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LABELLING REQUIREMENTS FOR INVESTIGATIONAL MEDICINAL PRODUCTS IN MULTINATIONAL CLINICAL TRIALS

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Abstract: The labelling of Investigational Medicinal Products (IMPs) plays a critical role in ensuring the safety, traceability, and regulatory compliance of clinical trials conducted across international borders. This study examines the diverse labelling requirements imposed by major regulatory authorities, including the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and other national bodies, highlighting both harmonized standards and jurisdictional discrepancies. Key elements such as product identification, dosage instructions, storage conditions, trial protocol references, and sponsor information are analyzed in the context of Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) guidelines. The paper also explores challenges faced by sponsors in multinational trials, including language translation, regulatory alignment, and logistical complexities. Ultimately, the analysis underscores the need for greater global harmonization to streamline trial operations, reduce administrative burden, and uphold participant safety across diverse regulatory landscapes.

Key Words: Investigational Medicinal Products (IMPs), European Medicines Agency (EMA), Labelling Requirements, Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) guidelines.

I. INTRODUCTION

In the realm of international clinical research, the labelling of Investigational Medicinal Products (IMPs) is a critical regulatory and operational requirement that directly impacts patient safety, trial integrity, and regulatory compliance. IMPs refer to pharmaceutical formulations used in clinical trials that are not yet approved for general medical use or are being tested for new indications, dosages, or formulations. As these products are administered to human subjects under controlled experimental conditions, their labelling must convey essential information to ensure proper handling, administration, and traceability.

The primary purpose of IMP labelling is to protect trial participants by clearly identifying the product, its intended use, and any specific instructions or warnings. This includes details such as the trial protocol number, dosage form, route of administration, storage conditions, expiry date, and the contact information of the sponsor. In blinded trials, labelling must also support the concealment of treatment allocation while maintaining compliance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) standards. International clinical trials introduce additional complexity due to the need for harmonization across diverse regulatory jurisdictions. Regulatory bodies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Health Sciences Authority (HSA) in Singapore, and others have established specific guidelines for IMP labelling. These guidelines vary in scope and detail, often requiring multilingual labelling, country-specific formatting, and adherence to local legal frameworks. For example, the EMA

mandates compliance with Annex 13 of the EU GMP guidelines, while the FDA emphasizes CFR Title 21 requirements for investigational drugs[2].

Moreover, the logistical challenges of multinational trials—such as re-labelling during shipment, managing auxiliary products, and ensuring consistency across trial sites—require robust planning and documentation. Sponsors must navigate these requirements carefully to avoid regulatory delays, protocol deviations, or risks to participant safety.

This introduction sets the stage for a deeper analysis of global labelling standards, common challenges in implementation, and emerging trends toward regulatory harmonization. Understanding these requirements is essential for clinical trial sponsors, regulatory professionals, and pharmaceutical manufacturers engaged in global drug development.

Labelling is an important and integral part of the approval of a medicinal product. This also applies to the investigational medicinal product (IMP) in clinical trials (CTs).

The IMP should be correctly labelled according to the mandatory information required by regulatory authorities. The label has to be permanently affixed to the container. The challenge is increased in multinational trials in which the necessity arises to give information in several languages (multi-lingual trials) as well as in trials in which several IMPs and/or medicinal products are used.
The compliance with the labelling requirements is important for all CTs during drug development. Non-compliance may cause problems during the later approval process for the marketing authorisation application (MAA) because this may be regarded as non-compliance with Good Clinical Practice (GCP).

The regulatory affairs (RA) manager is responsible for the labelling of a medicinal product, as he/she is the expert for the regulatory requirements as well as the interface to the contributing scientific experts. Therefore the RA manager should also coordinate the decision process for the labelling in CTs, also because this labelling is part of the basis for the future labelling.

1.1 Clinical Trials

CTs are conducted for a variety of reasons, the two major ones being:

- Academic research to gain more information about physiological processes underlying a certain disease
- The characterisation of the safety and efficacy of a new chemical entity (NCE) which is necessary for approval and evaluation of the clinical profile of an approved medicinal product in epidemiological studies

The different intentions also elucidate the range of different CT regarding the number of subjects, sites and investigators, which may be involved, the duration of treatment or the trial design.

