Labelling Requirements for Investigational Medicinal Products in Multinational Clinical Trials: Bureaucratic Cost Driver or Added Value?

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vorgelegt von

Dr. Astrid Weyermann

aus Herford

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Betreuer und 1. Referent: H. Jopp

Zweiter Referent: Dr. J. Hofer

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1 EXECUTIVE SUMMARY

The purpose of regulatory labelling requirements for investigational medicinal products (IMPs) in clinical trials (CTs) is to provide added value regarding

- Protection of the subjects
- Identification of the IMP
- Traceability of the IMP
- Proper use of the IMP
- Identification of the trial
- Proper documentation of the trial

The compliance with these requirements is important for drug development as non-compliance may cause problems during the approval process.

The detailed regulatory requirements for the labelling of an IMP are described and the differences are discussed for several countries of the ICH regions. It is concluded that especially the divergent national implementation of the EU-requirements may be regarded as a bureaucratic burden. This may result in increased costs especially in multinational clinical trials without providing additional benefit for subjects and safe conduct of the CT.

The regulatory requirements compiled and summarised by regulatory affairs (RA) provide the basis of the decision process to make the best-balanced choice for the labelling of the IMP. To assume the responsibility for the labelling throughout the life cycle of the medicinal product, RA will organise this decision process, which involves close cross-functional communication of several departments and where RA is the interface to all stakeholders of the workflow.

A proposal for the organisation of the workflow is described. It can be regarded as a *pars pro toto* example for several other workflows involving multiple departments and organised by RA. Possible alternatives for the labelling decision and also measures to avoid potential problems are discussed in general terms focussing on compliance issues, technical and logistic feasibility as well as adherence to timelines.

The RA manager optimises the labelling of IMPs in multinational CTs to reduce the bureaucratic costs and to maximise the added value of the labelling requirements.
Nevertheless, the question remains how to achieve international harmonisation of the regulatory requirements for the labelling of IMPs.

2 INTRODUCTION

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.

This master thesis is structured as follows: after more general information about CTs in this chapter, the regulatory requirements for the labelling are given in chapter 3. Then a flow chart for the decision process for the labelling in chapter 4 summarises what is discussed in detail in chapter 5.

2.1 Definitions

The definitions of the following terms are given in annex 9.1:

- Clinical Trial
- Multicentre Clinical Trial
- Investigational Medicinal Product
- Sponsor

These definitions are given in the ICH-guideline (E6) for GCP. Their implementation differs only slightly in the European Union (EU), Japan (JP) and the United States (US).

The definitions in the EU and Japan of CT and multicentre CT are more closely related to the ICH-definition than the corresponding US-definition in the Code of Federal Regulations (CFR). The EU definition added to the ICH wording the possibility to have more than one IMP and explicitly stated the possibility to have multicentre CTs in more than one European Member States (EU-MS). The Japanese implementation added as a purpose of CT the collection of documents for applications for manufacturing, import or variations. The paragraph of the CFR with

the relevant definitions was last amended in 1999, but is not harmonised with the ICH-guideline E6, which was published in 1997 in the Federal Register. The Federal Register definition of a clinical investigation elucidates the US perception that the use of a drug is either the use of an approved drug in medical practice or an experiment.

For the IMP the definitions differ considerably in the three regions. In the EU and the US the definition of the ICH was implemented with partly different wording. In Japan a very abbreviated version of the ICH-definition was implemented which omits approved IMPs but states that the use of the IMP is not necessarily aiming for approval. The US-definition of an Investigational New Drug (IND) on the CFR corresponds to the active substance. It therefore does not include information about the pharmaceutical form or placebos.

In all regions, a sponsor is defined by the responsibilities, which are taken over; in the EU and JP, the ICH-definition has been implemented in identical wording. In the US furthermore the sponsor is identified by the initiation of the trial whereas in the EU and JP the sponsor takes the responsibility also for this step of the CT.

2.2 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.

2.2.1 Types of clinical trials

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

2.2.1.1 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.

2.2.1.2 Design of Clinical Trials

In parallel or sequentially to the IMP, a placebo or one or more already approved comparator(s) can be investigated in another trial arm to compare the effects of the compound with the disease process without treatment or with existing therapy. These placebo-controlled or comparator-controlled trials are often needed for statistical assessment of the treatment effect on the predefined primary (and secondary) endpoints.

Trial subjects are then allocated in a randomised way into the different treatment groups to avoid bias. In an open trial, the investigator and the subject know which treatment is given. In single-blind trials, only the investigator is informed about the treatment dispensed, whereas in double-blind trials, investigator and trial subject only know the treatment options but not the treatment of this special subject.
In blinded trials, the blinding is established by a coding system for the IMP(s) which has to include a mechanism that allows rapid identification of the product(s) in case of a medical emergency but does not permit undetectable breaks of the blinding.

In trials with more than one treatment group, the different treatments can be given in parallel to two (or more) groups of trial subjects (randomisation then defines which treatment a subject receives) or in a cross-over design where the different treatments are given in a predefined order to all subjects (randomisation then allocates which treatment the subject receives first and which afterwards).

Depending on the disease under investigation and the available treatment options, support or escape medication might be necessary for preventive, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. An example is the simultaneous administration of (part of) the standard therapy together with the IMP (verum and placebo) to investigate an additional therapeutic option.

A CT can be conducted as a single site or multiple site trial, depending on the number of subjects to be recruited. If large trials with multiple sites are needed, the trial can be done in several countries in parallel. Especially the latter case is a challenge for the labelling decision process because requirements of all countries included in the multinational trial have to be taken into account.

2.2.2 Medicinal products in clinical trials

Depending on the design of the CT the IMP either is the product under investigation or the comparator and/or the placebo.

Support or escape medication which might also be administered in a CT is not defined as an IMP. Therefore the labelling requirements for IMPs do not apply.

Preparing exactly the same dosage form without drug can do blinding in placebo-controlled trials. This is usually feasible for a tablet of the same size, shape and colour. But the preparation of placebos for other pharmaceutical forms like, for example, a lyophilisate for solution for infusion can be a greater challenge for the pharmaceutical development to achieve the same appearance and characteristics before, during and after preparation of the solution.
A solid comparator for oral use can be blinded by over encapsulation.
Blinding in a comparator-controlled trial can also be done in the double-dummy technique where a placebo of the dosage form of the investigated drug or the comparator is applied together with the treatment. This is necessary when different dosage forms like a tablet and a solution for infusion or a topical treatment are investigated.

2.2.3 Activities during preparation of a clinical trial

Activities during preparation of a CT involve a lot of different functions between which clear and timely communication is essential for the efficient organisation of these preparations. In the following, only a general outline is given.

Related to the medical concept of the CT are activities like the development and agreement of the objectives and design of the CT, which has to comply with scientific state of the art and the appropriate guidelines in the planned markets. In case of doubt, clarification may be reached by asking for scientific advice of the relevant competent authorities (CA). Further activities include the preparation of the study protocol and the investigators brochure as well as the establishment of contacts with experienced investigators and opinion leaders for the planned indication.

Depending on the stage of development, the preparations for supply with IMP involves pharmaceutical research to develop the required dosage form, the conduct of the stability study for the IMP to establish storage conditions and shelf-life, the establishment of a packaging concept (especially for blinded trials) as well as the organisation of manufacturing, control, release and timely shipment to the sites.

