Trial medicine: from production to participants

Introduction

During clinical development the manufacturing and distribution facilities that are available for an authorised medicine may not be suitable for an investigational medicinal product (IMP), however this must not impact the quality of the IMP. All medicines both authorised and investigational must be manufactured, stored and distributed in accordance with good manufacturing practice guidelines (GMP), and some special consideration must be observed for IMPs. These are important to ensure the IMP can be safely administered to trial participants.

Manufacturing

How much trial medicine is needed for a clinical trial?

The amount of medicine used in a clinical trial (investigational medicinal product, IMP) required at each stage of clinical development differs:

- In early clinical trials (Phase I), small amounts (e.g. 5 to 50 g) are made in a laboratory.
- For Phase II and Phase III trials, larger amounts of IMP required for the trials (100 g to 1 kg) are manufactured in a production facility.

Once a clinical trial is approved, trial medicine requirements must be forecast and a plan for manufacture and supply put in place. IMPs can be either completely new medicines, or previously approved medicines used in a different way or tested in a new disease.

Considerations for manufacturing medicines for clinical trials

Type of medicine

Different medicines are produced in different ways, and some **manufacturing techniques** can be more complicated than others. For example:

- Biologics such as insulin are products of living cells or organisms and are therefore ‘grown’.
- Conventional medicines are manmade or ‘synthesised’.

Different medicines also have different **stabilities** and **shelf lives**. Therefore, manufacturers need to consider how much of an IMP can be made at any one time and for how long it will be active. For example, IMPs with low stability need to be made in smaller quantities but more frequently. The **form** of the medicine must also be considered. For instance, a medicine can come as a liquid, tablet, capsule or injectable solution.

Dosage and supply

It is important to ensure that an adequate quantity of the IMP is available for a particular clinical trial considering changes in the number of participants recruited to the trial, or stability of the medicine. Errors are not only costly but can also jeopardise the success of a trial and participant safety:

- **Over-forecasting** means too much medicine is produced, leading to waste (production costs are high).
- **Under-forecasting** means there will not be enough medicine to complete the treatment course and to successfully complete the trial.

Packaging

In the EU, the packaging of clinical trial medicine is regulated (the law defines what has to be printed on the package). In many clinical trials, the packaging must also allow for ‘blinding’ of trial medicines. The process of blinding is designed to ensure that participants and clinicians have no knowledge of whether a specific participant is taking the IMP or the comparator. Manufacturing processes must ensure that the trial medicine and the comparator appear the same, for example in colour and taste.

The design of the packaging must be carefully considered with regard to any physical difficulties that participants in the trial may experience. For example, ‘child-proof’ tops on bottles may be problematic for participants with arthritis.

Clinical trial location

An important consideration is where (in what region/range of locations) most of the medicine will be needed. Manufacturers have to decide where it is most sensible to make the IMP and how they will be able to supply it to the clinical trial centres, either in just one country or in a number of different countries. They must also consider the different rules and regulations for importing IMPs in various countries.

Quality control

Specific regulations apply to the production and quality control of IMPs – to minimise the risk to participants from poor quality control. In the EU, medicine manufacturers must follow the GMP guidelines for authorised and IMPs, which covers:

- **Quality management:** the system by which a manufacturer can monitor quality control.
- **Personnel:** the people involved in the quality control

process are suitably trained.

- **Premises and equipment:** the buildings and facilities used to make the trial medicine are clean and suitable for production.
- **Documentation:** collecting and storing information about the medicine and how it was produced.
- **Production:** how and under what conditions the IMP will actually be made (e.g. in sterile conditions) and how it will be blinded for the clinicians and trial participants.
- **Quality control:** the process of testing samples of the IMP to make sure that it is being correctly produced and meets specifications.
- **Recalls and returns:** the process for recalling an IMP if a problem is detected, including how unused medicines should be returned to the manufacturer.
- **Destruction:** how stocks of the IMP will be destroyed.

Distribution

An IMP is often distributed by:

- the manufacturer,
- the sponsor, or
- a contract research organisation (CRO) (a company hired to help the sponsor run its clinical trial).

The distribution of an IMP for a clinical trial can be complicated by the need to deliver small quantities to multiple clinics at different locations. Special storage conditions (for example low or constant temperatures) may need to be maintained throughout the distribution process.

Administration of IMPs

Medicines used in clinical trials can be given to participants in a range of different settings, from specialist clinical research centres, to units within general hospitals and other healthcare facilities. IMPs available in tablet or liquid form are often given to participants to take home, along with instructions on how and when they should be taken. Medicines that must be given to participants as an injection or an infusion often need the participant to visit their clinic.

Healthcare professionals (HCP) need to provide support and education to participants on how to take their medicine, how to store it at home, and give them any additional information to ensure that the participant can take the medicine in the way intended.

Some medicines used in clinical trials may have side effects that can be managed by using ‘rescue therapy’ provided to the participant in addition to the IMP. Healthcare professionals are responsible for making sure that participants understand when and how to take a rescue therapy if required. Participants will often be required to report back to the HCP about when and how often they had to use a rescue therapy. Therefore, it is essential that they are appropriately informed on how to record this.

Educating participants about the IMP they are taking, including when to take it, how to take it, and how to store it, is an important part of ensuring compliance (adherence) during the course of the clinical trial.

References

European Commission (2017). *EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines* Retrieved 12 July, 2021, from https://ec.europa.eu/health/documents/eudralex/vol-4_en

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