1.1.1 Types of clinical trials

There are several ways of dividing trials into categories, depending on which criteria are supposed to be emphasised:

1.1.1.1 Phases of Clinical Trials

They can be classified according to the kind of intervention made during the conduct of the trial compared to the usual treatment a subject receives. The basic categories then are interventional and non-interventional trials.

Interventional trials are further subdivided into Phases I to IV reflecting the step-wise proceeding of drug development.

- Phase I trials are intended to evaluate the human pharmacology of a drug. The scope of the trial is to assess the tolerance of the drug, to describe pharmacokinetics and pharmacodynamics, to explore drug metabolism and possible interactions or to estimate the activity of the NCE. Phase I trials are, for example, the first administration to humans or bioequivalence studies. They are usually conducted in healthy volunteers. NCEs against cancer often are exemption to this rule as a characteristic of oncologic therapy might be the

induction of possible pre-cancerogenic mutations.

- Therapeutic exploratory studies are Phase II trials. They investigate the use for the targeted indication, estimate the dose range for the next trials and provide information for the choice of the best design of the Phase III trials. Endpoints often are pharmacological or clinical measures as surrogate parameters. In Phase II trials, short-term treatment is usually given to a small number of subjects of a well-defined homogenous patient group.
- If the results of the Phase II trials are positive therapeutic confirmatory trials are conducted (Phase III) to demonstrate significant efficacy of the NCE and to establish the safety profile and the dose-response relationship. They are usually very large and often comparative trials assessing "hard" endpoints like mortality or morbidity. This allows the assessment of the benefit-risk- relationship during the marketing authorisation procedure. Phase IIIb trials are those started after submission of the MAA to collect more information about the medicinal product. They may also serve as a pre-marketing activity.
- Clinical trials of Phase IV evaluate the therapeutic use of an approved product. Examples are pharmacoeconomic studies or large safety studies to detect rare adverse drug reactions. Interventions in this kind of trial can, for example, be inclusion or exclusion of patients to get further information about a specific subgroup of patients or the evaluation of additional (blood) samples or other examinations that are not part of the usual standard therapy, and that are pre- defined in the trial protocol.

In non-interventional studies the participant is treated like a patient not included in this study and the marketed drug product is used as described in the approved Summary of Product Characteristics (SmPC). This allows getting more information, especially about the safety of the medicinal product.

1.2 Legal Framework of Clinical Trials

The conduct of CTs takes place in a highly regulated environment. Therefore a lot of national and supranational requirements apply.In 1964, the World Medical Association General Assembly adopted the ethical principles for medical research involving human subjects as the "Declaration of Helsinki". It is in first line addressed to physicians. Nevertheless, the amended Declaration is the worldwide-agreed policy for the conduct of CTs and the protection of the subjects. The requirement of ethical and scientific review of the trial protocol expressed in the Declaration is implemented in the national legal conditions for the conduct of CTs.In 1996, the ICH adopted the Guideline for GCP [E6 (R1)] that explicitly refers to the ethical standards of the Declaration of Helsinki. It defines GCP as an international quality standard for CTs with human subjects in ethical and scientific respects. Adherence to the guideline should assure the protection of the rights, safety and well- being of the subjects as well as the reliability of the data generated in the CT. The latter target is intended to facilitate acceptance of the same clinical data by regulatory authorities worldwide.The ICH-guideline and therefore also the Declaration of Helsinki are implemented in national law, especially in the three ICH regions EU, Japan and US. Detailed provisions and instructions are given in national guidelines.But apart from this, further national requirements have to be taken into account, these may not explicitly address the conduct of CTs but address the involved parties like investigator, manufacturer and pharmaceutical companies. For example the investigator who is employed at a university hospital additionally has to follow the requirements for governmental employees, from the side of clinical management board of his/her employer, from the local EC, from the medical board, and possibly also from the patients health insurance.As already mentioned in chapter 2.2.3 a positive opinion from the EC and an approval from the CA for the CT are necessary as well as a manufacturing authorisation for the site(s) where the IMP is produced (e.g. in Germany issued by the regional council, which is an additional authority to address).

