submission review facilitates early discussion of important design aspects including:
- key milestones of the project
- challenges to the technology transfer process
- the application of Quality Risk Management
- regulatory expectations and compliance

An important additional topic in relation to facility modifications is the impact on operations during the construction, fit out and qualification phases. Proposals for mitigation of risks to existing processes will be examined closely and, if necessary, additional information or alteration to proposals will be requested.

Advice is verbal and, while the general expectation is that the company will take this on board, it is not mandatory. In all cases the company is advised that the HPRA does not approve a facility off the plans. The decision on approval, or otherwise, is reserved for a formal GMP inspection(s), during which the application for an MIA or variation is assessed. Where a company indicates that it may make substantial design changes on foot of advice received, it is encouraged to present the updated plans for further review.

2.4 Review of plans for construction or fit-out of GDP facilities

Prospective applicants for wholesale distribution authorisations (WDAs) are encouraged to present the plans for their facilities for review by inspectors. The HPRA does not design facilities; plans must be at a reasonably advanced stage and, where necessary, presented as engineering drawings.

A pre-submission review for Good Distribution Practice (GDP) facility design is available upon request. This includes qualification and validation activities, prior to formal inspection related to an application for a WDA. Companies can meet with GDP inspectors prior to or during the building of a new facility or upgrading of a current site (see section 2.4 of this guide) to present their plans.

The pre-submission review facilitates early discussion on important design aspects including:
- key milestones of the project
- the application of Quality Risk Management
- regulatory expectations and compliance

Advice is verbal and, while the general expectation is that the company will take this on board, it is not mandatory. In all cases the company is advised that the HPRA does not approve a facility off the plans. The decision on approval, or otherwise, is reserved for the formal GDP inspection(s), during which the application for a WDA is assessed. Where a

company indicates that it may make substantial design changes on foot of advice received, it is encouraged to present the updated plans for further review and advice.

2.5 Batch certification of medicines

Where a company wishes to establish a batch certification operation in Ireland, the requirements around the need to apply for an MIA, due diligence and availability of appropriate batch documents and product samples can be clearly explained. Details of the contractual arrangements for manufacture, importation and distribution should be available for consideration.

2.6 Procurement and supply of medicines

Where a company wishes to establish a 'procure and supply' only operation (one which does not physically handle medicines), the HPRA can outline the requirements around the application for a WDA and the aspects of GDP that are expected. Full details of the supply chain for the medicines concerned should be available for consideration and evidence that the proposed wholesaling activities will be performed at the site. The need for the prospective applicant to establish the bona fides of suppliers and customers is emphasised.

2.7 Brokering of medicines

Where a person or entity proposes to become involved in the brokering of medicines, the requirement to apply for a broker's registration can be outlined. Details of the envisaged supply chains for the medicines concerned should be available for consideration. The person or entity seeking advice should also be able to provide details of the relationship(s) between the broker and the supplier(s) and purchaser(s) and whether these have been or remain to be formalised.

2.8 Importation and distribution of active substances used in medicines

Where a person or entity proposes to import and/or distribute active substances used in the manufacture of medicines, the requirements relating to an application for registration can be outlined. To facilitate the discussion, the proposed importer or distributor should have information on the source(s) of the active substances and the due diligence carried out in relation to their manufacture and supply chain.

2.9 Good Clinical Practice in the conduct of clinical trials on medicines in humans

Sponsors and/or investigators involved in the conduct of clinical trials of medicines in humans may seek advice on the interpretation of GCP guidelines or layout of facilities.

2.10 Good Vigilance Practice (for medicines)

Advice may be sought by marketing authorisation holders for human or veterinary medicines in relation to quality management systems around the collection, evaluation and reporting of pharmacovigilance data relating to their products.

2.11 Advertising of medicines for human use

Where a marketing authorisation holder is seeking clarification of the legal requirements around the advertising of medicines to the public and healthcare professionals, the requirements can be outlined.

Note: the HPRA does not, in general, prospectively review individual advertisements.

