# Manufacturing study medication for clinical trials

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**Regulations applicable to the manufacture of study medication are dependent on the extent of involvement of the hospital pharmacy in the process.**

Hospital pharmacists have many tasks in relation to the provision of clinical trials services in a hospital. Here we focus on the role of the hospital pharmacist relating to manufacturing study medication, since in this area there have been many developments recently.

Directive 2001/20/EC of the European Commission, the Clinical Trials Directive, defines an Investigational Medicinal Product (IMP) as "A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form" [1]. Furthermore, it is stated that the principles of Good Manufacturing Practice (GMP) should be applied to investigational medicinal products. It is in Directive 2003/94/EC that these principles and their guidelines are laid down [2]. With respect to investigator-initiated clinical trials this Directive recognises their importance and takes into account the special position of trials whose planning does not require particular manufacturing or packaging processes if carried out with IMPs with a marketing authorisation and applied within this marketing authorisation. Here the simplified provisions for labelling are applicable. The guideline on the requirements to the chemical and pharmaceutical quality documentation concerning the IMPs in clinical trials is also applicable with statements about the safety of IMPs from a pharmaceutical point of view and the reproducibility of the pharmaceutical quality of the IMPs [3].

Directive 2005/28/EC, the Good Clinical Practice Directive, states that manufacturing authorisation is required for total or partial manufacture of IMPs and for processes of dividing up, packaging, or presentation [4]. However, no such authorisation is required for reconstitution prior to use or packaging when performed in hospitals by pharmacists and for exclusive use in these institutions. Therefore, it is clear that hospital pharmacists play an important role in clinical trial support and management and can significantly assist the medical specialist in their hospital in performing industry-sponsored, but especially investigator-initiated clinical trials.

## Manufacturing study medication

Since in clinical trials there may be an added risk to participating subjects treated with IMPs, compared to patients using marketed products, Annex 13 (GMP), Manufacture of Investigational Medicinal Products, was added to the Directive. The application of GMP to the manufacture of IMPs is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from the manufacture of the investigational product. It is intended to ensure that there is consistency between batches of the same IMP used in the same or different clinical trials, and that changes during the development of an IMP are adequately documented and justified.

The production of IMPs differs from the production of regular marketed drugs. Their production involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way [5].

IMPs must be manufactured in a GMP-licensed production unit in accordance with GMP and labelled in accordance with Annex 13 (GMP). Even if only packaging, blinding or labelling operations of batches of IMPs are carried out in a hospital pharmacy, a manufacturing license is necessary. Next, the IMPs must be released for use by a Qualified Person (QP). The QP should in particular be responsible for ensuring that there are systems in place that meet the requirements of Annex 13 and should therefore have a broad knowledge of pharmaceutical development and clinical trial processes [5]. Staff should be adequately trained, have a thorough understanding of the application of GMP to IMPs, and be accustomed to produce batches of study medication in a non-routine way. A highly effective quality system specially aimed at manufacturing IMPs in a GMP-licensed production unit should be operational and available to the sponsor. Documentation needs special attention, not only specifications for materials and products, manufacturing formulae and instructions, but

## A thorough understanding of the application of GMP to IMPs is needed.

also the product specification file. This reference file contains all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an IMP [5]. If, for example, essential information is missing from a label of an IMP, there may be a risk for a participating patient. Therefore it is of crucial importance that labelling of IMPs complies with Annex 13.

In a hospital pharmacy with a GMP manufacturing license several hospital pharmacists with different responsibilities are needed: a production pharmacist responsible for the unit which manufactures the product, a pharmacist responsible for quality control, a pharmacist responsible for storage and dispensing, and a pharmacist responsible as QP. So it is clear that only the larger hospital pharmacies will qualify for manufacturing IMPs.

### Study medication ready for use

Clinical trials performed in hospitals are very often related to the use of IV medication, like cytostatics or biological drugs with an existing marketing authorisation, for a licensed or unlicensed application. According to the authorised form these study medications should be safely prepared in a ready-to-administer-to-patient specific dosage form. A manufacturing authorisation is not required for reconstitution prior to use or packaging where those processes are carried out in hospitals by pharmacists, or other persons legally authorised in the Member States to carry out such processes, and if the IMPs are intended to be exclusively used in these institutions [4]. In this case a hospital pharmacy does not need a QP either. Nevertheless, at least two hospital pharmacists should preferably be present for production and releasing duties. The Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme has published a guide to good practices applying to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients [6]. This guide may be referred to when inspections of a hospital pharmacy are carried out by national health authorities and is important for a hospital pharmacy when preparing study medication for which a manufacturing license is not necessary.

However, each Member State of the EU may have different regulations for 'dispensing operations'. For instance in the UK according to The Medicines for Human Use (Clinical Trials) Regulations 2004 a manufacturing authorisation is not necessary for the assembly of an IMP if the assembly is carried out in a hospital or health trust by a doctor or a pharmacist or a person acting under supervision of a pharmacist and under condition that the IMPs are assembled exclusively for use in the trial site in which the product is to be used [7]. In The Netherlands for a hospital pharmacy a manufacturing license is not obligatory when study medication is reconstituted or prepared ready to use for a specific patient. The hospital pharmacy does need to have a GMP or GMP for hospital pharmacies [8] statement issued by the Public Health Inspectorate.

### Conclusion

Many aspects of manufacturing clinical trials study medications are laid down in directives and guidelines and as such are recommendations. Therefore, it is dependent upon the professional judgement and expertise of hospital pharmacists to ensure that study medication is of immaculate quality, whether manufactured or prepared ready for use in a hospital pharmacy, and can be safely used in clinical trials.


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