II. METHADOLOGY

2.1 Regulatory Background in Europe

Good Clinical Practice

The Clinical Trials Directive 2001/20/EC was adopted to improve

- Protection of subjects in clinical trials through
  - Adherence to the Declaration of Helsinki
  - Risk assessment based on toxicological results

- Protection of confidential personal data
- Approval processes by ethics committees and competent authorities
- Informed consent of the subjects and special provisions for those not able to give legal consent

- Harmonisation of regulatory requirements in all EU-MS
- Competitiveness and effectiveness of European research taking into account the requirements of pharmaceutical industry and non-commercial researchers
- Transparency (databases on CTs [EudraCT] and pharmacovigilance EudraVigilance])
- Verification of compliance with GCP by inspections

This directive also points out the necessity for special provisions for labelling of IMPs. More details about this will be given in chapter 3.

The Commission Directive 2005/28/EC lays down principles and detailed guidelines for GCP as regards IMPs for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. It strengthens and clarifies some topics of the Directive 2001/20/EC, especially concerning GCP and inspections. It further extends available GMP-guidance for medicinal products to IMPs and also states detailed requirements for the manufacturing and import authorisation needed for IMPs.

The implementation of the directives mentioned above in the national law of the EU-MS is either already done or still in progress.

Compliance with GCP requirements during the conduct of CTs has to be explicitly confirmed in the final reports for each CT and in the clinical overview (module 2.4 of the MAA application dossier) for the whole drug development programme. Non- compliance with GCP requirements may therefore put at risk the whole MAA application.

Good Manufacturing Practice

The manufacturing of IMP includes not only the production and packaging itself but also the labelling with the information approved by the competent authority and the release of the final IMP.

The Commission Directive 2003/94/EC lays down the principles and guidelines of good manufacturing practice (GMP) with respect to medicinal products for human use and IMPs for human use. The title already indicates that the existing provisions for approved medicinal products are extended to IMPs. Requirements for labelling of IMPs are considered necessary to protect subjects in CTs and to ensure traceability of IMPs.

Requirements in non-EU Member States

Switzerland

In Switzerland the ICH-guideline E6 about GCP is implemented into national law although the Swiss are "only" observers of the ICH tripartite process. Further cross- references are also made to the relevant directives of the EU. Before the start of a CT, a positive assessment of the local responsible EC and a notification of the Swiss authority Swissmedic are required.

In summary, the requirements in Switzerland regarding the conduct of CTs can be regarded as in line with requirements in EU-Member States (EU-MS).

Japan

As Japan is member in the ICH process the relevant guidelines for the conduct of CTs are implemented. Therefore approval of an institutional review board (EC) and notification of the authority (Pharmaceuticals and Medical Devices Agency which then notifies the Ministry of Health Labour and Welfare) are needed for the conduct of a CT.

United States of America

In the US, the ICH guidelines are also implemented as the authority and industry association participate in the consultation process. The principles of GCP and GMP as well as the requirement of previous assessment of the CT by the responsible IRB and authority are applicable for CTs in the US.

The review by the authority FDA (Food and Drug Administration) is carried out on the basis of an IND application, which is an exemption to the requirement of approval for drugs applied to man. The IND is submitted for the first CT in humans, including results of chemical and pharmaceutical development and nonclinical testing as well as the trial protocol. For additional CTs with the same compound, this IND is amended with the subsequent trial protocols (including labelling/updated labelling).

The FDA does not officially approve CTs. When a sponsor submits a study protocol to the FDA as part of the initial application for an IND, the FDA has thirty days to review the application and place the trial on hold if there are any obvious reasons why the proposed trial should not be conducted. After 30 days without feedback from the FDA the CT can be started.

2.2 Implementation of the EU-labelling requirements Austria

Austria has not implemented specific labelling requirements for IMPs.

In the Austrian Drug Law it is stated that the information "for clinical trial use only" ("zur klinischen Prüfung bestimmt") should appear on the label.

According to the IDRAC explanatory document on the IMP, the following information should be labelled additionally:

- Name of the manufacturer
- Trial reference code
- Batch number
- Expiry date (period of use)
- Storage conditions

With the exception of the name of the manufacturer, all this information is also required according to Annex 13. The information on the Austria label seems to be focussed on the IMP and the particulars required for its identification and tracking.
It may be possible to argue that the sponsor is responsible also for the manufacturing of the IMP and, consequently, it may be considered to be not necessary to label the manufacturer in addition if the sponsor is already labelled.