Additionally, a lot of administrative requirements have to be taken into account. Some steps in the supply of the IMP may involve one or more contract manufacturers with who appropriate agreements have to be made in advance. Development, manufacturing and control of the IMP have to be documented for GMP compliance. If the medication in the trial includes a narcotic drug or a biotechnology derived substance, additional documentation and/or applications are necessary. In case the IMP has to be shipped to different sites, if need be even internationally (e.g. from the US in the EU or vice versa), the necessary applications for export and import have to be made in due time to avoid delays. The compilation of the investigational medicinal products dossier (IMPD) and other documents for the clinical trial application (CTA) is another time-consuming process. Among these documents is the labelling of the IMP, which will be discussed extensively in the following chapters. Finally, a positive opinion of the ethics committee (EC) / institutional review board (IRB) and a CTA of the CA is necessary to start the CT.

2.3 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).

2.3.1 Regulatory Background in Europe

2.3.1.1 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.

2.3.1.2 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.

In “Good Manufacturing Practices” (Volume 4 of the Notice to Applicants), a special Annex 13 gives detailed guidance on the manufacture of IMPs. It is identical to Annex 13 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. In this Annex 13, specific requirements for the labelling are given which are presented in annex 9.2 and discussed in chapter 3 of this master thesis.

2.3.2 Requirements in non-EU Member States

2.3.2.1 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).

2.3.2.2 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.

2.3.2.3 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.

3 REGULATORY COMPLIANCE: LABELLING REQUIREMENTS

The contents of the information on the labelling are defined in regulatory guidelines and approved by the competent authorities. The labelling of medicinal products is part of the manufacture. The qualified person (QP) can only release medicinal products when they are labelled according to the authority approval.

Samples of the label attached to IMP containers are part of the essential documents for the conduct of a CT. Before the trial starts they have to be archived in the files of the sponsor to document compliance with the applicable regulatory labelling regulations and appropriateness of the instructions provided to the trial subjects. In blinded trials, the labelling of IMPs should also protect the blinding.

According to the ICH-guideline on GCP, the sponsor should determine storage conditions and shelf life of the IMP as well as establish and communicate the relevant instructions for preparation and use of the IMP. It is pointed out that all involved parties (e.g. monitors, investigators, pharmacists, storage managers) need to be informed of these determinations. This could be done, for example, on the labelling.

General legal requirements for the labelling of IMPs in the EU are laid down in article 14 of the Directive 2001/20 and article 15 of GMP-Directive 2003/94/EC. The detailed provisions are given in Annex 13 of the EU Guide to GMP.
The same labelling requirements are also given in Annex 13 Manufacture of IMPs of the PIC/S Guide to GMP for Medicinal Products.

All information has to at least appear in the official language(s) of the concerned countries on the outer packaging of the IMP or, in cases when there is no outer packaging, on the immediate packaging.
In the Annex 13 itself is stated that the required information should be included on labels, unless its absence can be justified. As an example when the absence of information can be justified it mentions the use of a centralised electronic randomisation system.
The reason why certain information is expected to be labelled is stated in Annex 13 together with the requirement. This facilitates the implementation of the correct information on the labelling of a specific trial.

Both the outer packaging and the immediate container itself have to contain the same extensive information if they may be separated during conduct of the trial. Apart from the requirements in this general case, the GMP guideline on IMPs (Annex 13) also lays down adapted provisions for cases where a reduction of information is considered appropriate. These cases are the labelling for immediate containers where the immediate container and the outer packaging remain together, for small packaging units or blisters as well as for IMPs intended for non-interventional CTs with the approved product.

The detailed requirements for some non-EU-MS will be discussed in chapter 3.5.

Reasons for provisions about the labelling are

- To ensure protection of the subjects
- To enable identification of the IMP
- To ensure traceability of the IMP
- To facilitate proper use of the IMP
- To enable identification of the trial
- To facilitate proper documentation of the trial

The purpose of labelling requirements for IMP are already given in the guidance documents. This underlines the intention to provide benefit and added value for the subjects and the proper conduct of the CT and aims to prevent a general and superficial misinterpretation as a bureaucratic burden increasing the costs only.

3.1 Information related to the Clinical Trial

3.1.1 Name, address and telephone number of sponsor, contract research organisation or investigator

The requirement to state the name, address and telephone number of the sponsor, the contract research organisation (CRO) or the investigator on the labelling is made to ensure that the subject receives the contact details of the main contact for information on the product, the CT and emergency unblinding.

Annex 13 allows the exemption that address and telephone number do not have to appear on the label when the subject has been given a leaflet or card which provides these details and has been instructed to keep this in his/her possession at all times. This information can also be omitted on the immediate container where this and the outer packaging remain together throughout the CT as well as on blisters or small packaging units.

This information may be important for the subject in case of any questions, but in emergency situations also for other persons to receive the necessary information for appropriate support. Especially for the latter, fast access to information about the IMP used and the conduct of the trial may be mandatory to provide the required emergency treatment to the subject. Therefore this information is best provided where it is easily accessible. This can be on the labelling of the IMP as this could be most easily found or on the leaflet/card stored either with the IMP or in the wallet of the subject.

The name of the sponsor together with the trial reference code allows an unambiguous identification of the trial and the (blinded) IMP. It is therefore considered to be essential information. The exemption in the guidance document already underlines that the information about address and telephone number as such is important but not necessarily on the labelling.

3.1.2 Trial reference code

The trial reference code should allow identification of the trial, site, investigator and sponsor. It only has to be stated on the labelling if not given elsewhere in the documentation handed out the subject. On the other hand, it is information required on the immediate container itself, even when it either stays together with the outer packaging or is a small packaging unit or blister. Only on the labelling, the trial reference code is closely linked with the IMP to be used.

A trial reference code may especially be necessary when the same IMP is used in several trials in parallel to avoid confusion at all stages of the distribution chain (as all other information on the labelling may be identical) and to allow traceability of the IMP. This information is therefore essential all the people involved the conduct of the CT.

The trial reference code can be regarded as the analogue to the trade name of approved medicinal products. The important difference is that the trial reference code is unique for a trial of a certain sponsor, but not necessarily for all CTs of all sponsors. Involuntarily another sponsor may choose the same code, which then may lead to confusion if the name of the sponsor is not labelled because this code is not subject to an approval procedure like the trade name check. Therefore both particulars, the sponsor and the trial code, are essential to identify without ambiguity the CT and (indirectly) the IMP.

3.1.3 Trial subject identification number or treatment number

The information about the trial subject identification number or treatment number is necessary in blinded trials with more than one treatment. In this case the number allows identification and traceability of the IMP as well as of the subject who is treated with it. The latter is also applicable for open trials.

Where relevant, also the number of the visit has to be given on the labelling. This may be necessary in crossover designed CTs where the same subject receives IMP and comparator or different dosages of the IMP in a blinded sequence to allow documentation of the correct treatment scheme.

This information also belongs to the particulars, which cannot be omitted on special immediate containers (either remaining together with the outer packaging or being small or being a blister pack).

As this information is linking one special package of the IMP with the conduct of the CT, it has to be printed on the labelling. The proper administration of the IMP may depend on these numbers, which is essential for the safety of the subjects and the proper conduct of the CT. In blinded CTs omission of this number may result in ambiguity, which IMP was applied to a special subject, which may render the whole CT useless, as evaluation may be impossible.

3.1.4 Name of the investigator

The name of the investigator is only required on the labelling if not already included in the main contact information (see 3.1.1) or the trial reference code (see 3.1.2).

As the investigator is the main contact for the subject, this information is useful in a CT with several investigators for the subject as well as for documentation and follow-up purposes to facilitate proper conduct of the trial.

Especially for the latter reasons, identification on the labelling may be useful. But this information is clearly not essential for the conduct of the CT or the safety of the subjects. This information might be suitable to be given on the subject card or in another document handed out to the subject. Usually the subjects can be expected to remember who is their treating investigator (or at least where the written information can be found).

