HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Registration of Processes under Article 61(5) of the Clinical Trial Regulation

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

INTRODUCTION

Article 61(5) of the Clinical Trial Regulation (EU Regulation 536/2014) (CTR) provides an exemption from the requirement to hold a manufacturer's authorisation for the following processes:

a) Re-labelling or re-packaging of investigational medicinal product (IMPs)
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 pharmacopeial monograph,

where these processes are carried out by authorised staff at a hospital, health centre or a clinic participating in the clinical trial. The European Union (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022 defines, at national level, the persons authorised to carry out these activities and includes a retail pharmacy business within the definition of a clinic. These national regulations also describe the requirement for the Health Products Regulatory Authority (HPRA) to maintain a 'Register of Exemptions' in relation to processes described above. Applications for inclusion of a process on the Register of Exemptions should be made on the 'Application for register for exemption' form.

QUESTIONS AND ANSWERS

The following questions and answers provide additional guidance on inclusion of processes on the Register of Exemptions and explain how processes are regulated by the HPRA.

1 What is the Register of Exemptions?

Article 61(5) of the 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.

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).

3 Can authorised staff of one hospital, health centre or clinic carry out an Article 61(5) process on behalf of other hospitals, health centres or clinics?

Yes, if the other hospitals, health centres or clinics are in Ireland and they 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 (CTD) 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 CTR.

5 Does a process carried out in relation to an IMP for a trial which has transitioned from the CTD to the CTR need to be registered?

Yes. If a trial approved under the CTD has transitioned to the CTR any processes carried out within the scope of Article 61(5) must be registered.

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

Yes. Processes relating to IMPs for clinical trials conducted under the CTR should be registered prior to commencement of the activities.

7 Can authorised staff in a research organisation within a hospital, health centre or clinic carry out an Article 61(5) process?

It may be acceptable for an Article 61(5) process to be carried out by research organisations within a hospital, health centre or clinic provided that the person who will be responsible for the process can act on behalf of the hospital, health centre or clinic. In this scenario, a written agreement should be in place between the parties. Research organisation personnel performing Article 61(5) processes should be appropriately qualified and should be delegated these activities by the principal investigator.

8 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, as follows:
'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.'

9 Is placing of a pharmacy dispensing label on an IMP considered a re-labelling process which must be registered?

No. Application of a routine pharmacy dispensing label, or other labels used as part of routine clinical practice, to an IMP, is not considered a re-labelling process which requires registration.

10 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 re-packaging and re-labelling process.

11 Could blinding an IMP fall within scope of a process performed under Article 61(5)?

Blinding of an IMP by altering labelling and/or packaging to render the test product indistinguishable from a comparator or placebo, may fall within scope of re-packaging / re-labelling processes covered under Article 61(5). Details of the intended blinding process should be provided with the application for registration of this process.

12 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.

13 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.

14 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 doctor's 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.

15 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).

16 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, health 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, are expected to closely adhere to these guidelines, in particular Annex 1, unless there is strong documented justification supporting an alternative approach.

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

Yes. The HPRA may conduct inspections of the processes carried out under Article 61(5) using risk based criteria. 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.

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

No. The HPRA does not routinely conduct inspections of processes prior to registration but reserves the right to conduct an inspection if necessary based on risk.

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

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

20 Are fees charged in relation to the registration and inspection processes?

Fees are charged in relation to the registration of exempt processes and any subsequent inspection of registered processes in accordance with the Guide to Fees for Human Products on the HPRA website.

CONTACT DETAILS

For further information or guidance, please email compliance@hpra.ie.