HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Stakeholder Consultation on Registration of Processes exempted under Article 61(5) and applicable requirements under Article 61(6) of the CTR

INTRODUCTION

Article 61(5) of the Clinical Trial Regulation (CTR) (EU Regulation 536/2014) provides an exemption from the requirement to hold a manufacturer's authorisation for the following processes, where they are carried out in a hospital, health centre or a clinic participating in the clinical trial;

a) Re-labelling or re-packaging of the investigational medicinal product (IMP)
b) Preparation of radiopharmaceuticals used as diagnostic IMPs
c) Preparation of an IMP in accordance with a doctor's prescription or in accordance with a pharmacopoeial monograph.

Register of Exemptions

The European Union (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022 (S.I. No. 99 of 2022) defines, at national level, where the above processes can be performed and by whom. These national regulations also describe the requirement for these processes to be included on a 'Register of Exemptions' which is maintained by the HPRA.

A HPRA set of 'Questions and Answers on Article 61(5) Processes' has been drafted and includes a number of questions and answers to assist in identifying which processes are required to be included on the Register of Exemptions. These questions and answers are included as Appendix 1 to this consultation document.

The HPRA will publish an application form and associated guidance to be used for the purpose of registering processes which fall within scope of Article 61(5).

Appropriate and proportionate requirements that should apply to exempted processes

Under Article 61(6) of the CTR, the processes may also be inspected against appropriate and proportionate requirements. The Minister may publish these requirements as provided for in Regulation 30 (1)b of SI 99 of 2022.

The HPRA proposes that the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments is the appropriate core guidance for these processes. There are also questions and answers in this document dealing with its application and the inspection process.

STAKEHOLDER CONSULTATION

We are seeking feedback from stakeholders on the draft Questions and Answers on Article 61(5) Processes through this public consultation. We are also seeking feedback on our proposal to refer to the 'PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments' as the core guidance for the appropriate and proportionate requirements for the exempted processes.

How to participate in this public consultation is outlined below.

Documents for stakeholder consultation

Comments are invited from stakeholders on the following:

- The use of the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments as the basis for the appropriate and proportionate requirements for exempted processes carried out under Article 61(5) of the CTR.
- Questions and Answers on Article 61(5) Processes (See Appendix 1 below)

Format for submission of comments

Please identify the relevant document to which the comment applies.

- If the comment is general in nature then please state 'General Comment'
- If the comment relates to a specific aspect of the document, then please reference the particular section of the document to which the comment applies.

With regard to the Q&A document, additional questions or scenarios may be posed during this consultation period and a revised version of the Q&A may be circulated.

Please submit any comments to article61.5@hpra.ie by 22 August 2022.

APPENDIX 1- QUESTIONS AND ANSWERS ON ARTICLE 61(5) PROCESSES

1) What is the Register of Exemptions?

Article 61(5) of the Clinical Trial Regulation (CTR) provides for conduct of specific processes at hospitals, health centres or clinics without the need for a manufacturer's authorisation. S.I. No. 99/2022 European Union (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022, describes the requirement to include these processes on the Register of Exemptions which is maintained by the HPRA.

2) Does an authorised manufacturer need to register the processes described in Article 61(5) with the HPRA?

No. However, the type of activity (e.g. packaging) must be covered within the scope of the manufacturer's authorisation under which the site in question operates.

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The following questions are posed in the context of the processes described in Article 61(5) being carried out in a hospital, health centre or clinic (which can include a dispensing pharmacy).

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3) Can one hospital, health centre or clinic carry out an Article 61(5) process on behalf of another hospital, health centre or clinic?

A process which is being performed at a hospital, health centre or clinic may be carried out on behalf of other hospitals, health centres or clinics in Ireland which are participating in the same clinical trial.

4) Does a process carried out in relation to an IMP for a trial which is being conducted under the Clinical Trial Directive 2001/20/EC need to be registered?

No. The requirement for registration of these processes only applies to clinical trials which are conducted under the clinical trial regulation (CTR).

5) Does a process carried out in relation to an IMP under the CTR have to be registered prior to commencement of the process?

After the 31 January 2023, processes relating to IMPs for clinical trials conducted under the CTR should be registered prior to commencement of the activities. For clinical trials operating under the CTR prior to this date, an application for registration should be submitted in relation to any processes before 31 January 2023.

6) Do the processes of reconstitution or dilution of an IMP need to be registered?