3.1.5 Directions for use

Directions for use are necessary to ensure the proper use of the IMP and therefore ensure protection of the subject. But reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product.

The information is of relevance for the subject or the person administering the IMP and therefore the proper conduct of the CT. Either a full explanation of the directions for use or a reference where this information can be found is required to appear on the labelling.
This is a pragmatic approach, especially for unusual administration schemes requiring some guidance. For the correct and safe conduct of the trial it may be a further support that the subjects are reminded of the proper use of the IMP on the labelling where it can be easily seen before administration.
But omission would not impair the proper conduct of the trial as the directions for use are given orally and also in writing – but not necessarily on the label – to the subjects. Although the directions for use are important for the subjects, the information can also be given on another document.
The question remains if a reminder where the directions for use can be found is really necessary on the label of the IMP where space is limited.

3.1.6 “For clinical trial use only”

The statement “for clinical trial use only” or a similar wording indicates that the IMP is not (yet) approved and the evaluation of benefit-risk-ratio is still ongoing. This may provide clearer identification to subjects than the numbers and codes on the labelling. It may also prevent misuse of the IMP, i.e. administration outside the scope of the trial.

This information as a reminder about the status of the IMP is therefore essential for the subject as well as his/her relatives or other contact persons. On the label, the information is nearest to the IMP.

3.2 Information related to the Investigational Medicinal Product

3.2.1 Pharmaceutical dosage form, route of administration, quantity of dosage units

The pharmaceutical dosage form, the route of administration and the quantity of dosage units in a IMP package are information for all persons handling the IMP during the distribution chain (from manufacturing to the subject) to enable identification and proper use of the IMP.
Additionally to the above stated items in the case of open trials, the name/identifier and strength/potency have to be given on the labelling which is important for full information of the subject.

In the case of immediate containers, which remain together with the outer packaging throughout the conduct of the CT and also in case of small immediate containers, the pharmaceutical dosage form and the quantity of dosage units can be omitted. Another exception is the route of administration, which does not have to appear on the labelling of the immediate container of oral solid dose forms when this container is not separated from the outer packaging during the trial.

It is important to state the pharmaceutical dosage form as additional information about the identity of the IMP on the labelling. But this information is not regarded as essential for the safety of the subject or identification of the IMP (which can be done by the information already on the label). The dosage form can be mentioned in another document together with the detailed directions for use.
The information about the route of administration is essential for the proper use of the IMP and therefore the conduct of the CT. Although the detailed directions for use are either given on the labelling or cross-referenced to another document handed out to the subjects, the route of administration can be regarded as the basic information related to the proper use. This information is either directed to the investigators administering the IMP or the subjects if they take the IMP. To avoid major medication errors (for example i.v. instead of i.m. injection or oral instead of buccal administration) this should be stated on the label.
The quantity of dosage units have to be stated on the label as this information is essentially related to the packaging process, the distribution and the accountability of the IMP, like handing out the appropriate amount of IMP to subjects, checking their compliance or collecting all distributed IMP after the end of the CT. To avoid any ambiguity the quantity of dosage units should be labelled on the IMP.
The identification of the IMP in open trials can be achieved by giving the name and the strength of the medicinal product as usual for approved medicinal product. This information is essential for the subjects, investigators and other persons involved in the conduct of the trial because it enables them to learn more about the IMP.

3.2.2 Batch and/or code number

The batch and/or code number (also called lot number or control number) of the IMP are important to identify the contents and its quality as well as the complete manufacturing process including the packaging operation. In all cases, they have to be displayed on the outer packaging and immediate container, even when they remain together or the latter is small or a blister.

The statement of the batch number on the labelling enables clear identification of the specific batch of the IMP. This is needed for the tracking of the IMP from manufacturing, control, release by the QP to the distribution to the subjects. It ensures traceability of the IMP and therefore the protection of the trial subjects. If the shelf-life of the IMP can be extended due to new stability data the IMP has to be re-labelled per batch or if anything is wrong with a special batch of the IMP this batch can be recalled. The information is therefore essential for the persons responsible for the proper conduct of the trial.

3.2.3 Storage conditions

The storage conditions are important to be followed to ensure the stability of the IMP and are therefore part of the essential requirements for safe use of the IMP.

The information is addressing all persons handling the IMP from manufacturing staff to the subject and is required to be communicated in the ICH guideline on GCP. It is important that the IMP is always stored properly to prevent degradation of the active substance and deterioration of pharmaceutical particulars (for example change in the hardness of tablets), which would impair the efficacy, and safety of the IMP.

The storage conditions are necessary on the labelling, as this is closest to the IMP, which has been stored. Only giving the information elsewhere would put the stability of the IMP at risk as it may be overlooked or forgotten.

3.2.4 Period of use

The period of use given as use-by date, expiry date or re-test date as applicable have to be stated in month/year format and in a manner that avoids any ambiguity. The period of use is tightly linked with the storage conditions.

As the stability studies of the IMP are often ongoing during the CT it may be necessary to change the period of use according to the available data by adding an appropriate label to the IMP. For quality assurance/GMP reasons this additional label should also state the batch number and should be fixed without hiding the original batch number. The re-labelling has to be done according to GMP and under the responsibility of the QP.

The period of use is important for persons responsible for the quality of the IMP as well as for investigators and subjects who receive, store and administer it. It is implicit that the period of use has to be stated on the labelling of the IMP, as this is specific to a certain batch.

The period of use is essential to subjects and investigators as well as monitors as it allows returning the IMP after expiry. It is not considered to be pragmatic to have a regularly updated list or any other means of substitute to provide the information about the period of use to the CT sites or to recall certain batches when the latest stability data are not favourable. When the IMP is returned, broader stability data might be available, but if this is not the case the safety of subjects might be impaired. Nevertheless, it is also recognised that the labelling of the period of use is associated with additional workload with respect to re-labelling of the extended shelf life.

3.2.5 "Keep out of reach of children"

This warning is required for all medicinal products and is also applicable for IMPs about whose risk-benefit-ratio even less is known than about that of approved drugs. This is especially true for the effects of accidental ingestion by children This warning is not required when the product is for use in trials where the product is not taken home by subjects as it is then unlikely that children will get hold of the IMP. This limitation points out that this information is addressing the subject.

As it is the IMP which may put children accidentally administering it at risk, this essential warning has to be put as close as possible to the IMP which is on the labelling. This should prevent that subjects store the IMP at a place where children may get and administer it accidentally as this, depending on the IMP, may be fatal or life-threatening for the child.

3.3 Deviating requirements for approved investigational medicinal products

For interventional CTs in the EU during which an approved medicinal product is used in the approved indication and without further packaging steps like blinding only two further trial-related particulars have be added to the original container. This is, first, the name of the sponsor, contract research organisation or investigator and, second, the trial reference code, which allows identification of the trial site, investigator and trial subject. This additional information should not obscure the original labelling.

It should be noted that in the Annex 13 for the approved IMP in CTs with the above-mentioned characteristics, only the name is required and not, as for other IMPs, also the address of the sponsor, CRO or investigator. If the sponsor is identical with the marketing authorisation holder this information is already included in the original labelling.

In non-interventional trials the marketed product is received via the established distribution chain and is used with the approved labelling. No further labelling information due to the use in the non-interventional trial has to be applied.

3.4 Implementation of the EU-labelling requirements

As an example, the implementation of the EU labelling requirements is shown for several countries. An overview is given in the annex 9.3. More details are discussed in the following sections.

3.4.1 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.

3.4.2 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.

3.4.3 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.

3.4.4 France

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

3.4.5 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.

3.4.6 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.

3.4.7 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.

3.4.8 Spain

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

3.4.9 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.

3.4.10 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.