Therefore it seems possible to create one German labelling for Austria and Germany combining the requirements of both countries.

Belgium

Belgium has implemented the Annex 13 labelling requirements completely and without any amendments.

Nevertheless the requirement to give the information in the local language (German, French and Flemish) may cause some difficulties concerning the space on the label. Harmonisation with other countries (AT, DE, FR, NL) should be possible, as at least France and the Netherlands also have implemented Annex 13 without amendments.

Czech Republic

In the Czech Republic, it is not necessary to submit examples of the labelling with the CTA application. Requirements for the labelling follow Annex 13 with some deviations.

One deviation is that not the contact details of the main contact on IMP, CT and emergency unblinding are necessary on the label but only the name of the sponsor.

Furthermore it is explicitly stated that instructions for use and the information "for clinical trial use only" have to be given in Czech language.
In this context it is remarkable that the Czech CA can approve the placing on the market of individual batches for authorised medicinal products with the labelling in a foreign language. As a conclusive next step, it seems possible that also an IMP can be labelled in foreign language.

Both deviations from the Annex 13 result in reduced requirements of space on the labelling and facilitate a common label with other countries.

France

In France, the Annex 13 requirements for the labelling of the IMP were implemented in May 2006 without any deviations.

Germany

In Germany the Annex 13 requirements where implemented with some deviations, and further requirements where added.

For the subjects, the labelling of contact details (name, address and telephone number) of the sponsor and of the CRO (instead of "sponsor or CRO") offers more possibilities to receive information about the trial. This German requirement may be regarded as an over-fulfilment of the requirements as one contact point in addition to the investigator should be sufficient to provide satisfactory information for the subjects on the product, the trial and emergency unblinding.

The required EudraCT-number is only useful for the subject in the CT if he/she is requesting more information from the CA where the trial related information is archived according to this number. For the purpose of identification of the CT the trial code would be sufficient. But this information is also allowed to be given in a separate document.

Precautions for disposal are required in analogy to new SmPC requirements. Nevertheless the information is addressed to persons involved in the conduct of the CT, as study medication has to be returned from the subjects to allow assessment of compliance. These persons could also be informed via other means than the labelling.

In Germany it is not required to explicitly label the investigator, but it has to be possible to identify him/her from the trial reference code.

The same information as in all other languages on the same label also has to be displayed in German language. This does not mean that wording discrepancies have to be reflected. But additional information given in foreign languages – either required or voluntary – also have to be labelled in local language to inform the trial subjects as completely as possible.

In conclusion, the labelling requirements in Germany show several discrepancies compared to the Annex 13 and more differences than other member states. Some of them increase the bureaucratic burden without obvious benefit for the subjects or the proper conduct of the CT.

Italy

In Italy, Annex 13 is implemented with several deviations.

It is not necessary to label the route of administration, the quantity of dosage units, and in the case of open trials, the name/identifier and the strength/potency, the trial subject identification number/treatment number and where relevant, the visit number and the directions for use.

Information about the sponsor has to be labelled but not of a CRO who could be the main contact for

information of the subjects.

But in an addition to the Annex 13 labelling requirements, the address of the clinical centre is requested. Because also the name and address of the investigator have to be labelled this might only be relevant for cases where the trial is conducted in a clinical centre and the investigator can also be met for consultation in another clinical practice.

The Italian requirements are reduced compared to Annex 13. Focuses are contact addresses for the trial subject (although deviation from Annex 13) and basic information about the IMP needed for quality assurance.

The Netherlands

Annex 13 was implemented in the Netherlands with the one deviation that only the name of the sponsor instead of the name, address and telephone number of the main contact has to be labelled.

This implementation facilitates the creation of a common label with Belgium.

Spain

Spain implemented the Annex 13 requirements for the labelling of the IMP without any deviations.

Sweden

With minor deviations, the Annex 13 requirements were implemented in Sweden. These deviations are the possibility to omit address and telephone number of the sponsor or its representative if this information is given on a patient card the subject is instructed to carry always with him/her and the requirement to label only the name of the principal investigator.

United Kingdom

In the UK, the labelling requirements for IMPs directly cross-refer to Article 15 of Commission Directive 2003/94/EC (on GMP) where the requirements concerning the purposes of the labelling are given but no details concerning the contents.
The details for the labelling given in Annex 13 of the EU Guide to GMP can be considered to fulfil these objectives.