Registration is not required for the reconstitution processes for IMPs which fulfil the conditions outlined in the Detailed Commission guidelines on good manufacturing practice for investigational medicinal products:

'Reconstitution of investigational medicinal products is not considered manufacturing, and therefore is not covered by this guideline. The reconstitution is understood as the simple process of dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or diluting or mixing the investigation medicinal product with some other substance(s) used as a vehicle for the purpose of administering it to a trial subject.

Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product. An investigational medicinal product must exist before a process can be defined as reconstitution.

The process of reconstitution has to be undertaken as close in time as possible to administration and has to be defined in the clinical trial application dossier and document available at the clinical trial site.'

7) Is placing of a pharmacy dispensing label on an IMP considered a relabelling process which must be registered?

Application of a routine pharmacy dispensing label, or other labels used as part of routine clinical practice, to an IMP, is not considered a relabelling process which requires registration. Application of a label to comply with clinical trial regulation labelling requirements, as outlined in Chapter X of Regulation 536/2014, requires registration.

8) Does the process of subdividing the IMP and labelling the product in separate containers intended for different clinical trial subjects have to be registered?

Yes. This process requires registration as a repackaging and relabelling process.

9) Does the process of blinding an IMP need to be registered?

Blinding of an IMP does not fall within scope of the processes covered under Article 61(5) and must be carried out by the holder of a manufacturer's authorisation for IMPs. This includes the processes required to blind the dosage form (e.g. over-encapsulation) or alterations to packaging to render the test product indistinguishable from a comparator or placebo.

10) Is the preparation of a radiopharmaceutical intended for use as a diagnostic IMP required to be registered?

Yes. The process of preparing a diagnostic radiopharmaceutical which is an IMP must be registered.

11) Does the process of preparing an IMP in a pharmacy in accordance with the requirements of pharmacopoeia (officinal preparation) have to be registered?

Yes. The process must be registered and the product must be prepared in a dispensing pharmacy and supplied directly to the patients served by the pharmacy in question.

12) Does the preparation of an IMP in a pharmacy in accordance with a doctor's prescription (magistral preparation) have to be registered?

If the preparation is in accordance with the approved instructions for the IMP, e.g. reconstitution or dilution, then this process does not have to be registered. However, if the preparation to the doctors order involves processes which are not included in the approved instructions for the product concerned (e.g. on product packaging) then this process should be registered, e.g. crushing tablets and mixing with a diluent in order to prepare an oral suspension for administration.

13) Can a hospital, health centre or clinic import a product from a third country for use in a clinical trial?

No. Importation from a third country is not covered within the scope of activities under Article 61(5).

14) What are the appropriate and proportionate requirements to be applied to processes conducted under Article 61(5) of the CTR?

Article 61(6) of the CTR requires that the competent authorities determine appropriate and proportionate requirements to be applied to the processes which are exempted from the requirement for a manufacturer's authorisation under Article 61(5). The HPRA considers that the

appropriate guidance for conduct of these processes is the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments.

Implementation of these guidelines will only apply to the processes which are carried out under Article 61(5) and not to any other activities which may be taking place at the hospital, heath centre or clinic. The extent to which these requirements apply will depend on the risks associated with the process.

The processes should be assessed by the registrant against the requirements described in these guidelines. Controls other than those described in these guidelines, which the registrant has justified within its quality system to provide an equivalent level of protection for clinical trial subjects and integrity of the clinical trial data, may be acceptable. Higher risk processes, such as those involving aseptic manipulations of a dosage form, will be expected to closely adhere to these guidelines, in particular Annex 1, unless there is strong documented justification supporting an alternative approach.

15) Will the HPRA conduct inspections in relation to the processes carried out under Article 61(5)?

In accordance with Article 61(6) of the CTR, the HPRA may conduct inspections of the processes carried out under Article 61(5) based on risk. The purpose of these inspections will be to determine if the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments has been satisfactorily implemented in relation to the processes carried out.

16) Will the HPRA conduct inspections prior to registration of a process?

It is not currently planned to conduct inspections of processes prior to registration. However, based on risk should the HPRA consider an inspection necessary, the applicant will be informed.

17) Will the registrant be informed if the HPRA intends to conduct an inspection?

The HPRA will inform the registrant of its intention to conduct an inspection in relation to these processes.

18) Will fees be charged in relation to the registration and inspection processes?

The HPRA is conducting a separate fee consultation process.