3.5 Requirements in non-EU Member States

3.5.1 Switzerland

Compared to the EU regulatory requirements no additional information is necessary. The Swiss requirements directly refer to the EU directives and implement these, which is a valuable contribution to harmonised labelling in multinational trials.

As part of the documentation of the CTA application, Swissmedic requests copies of the labelling for the IMP, including batch number as well as certificates of analysis. This reflects a focus on the pharmaceutical quality of the IMP.

Because the labelling should be in the local language, a CT in several regions in Switzerland may require labelling in German, French and Italian. The necessity of up to three labelling versions in different languages is a challenge for the labelling of IMPs.

Concerning “for clinical trial use only” or similar wording, differences in the wording of the regulatory requirements in the EU and Switzerland where the same information is given with the expression “clinical trial medication” may exclude harmonisation. It depends on the success of negotiations concerning one harmonised wording giving the required information if the regulatory requirements are perceived as a useful guide for necessary information or as a bureaucratic burden.

3.5.2 Japan

The sponsor shall indicate the following information on the labelling of the IMP in the Japanese language:

- "For trial use only"
- Name and address of the sponsor of the CT (if the person does not reside in Japan, the name and country of the sponsor of the CT and the name and address of the CT in-country caretaker).
- Chemical name or identification code
- Batch number / manufacturing code
- Storage conditions and expiry date

In Japan, the labelling requirements focus on the identification of the IMP and the necessary information to maintain its quality during the CT.
Further a contact address in Japan has to be labelled for the trial subjects. The reason might be that, on the one hand, subjects could be reluctant to contact any address abroad due to higher effort and expense and that, on the other hand, foreign contact persons are considered unlikely to be able to provide comprehensive information in Japanese language.

Information about the specific CT (in case there are several with the same substance) can only be deducted from the batch number if no further information than the required particulars is labelled.

The Japanese definition of an CT is very similar to the ICH- and EU-definition. The definition of an IMP was derived from the ICH-wording but the differences do not provide an explanation for the different labelling requirements compared to the EU.

3.5.3 United States

In the United States, the labelling requirements for INDs are comparable to the ones for approved drugs. The label shall state the following information:

- "Caution: New Drug Limited by Federal (or United States) law to investigational use."
- Name and place of business of manufacturer, packer, or distributor.
- Quantity of contents (weight, measure, numerical count)
- Proprietary and established name of the drug (without compromising compliance with the blinding and assignment of the test substance versus the control) and its quantity
- Lot or control number yielding the complete manufacturing history

As an exemption it is not necessary to label the expiry date of the IND if appropriate specifications are met and this is demonstrated by stability studies and if the IND does not need reconstitution before use.
If the labelling information is also provided in Spanish language the required information has to be stated completely and in faithful translation.

The label has to be of appropriate space and the information has to appear in readable font size. The information on the labelling should not be false or misleading or state that the IND is safe or effective for the purpose of the CT.

A copy mock-up or printed representation of all labels and labelling to be provided to each investigator should be submitted. Information amendments should include updates of the labelling information provided in the previous IND. Because the labelling is part of the new protocol this requirement can be easily met.

The labelling requirements reflect the definition of an IND, which is independent of the pharmaceutical form, and, therefore, any information related to this in not required on the labelling. Furthermore these labelling requirements derived from the ones for approved drugs may be explained as a result of the definition of a clinical investigation, which is regarded as every use of a drug except the use of an approved drug in the course of medical practice.

3.6 Summary of labelling requirements

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.

3.6.1 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.

3.6.2 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:

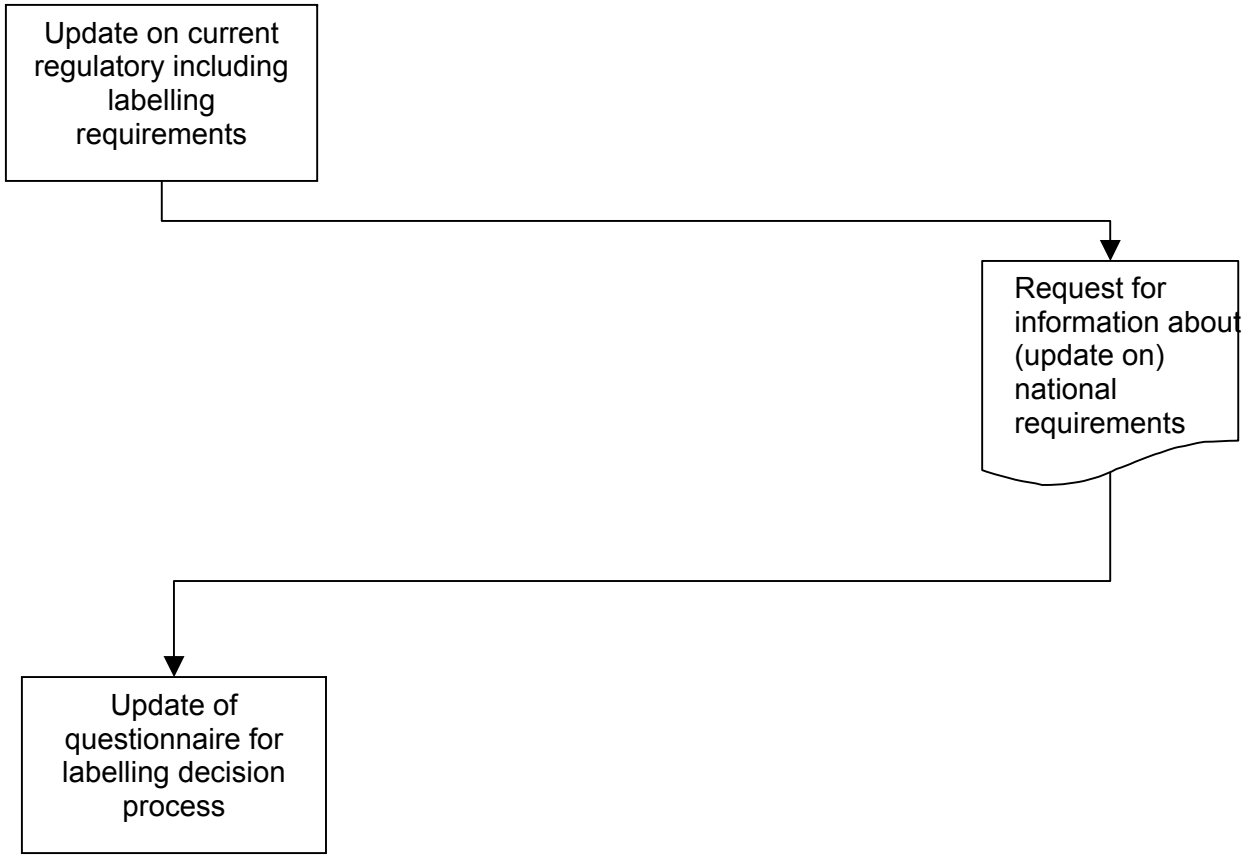
- Address and telephone number of the sponsor, CRO or investigator
- Name of the investigator
- Directions for use
- Pharmaceutical form
- Name of the manufacturer
- EudraCT number
- Precautions for disposal
- Same information in all languages (at least when additional country-specific requirements have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