2.12 Export certification for medicines, medical devices and cosmetics

Advice may be sought by prospective applicants for export certificates. Important factors include:

- for medicines; their authorisation status (If not the subject of a marketing authorisation, they must be manufactured in Ireland.)
- for medical devices, that they are appropriately and currently CE marked
- for cosmetics, that they are appropriately and currently notified via the EU portal, CPNP

2.13 Blood, tissues and cells and organ establishments

Prospective applicants for establishment authorisations are encouraged to present the plans for their facilities for review by inspectors. The plans must be at a reasonably advanced stage and presented as engineering drawings. The process followed in reviewing plans and providing advice is similar to that outlined in sections 2.3 and 2.4 of this guide.

2.14 Manufacturers, Responsible Persons and distributors of cosmetics

Where a person or entity proposes to, or is already engaged in, manufacturing or distributing/selling cosmetics in Ireland, the requirements to ensure compliance can be outlined. Similarly, where a person or entity located in Ireland proposes to, or already is, acting as the Responsible Person for a cosmetic on the EEA market, their obligations as Responsible Person can be explained, particularly the Product Information File and Cosmetic Product Safety Report requirements.

2.15 Companies involved in the manufacture or distribution of precursor chemicals or controlled drugs

Where a company wishes to perform activities involving precursor chemicals or controlled drugs, the HPRA can outline the requirements around the application for such licences and/or

registrations, and the aspects of security, control and bona fides of suppliers and customers that are expected.
Note: 'manufacture' may relate to the actual manufacture of the controlled drug active substance or precursor chemical itself, or its use in another manufacturing process or laboratory testing. There are import and export requirements for the movement of controlled drugs in and out of Ireland and for precursor chemicals in and out of the EU.

2.16 Other/general regulatory advice

Regulatory advice may also be requested on non-specific issues such as:
- proposed arrangements for handling of quality defects and recalls of medicines
- use of the notification system for exempt medicinal products
- use of the PharmaTrust system for import or export licenses for controlled drugs

2.17 General points in relation to all types of advice

Advice will not be given in certain circumstances as outlined in the examples below for illustration (this list is not exhaustive):
- where a company, organisation or individual has been inspected, the request for advice relates directly to findings and the inspection has not yet been closed out
- where concerns have been raised during assessment of any advertisements for medicines, technical files for cosmetics, etc.
- activities outside the scope of this guide

3 MAKING A REQUEST FOR GXP ADVICE

To request a pre-submission meeting for an MIA, complete the form 'Request for pre-submission meeting for MIA' (available on the HPRA website under 'Make a submission') and return by email to compliance@hpra.ie. For all other types of GXP advice, email compliance@hpra.ie stating the type of advice sought and the desired timeline.

Following receipt of the pre-submission request, every effort will be made to arrange a meeting within a week or two. If the appropriate HPRA staff member(s) are not available within the desired timeline and a delay is expected the applicant will be advised of its likely duration.

A draft list of questions, in broad outline, must be supplied with the request. Where advice relating to facility layout is sought, it should be confirmed that engineering drawings, with appropriate commentary, will be provided before or at the time of the meeting. The questions asked should be as clear as possible.

In some instances, following review of the questions, it may be considered that these can be answered in writing without the necessity for a meeting. In such instances, the written responses will be forwarded to the company.

There is no fee relating to pre-submission meetings or GXP advice.

4 DOCUMENTATION PROVIDED BEFORE THE MEETING

Where it is considered that additional documentation is required in advance of a meeting, the company will be advised of this.

5 MEETING

In general, the meeting will be at the offices of the HPRA. If necessary, experts may join by teleconference. The meeting will be chaired by HPRA staff.

At the start of the meeting the company will be asked to provide a brief introduction and overview of the topic to be discussed.

While the advice will, in the main, be verbal, agreed actions will be recorded and circulated to the company for confirmation.

6 CONTACT DETAILS

For further information or guidance, please contact:

Email: compliance@hpra.ie (Please include 'GXP advice' in the subject line.)

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