Points to consider when preparing the IMP dossier

Analytical validation

The Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) require that a tabulated summary of the results of the validation of analytical methods used in the control of the drug substance and drug product is included in the IMP dossier. There is no requirement for the inclusion of a full validation report. This should not be provided.

Batch analysis data

The Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) require the provision of representative batch analysis data. Batch analysis data for each company listed in the IMP dossier as a proposed site of manufacture for drug substance and for drug product should be provided. In this context, a company is regarded as a legal entity. In the same way, a substantial amendment supported by batch analysis data will have to be submitted and approved prior to the inclusion of manufacturing sites which represent a new company (legal entity). For biological and biotechnological products, batch analysis data will be required for each site of manufacture.

Retest period

The Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) requires the provision of stability data summarised in a tabular format. To ensure that the drug substance complies with its specification at the time of manufacture of the drug product, a re-test period based on the available stability data should be included in the IMP dossier. Extrapolation may be used in the setting of the re-test period. Where the drug substance continues to meet its approved specification and where the proposed re-test period is matched by acceptable real time stability data, no substantial amendment will be required to extend the re-test period. These provisions also apply to setting the shelf life for a biological and biotechnological drug substance.

Shelf life Section

The Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (external link) requires that a shelf life based on available stability data be set. Extrapolation may be used. Where an acceptable shelf life extension plan is included in the IMP dossier, no substantial amendment will be required to extend the shelf life of the drug product. For products coming within the scope of the 'Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials', an acceptable shelf life extension plan should comprise the following elements:

- specification against which the product is tested
- criteria used to extrapolate data
- analysis of trends
- proposed extension based on available real time data and acceptable accelerated data – this should not exceed four times the available real-time data to a maximum of 12 months or 12 months plus the available real-time data, ie:

Three months real-time data	12 months shelf life
Six months real-time data	18 months shelf life
12 months real-time data	24 months shelf life
24 months real-time data	36 months shelf life

The same principles can be applied to biological and biotechnological products where an acceptable shelf life extension plan should comprise the following elements:

- specification against which the product is tested
- proposed extension based on available real time data.

IMP dossier design
Where an IMP comprises multiple strengths of the product, only one IMP dossier is required. This should cover all strengths of the product. The provision of one dossier per product strength is not required.

Non-IMP dossier design
Guidance on the dossier requirements for non-IMPs can be found in the following guidance document, Guidance on Investigational Medicinal Products (IMPS) and 'Non Investigational Medicinal Products' (NIMPS) (Rev. 1,March 2011 located on the EMA website

Labelling
The European Commission's guidance requires the submission of trial labelling as part of the application for a clinical trial authorisation.

Where a sponsor wishes to claim an exemption from the need for trial specific labelling (under the provisions of Regulation 46 of SI 2004 No 1031, a statement to this effect has to be included in the application. This file should be named following the requirements for naming the file containing the labelling sample [4.12 Label].

Where labelling is revised after the clinical trial authorisation is approved, this may constitute a substantial amendment. However, there is no requirement

for the prior submission and approval of a substantial amendment where the change is to alter the particulars of items in the approved labelling eg a new

expiry date or a change in sponsor name or where the change is repositioning of the components of an approved label.

Manufacturer's authorisation

The manufacture and/or assembly (packaging and labelling) of an investigational medicinal product can only be undertaken by the holder of an authorisation for the manufacture of investigational medicinal products. A copy of the manufacturer's authorisation should be provided for each EU site undertaking any manufacturing step in the preparation of the test product or any comparator. Blinding of a comparator product by over encapsulation is manufacture.

This requirement to hold a manufacturer's authorisation does not apply in the following situations:

1. the manufacture or assembly is in accordance with the terms and conditions of a marketing authorisation relating to that product

2. the assembly is carried out in a hospital or health centre by a doctor, a pharmacist or a person acting under the supervision of a pharmacist; and the investigational medicinal products are assembled exclusively for use in that hospital or health centre, or any other hospital or health centre which is a trial site for the clinical trial in which the product is to be used.

Where manufacture and/or assembly occur outside of the EU, the product has to be imported by the holder of a manufacturer's authorisation covering the activity of importation of IMPs. A copy of the manufacturer's authorisation should be provided as part of the application. In addition, a copy of the QP declaration on GMP equivalence to EU GMP should be provided.

A template for the qualified person's declaration equivalence to EU GMP for Investigational Medicinal Products manufactured in third countries is available under Chapter III of EudraLex Volume 10 on the European Commission website:

EudraLex - Volume 10 Clinical trials guidelines

The QP declaration is usually signed by a QP named on the manufacturer's authorisation of the importer but may be signed by a QP at the batch release site if this is different. In such cases, a copy of the manufacturer's authorisation for the batch release site is also required. The QP declaration is trial and product specific.