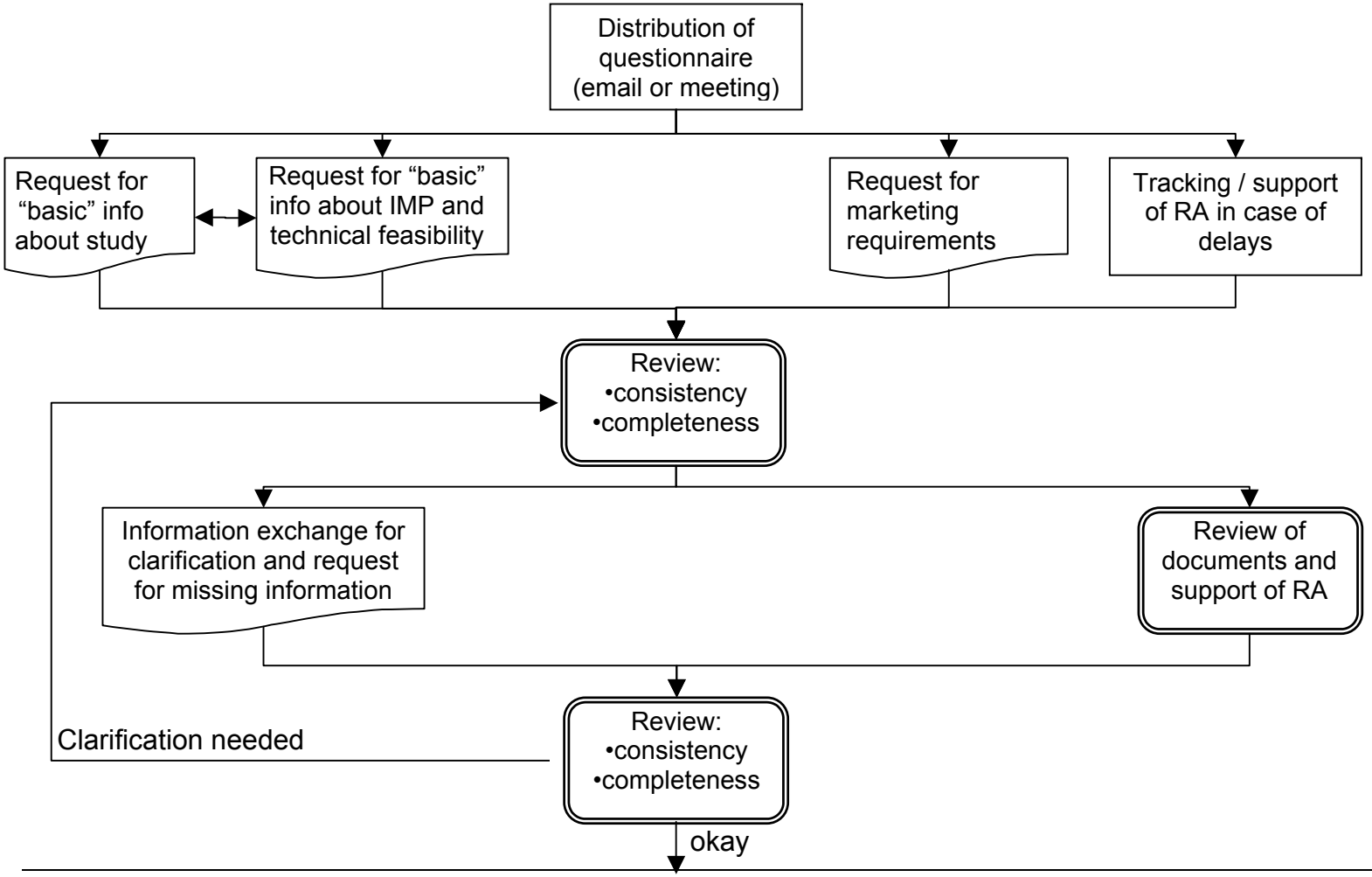
It depends on the skills and the detail oriented efforts of the RA manager if negotiations with the CAs can increase harmonisation of the labelling requirements for a special CT.
If a harmonised implementation of requirements within all EU-MS could be realised this would already represent a significant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

4 DECISION PROCESS FOR THE LABELLING – FLOW CHART

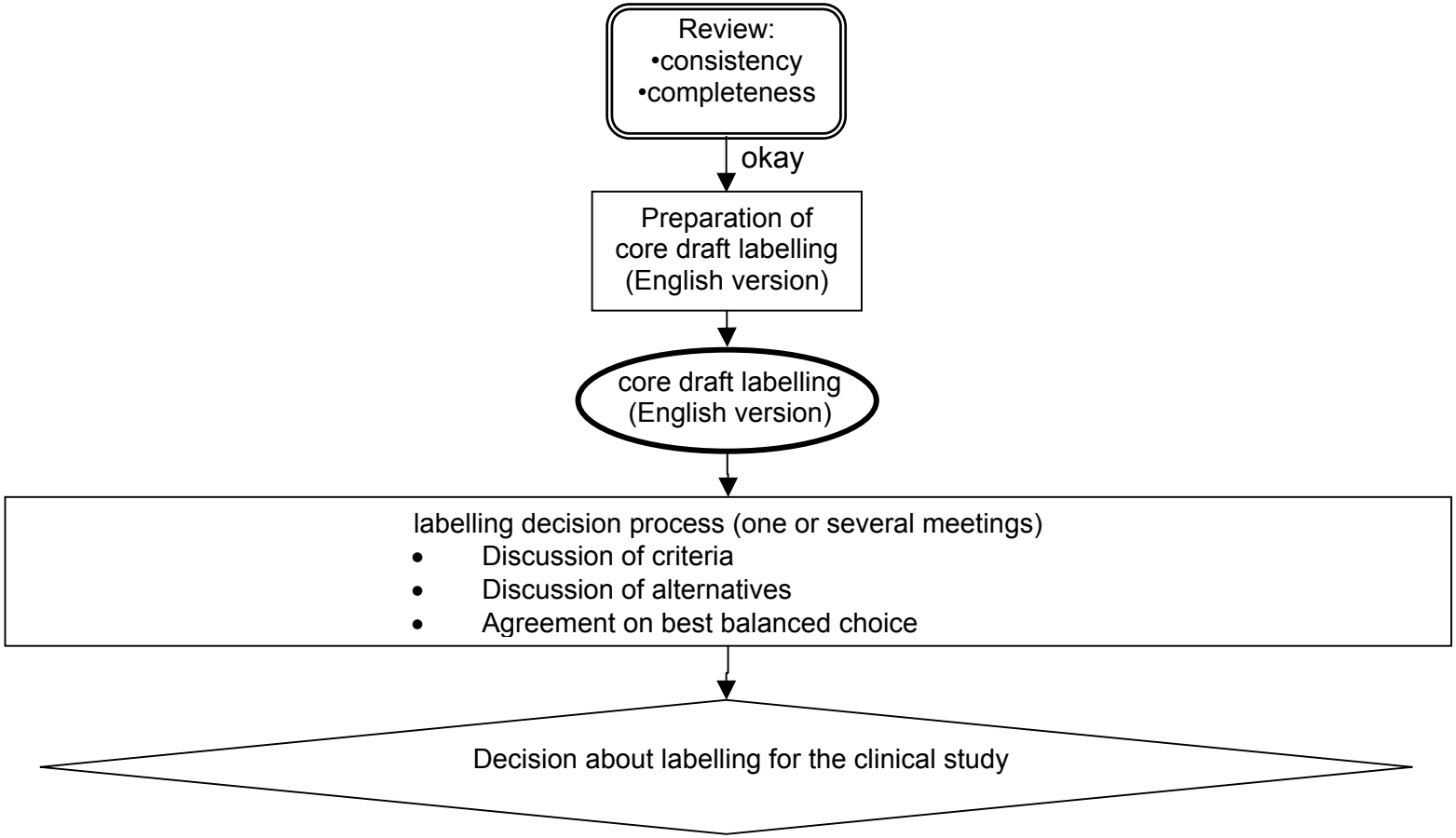
Clinical Research	Pharmaceutical Quality	Regulatory Affairs	Marketing	Project Management	Local Representatives