This pragmatic way of implementation of EU-requirements has the great advantage that full harmonisation is achieved and revision of the guidance document does not require any further actions.

III DISCUSSIONS AND SUMMARY

Appropriate labelling of IMPs should ensure the safety of subjects and the proper conduct of the CT. Therefore it should be possible to justify absence of some information which is either already included otherwise or unnecessary in the special case.

4.1.1 Essential requirements for the labelling

Some regulatory requirements can be considered to be essential for the labelling of IMPs:

- Name of the sponsor, CRO or investigator (main contact for information on the IMP, CT and emergency unblinding)
- Trial reference code to allow identification of CT and used IMPs
- Trial subject identification number/treatment number and where relevant visit number to allow proper handling of the (blinded) IMP during the trial
- "For clinical trial use only" or similar wording to inform subjects and all other persons having (accidental) access to the IMP about the ongoing risk-benefit- evaluation of the active substance
- Route of administration

- Quantity of dosage units
- In case of open trials the name/identifier and strength/potency
- Batch or code number to identify the contents and packaging operation
- Storage conditions to secure stability of the IMP
- Period of use to allow return of IMP after expiry although broader stability data might be available until then and this is associated with additional workload
- "Keep out of the reach and sight of children" to remind subjects not to put the safety of children at risk

These essential requirements are also reflected by the regulatory requirements for the labelling. They can therefore be regarded as an added value facilitating the design of IMP labelling.

4.1.2 Further requirements for the labelling

Further requirements to appear on the labelling of the IMP are duplications of information already included in the items above or may be sufficient to be stated elsewhere in the documentation handed out to the subjects. These are:

- Address and telephone number of the sponsor, CRO or investigator
- Name of the investigator
- Directions for use
- Pharmaceutical form
- Name of the manufacturer
- EudraCT number
- Precautions for disposal
- Same information in all languages (at least when additional country-specific requirements have to be labelled)

It should be possible to state duplicate information and especially the additional country-specific requirements in a leaflet. Especially in circumstances where this information does not provide additional benefit for the subjects and the safe conduct of the CT, some regulatory requirements on the IMP labelling may then be regarded as bureaucratic cost driver.

It depends on the skills and the detail oriented efforts of the RA manager if negotiations with the CAs can increase harmonisation of the labelling requirements for a special CT.
If a harmonised implementation of requirements within all EU-MS could be realised this would already represent a significant improvement. But the question remains how international harmonisation of the regulatory requirements for the labelling of IMPs can be achieved.

Conclusion: The correct labelling of an investigational medicinal product is an important and integral part of the conduct of a clinical trial.The labelling has implications not only for the safety and protection of the subjects but also for the identification, tracability and adequate use of the IMP as well as the identification and proper documentation of the clinical trial.Regulatory requirements provide guidance and added value with respect to these purposes. The deviations in the national implementation and some requirements also in particular settings of clinical trials, might be regarded as a bureaucratic cost driver when strict adherence to the guidance will not provide the intended benefit for the subjects and the safe conduct of the trial.The decision process on the labelling of the IMP is a complex task involving the expertise of several departments and therefore needs to be well organised.Purpose of the decision process is to define the best-balanced choice for the labelling of the IMP regarding regulatory compliance, optimisation of timing, and consideration of costs as well as facilitation of manufacturing and CT logistics. Alternatives for the labelling of the IMP in a multinational CT exist regarding the number of different labels to be produced, the timing of activities and technical issues. Early during the decision process, potential problems have to be considered and preventive measures to avoid them should be developed.As the regulatory requirements are the starting point for any considerations on the labelling and the RA manager is consistently not only involved, but in the centre of the workflow, regulatory affairs should be responsible to co-ordinate the labelling decision process of the IMP and throughout the life-cycle of the medicinal product.The RA manager has the task to optimise the labelling of IMPs in multinational CTs. Striving for harmonisation in skilful negotiations with the CAs can reduce the bureaucratic costs. This further increases the added value provided by the detailed labelling requirements.A

harmonised implementation of requirements within all EU-MS would represent a significant improvement on the way to an international harmonisation of the regulatory requirements for the labelling of IMPs. But currently it is unclear how the latter can be achieved.

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