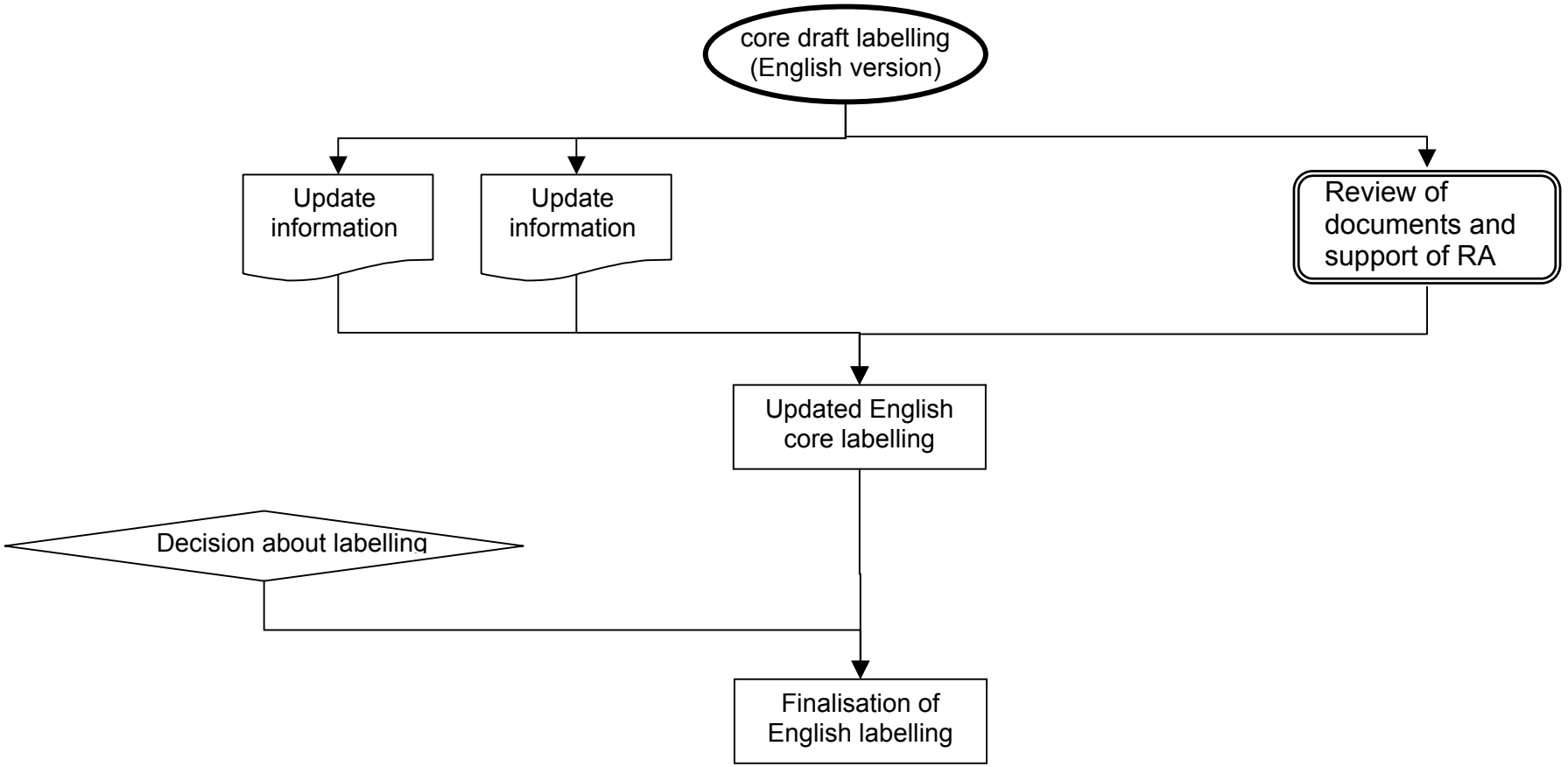
Clinical Research	Pharmaceutical Quality	Regulatory Affairs	Marketing	Project Management	Local Representatives



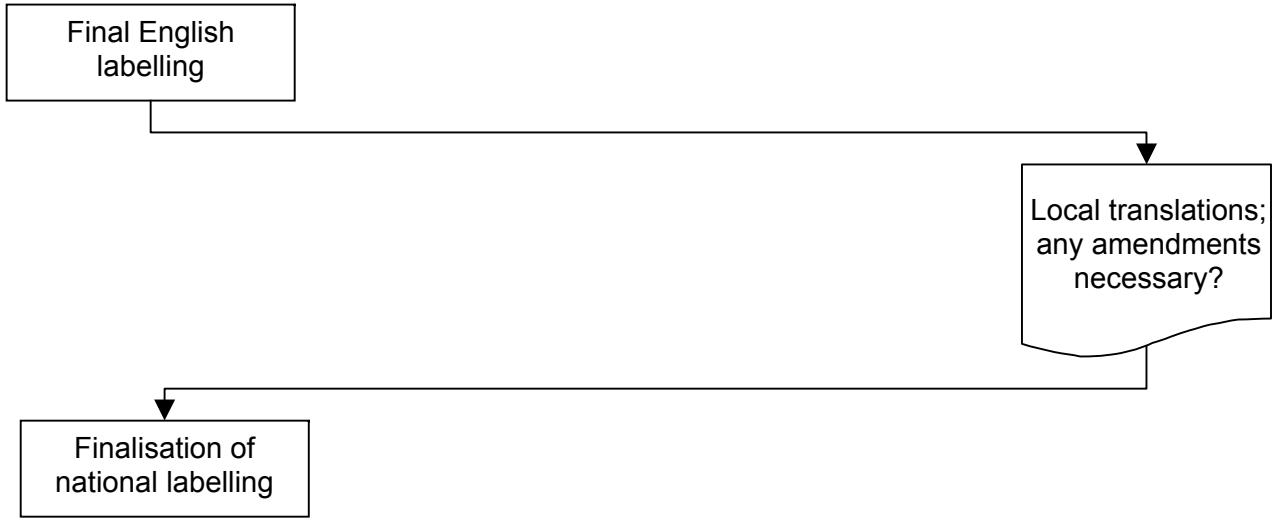
Clinical Research	Pharmaceutical Quality	Regulatory Affairs	Marketing	Project Management	Local Representatives



Clinical Research	Pharmaceutical Quality	Regulatory Affairs	Marketing	Project Management	Local Representatives



Clinical Research	Pharmaceutical Quality	Regulatory Affairs	Marketing	Project Management	Local Representatives



5 DECISION PROCESS FOR THE LABELLING

The decision process about the labelling of the IMP(s) for a specific CT is a task that requires input of (nearly) all stakeholders that are involved in the conduct of the trial. The labelling of medicinal products including IMPs is a core responsibility of RA. The design of an appropriate labelling for the IMP of a CT can therefore be seen as a *pars pro toto* example for a decision process under the responsibility of RA.

5.1 Decision statement for the team

The task for the labelling team can be summarised in the decision statement to find the best-balanced choice which label(s) should be used for the IMP in a certain multinational clinical trial with defined countries for the conduct of the CT.

5.2 Objectives for the labelling

The labelling of the IMP has to fulfil several criteria, which are either mandatory or "only" desirable. It generally depends on the special circumstances of a specific CT how the want-criteria are weighted in relation to their relative importance.

5.2.1 Regulatory Compliance of labelling information

It is mandatory that the labelling complies with the relevant regulatory requirements (must-criterion). Non-compliance may result in requests from the competent authority for amendment or clarification by the sponsor and can therefore delay the approval process.

The divergent national requirements in the countries where a specific trial will be conducted increases the regulatory challenge to comply with all labelling requirements.

Depending on the assessment of the importance of a special topic related to the criterion "regulatory compliance" the labelling might omit or replace some information and try to use the assumed margin of tolerance. An experienced RA manager acquainted with the competent authorities can assess where argumentation concerning deviations from complete regulatory compliance might be successful.

If space on the label is very limited (comparable to a small container) and the start of the trial is not time-critical (allowing re-design of the labelling if necessary to receive the CTA) some information not regarded as essential for the safety of the subjects and proper conduct of the trial might be omitted on the labelling, e.g. the company logo labelled instead of the full name and address which will only be stated in the leaflet.

5.2.2 Optimisation of timing

A must-criterion for the labelling is that the labelling is available in time to avoid any delays of the start of the trial. The early start (and finalisation) of a trial is closely related to the time to market of the IMP, especially in high-recruiting countries.

Therefore the start of the trial should be planned to happen as soon as possible after approval of the trial. In a multinational trial the approvals from competent authorities and the positive votes from the ECs cannot be expected to arrive at the same time.

The re-labelling of an IMP requires time and money. Especially the delay of the beginning of the CT is relevant to this criterion. Examples where re-labelling might be necessary before the start of the trial are the availability of more stability data allowing the extension of shelf life, i.e. postponement of the expiry date (of IMP labelled too early) and regulatory non-compliance due to previously unknown national requirements or due to a voluntary decision to omit certain information. As this will happen closely before the planned start of the CT the delay can only be compensated by faster recruitment (if at all).

According to GMP, the release of IMP for shipment to the sites of a certain country should only be done after CA and EC agreed to the conduct of the trial.

5.2.3 Consideration of costs

The direct and indirect costs of the process, which have to be taken into account, are a want-criterion.
Usually the work involved in the labelling is more expensive than the label itself. The consideration of costs furthermore includes aspects of facilitation of manufacturing and trial logistics.

Therefore it is important to avoid (unnecessary) duplication of any steps, e.g. by a too early finalisation of the labelling which then has to be changed due to changes in study design or countries to be included into the trial.

In contrast to the EU, no shelf life has to be stated on the labelling in the US. Re-labelling due to postponement of the expiry date is therefore a manufacturing step, which could be omitted if a separate label was chosen for the US.

5.2.4 Facilitation of manufacturing of the investigational medicinal product

The facilitation of the manufacturing of the IMP is also very important (want-criterion). Therefore it is advisable to not have more different labels than absolutely necessary, as it would be easiest to have only one label to apply to the IMP.

It should also be taken into account how many batches of the IMP are needed. If the batch size is too small and several of these small batches have to be produced, this also means additional workload for the pharmaceutical quality departments (responsible for manufacturing, control and release). On the other hand, the

uncertainty about the regulatory compliance of the labelling only applies to the first batch (which might need re-labelling in case of necessary amendments).

It might not be advisable to only label the IMP with country-specific labels after each national approval of the labelling, although this would make sure that the IMP is already labelled with regulatory compliant information in the first step. But this again requires sequential labelling campaigns of the manufacturer on short-term notice leading to planned delay in time compared to labelled IMP ready for shipment and an increase in costs. Additionally, this would mean the maximal amount of labels to be used in the CT.

5.2.5 Facilitation of clinical trial logistics

A further desirable want-criterion is the facilitation of trial logistics. This could be achieved by focussing on the question if one label for the IMP in all countries is possible.

During the conduct of the trial, higher recruitment than expected in a special country might require shipment of available IMP intended for other countries to this high-recruiting country to be able to finish the trial earlier than planned. In case of multi-language labels, this shipment is easiest and fastest possible without re-labelling of the IMP.

The re-labelling due to extension of the shelf life / postponement of the expiry date is not only cost intensive but also time consuming and a challenge for trial logistics. As it has to be done under the responsibility of the QP, the IMP needs to be collected from the CT sites, or the trial monitors can be trained to perform this at the sites. As no shelf life has to be stated on the labelling in the US, a separate label for the US could facilitate trial logistics.

5.2.6 Summary of Criteria

Must-Criteria have to be the mandatory, measurable and realistic. All of them have to be fulfilled by the alternatives eligible for further evaluation (Go/No Go-Decision). Regulatory Compliance and optimised timing of the labelling process are regarded as must-criteria for the labelling decision process.

Want-Criteria are “only” desirable. For the labelling decision process these are the criteria consideration of costs as well as facilitation of the manufacturing of the IMP and of CT logistics.

To make a complete order of importance the Must-Criteria have to be transferred to Want-Criteria. Then the team has to assign weights to the criteria. The ranking depends on the importance of the criterion for the decision to be prepared.

As a general case, the ranking for increasing importance, corresponding an increased weight, of the criteria would be as follows:

1. Consideration of costs
2. Facilitation of IMP manufacturing
3. Facilitation of CT logistics
4. Optimisation of timing
5. Regulatory compliance

5.3 Alternatives

All alternatives need to be evaluated during the decision process, which has to be based on the pre-defined criteria to make the best-balanced choice about the labelling of the IMP.

Alternatives are combinations of the number of different labels for a specific trial and the timing of activities during their preparation. In some cases, deviations from strict regulatory compliance may also be considered, provided sound arguments for these deviations can be given to the CA. Furthermore, technical aspects should be taken into account.

5.3.1 Number of different labels

The number of different labels for the same multinational trial can vary from one label for all countries to one label for each country. This, of course, has implications on all organisational and logistic steps during trial preparations and conduct.

5.3.1.1 One label for all countries

One label for all counties may facilitate logistics considerably. Examples are the prevention of mix-ups during labelling and distribution (not matching languages of label in immediate and outer packaging, if applicable), simplified assessment of label balance (number of used labels matching the number of IMP packages) or the shipment from one country to another (if needed during the conduct of the CT).
On the other hand, if it has to be changed for one country this also means a change for all other countries. Depending on the number of countries involved in the CT, one label may also be difficult to produce due to its limited size.

5.3.1.2 One label for each country

One label for each country would be the maximal number of labels possible. This might cause an unreasonably high workload for manufacturing and inflexibility for logistics.
But this also would allow close adaptation on the national requirements of each country without problems regarding the size of the label (or at least less difficulties if the container is very small).

5.3.1.3 Some labels for several countries each

A compromise could be the grouping of several countries and languages resulting in a small amount of different labels.
It would be reasonable to put countries with the same (like Austria and Germany) or related languages (e.g. Scandinavia, Baltic states or countries with romance languages) on one label or to combine countries requiring several languages (like Belgium or Switzerland) with the countries in which these languages are also required.

5.3.1.4 Special label for the US

As the expiry date does not have to be stated on the label of the IND in the US it might be worthwhile to have an exclusive label for the US in order to avoid re-labelling in case of availability of data allowing a postponed expiry date.

5.3.2 Timing of activities

The timing of activities is another topic where a decision must be taken between different alternatives. As the workflow regarding the labelling and the cross-functional cooperation during the trial preparations needs to be maintained only (more or less) limited timeframes are available during which a certain activity has to take place. Additionally, the setting of timelines for the labelling activities has to plan for success without neglecting the possibility of delays (for whatever reason), which could have an impact on the whole trial preparations.

5.3.2.1 Initiation of the labelling decision process

It may be important to initiate the decision process for the labelling at an early stage during the preparations of the CT to allow time for the necessary steps and the discussion about the best-balanced choice.

The first task might be for RA and the local representatives to provide regulatory input to update the regulatory requirements on the labelling of IMP. As this is not trial specific it may also be possible to receive this information from a regularly updated database.

Colleagues from all other involved departments are then informed about the outline of the labelling decision process, the regulatory requirements, which have to be met, and the tasks to be fulfilled by the different colleagues during this process. This could be done by email or during a meeting, which is either for the overall coordination of the CT preparations or concentrated on the labelling aspects of the trial.

The initiation of the labelling process should take place sometime between the decision to conduct a certain CT (e.g. defined by the trial objectives) and the definite decision about the trial design.

5.3.2.2 Finalisation of the English core labelling

The English core labelling for the multi-national label can only be finalised after the final decision about trial design.
As the trial protocol has to include a description of the dosage form, packaging and labelling of the IMP (in the chapter trial design), an agreement on the English core labelling to be included in the CT protocol needs to be achieved. This then reflects the design of the CT.

In conclusion, the English core labelling needs to be finalised in the time frame between the decision about the CT design and the finalisation of the trial protocol.

5.3.2.3 Finalisation of the national labelling

Based on the English core labelling, the national translations and country specific adaptations have to be designed. For a multinational label this requires a decision about the participating countries. The final national proposals to be submitted with the CTA application have to be agreed upon some time in advance of the submission to the CAs to allow the smooth compilation of the submission package by RA in cooperation with the local representatives.

To summarise, the national labelling should be finalised between the availability of the English core labelling and the CTA submission to the CA and EC.

5.3.2.4 Manufacture, Packaging and Labelling

The manufacturing of the IMP(s) might take place as soon as possible after the development of the dosage form(s) due to the time needed for the quality assurance of the IMP and the initiation of the stability study which should be possible with a preliminary label only indicating IMP related information.

For CTs with several and especially with blinded IMPs the packaging and labelling process usually is a very critical step as errors are difficult to detect but could make the whole trial useless. A clear labelling therefore is very important.

If different IMPs are needed for the CT they can either be stored as bulk (requiring additional investigations about the stability under these conditions) or be packaged and labelled immediately after manufacturing. In the latter case and if the IMPs are blinded the labelling is important to avoid a mix up of the different IMPs, but this, of course, requires a decision about the national labelling (to avoid re-labelling). But it also has to be considered that during the approval process of the CTA, requests regarding changes of the labelling might be received.

The release by the QP is not possible without favourable opinion from the responsible national EC and approval from the CA of each country. Supply of IMP to the CT sites therefore is not possible until the required documentation has been obtained.

In summary, the timing of manufacturing and labelling has the highest flexibility during this process and also a great impact on the beginning of the trial. It should therefore be considered carefully.

5.3.3 Regulatory compliance

As a general rule, strict regulatory compliance is highly recommended to avoid any problems for the approval and conduct of the CT.

Nevertheless, it may be necessary and appropriate in certain situations to slightly deviate from the requirements. Of course, this should only be considered if the safe conduct of the trial will not be impaired, reasonable arguments for the deviations are available which are likely to be accepted during the approval process, and strict compliance would cause relevant technical or organisational problems. Based on the individual case, this alternative could also be taken into account.

As the guidance documents are intended to provide added value to the safe conduct of the CT, it is explicitly mentioned (in Annex 13) that omissions might be possible if the absence can be justified or when the information is provided elsewhere.

5.3.4 Technical issues of labelling

A range of technical issues has to be taken into account to assure that the labelling information permanently stays on the packaging of the IMP.

The packaging material and its size and shape are chosen according to the dosage form of the IMP as well as according to an optimisation of storage conditions and shelf life. Additionally, facilitation of production, storage and handling during the trial should be considered. This may include automation and/or digital verification of the labelling.

It depends on the packaging material if the labelling information can directly be printed on it or if a label with the information has to be tagged on the packaging. If a label is used the adhesive material needs to be adapted to the container material and the storage conditions.

Furthermore, the material on which the information is printed and the printing “ink“ have to be adapted to each other. It is also important that the longevity of the printed information takes into consideration the recommended and the possible environmental conditions.

The labelling should prevent unauthorised breaking of the blinding and unauthorised changes of information.

The amount of information, which can be given on the labelling, depends on the size of the package. Nevertheless, it may be useful for the conduct of the trial to have multiple panel labels if technically feasible. One panel would then be permanently fixed on the packaging for information and identification; another one would be

removable for inclusion into the CRF to identify the administered IMP (of course without breaking the blind).

A technical possibility to reduce the amount of information required on the labelling is the use of a centralised electronic randomisation system. This is explicitly mentioned in the Annex 13 and therefore relevant at least for the EU.

5.4 Decision Analysis Matrix

A form for a decision analysis matrix is presented in annex 9.4.

For a specific case the available alternatives have to be clearly defined, for example with regard to the countries involved in the CT, the number of countries for whose labelling the size of the label is appropriate or the groups of countries to be combined for the alternative “some labels for several countries each”, possibly even resulting in several alternatives with respect to different groups.

In this example for a *fictive* CT the decision analysis matrix was filled to elucidate the process:
The alternatives for which the must-criteria are fulfilled are evaluated further. For each criterion the alternatives are ranked and this score is multiplied with the weight. The alternative with the highest sum of the weights can be regarded as the best-balanced choice.
For this alternative a potential problems analysis (see chapter 5.6) has to be performed to define preventive and contingency measures.

5.5 Organisation of the workflow

During the decision process for the labelling of the IMP in a multinational CT, contributions of the following functions are needed:

- Regulatory affairs
- Clinical research
- Pharmaceutical quality (responsible for manufacture including the labelling step, quality control and release of the IMP)
- Marketing
- Project management
- Local representatives (affiliates or CROs)

The coordination of the decision process should be the responsibility of RA. The flow of information from the scientific experts for the IMP and the CT starts with the regulatory requirements and can be structured in the same way as the compilation of the IMPD and the collection of information for the CTA at CAs and ECs. The allocation of the coordination to RA secures continuity during the life cycle of the medicinal product for submission of the MAAs and after its approval.

Other departments like those for clinical research or pharmaceutical quality have a major contribution of information for the labelling but they have to receive the most recent regulatory requirements for initiation of the process and should be asked to report all information for the submission (of the CTA as well as the MAA) to RA.
Disadvantage of the project management is that they have to collect and distribute all requirements and all information like a “post office” without own input except the coordination; nevertheless, project management can offer very helpful support in the decision process without being responsible for the coordination.

An open cross-functional communication and regular update information about the status of the labelling process and the resulting labelling drafts are important for a smooth and successful process.

5.5.1 Tasks of involved departments

A project team including representatives from all involved departments often is responsible for the development programme (for a NCE, line extension or generic). The aim of this development programme is to generate all data and documents required for a MAA. Stepwise but well in advance, the general outline of this development programme is discussed by this team. The development programme also presents a proposal for a decision of the whole company, i.e. in practice a general management decision.

The objectives and the planned timeline for a specific CT are therefore established before or at the beginning of each development phase (reflected in the phases of CTs presented in chapter 2.2.1.1). The involved departments therefore have the possibility to prepare for the prerequisites like capacities, equipment or earlier finalisation of a certain task (e.g. data from a nonclinical study, results of another CT, development of new pharmaceutical form, …) in advance.

5.5.1.1 Regulatory Affairs Department

Regulatory affairs should be responsible for the labelling of medicinal products from CTs to the approved product. They have an all around overview over the process and its requirements as well as established contacts to all stakeholders of the labelling and approval process. Therefore RA coordinates the labelling decision process.

Because the choice of countries to be included is often finalised later than the study protocol and because the national requirements are usually not study specific these general requirements can be regularly requested from the local representatives to be available on short notice (depending on the number of CTs a company is conducting and the frequency of changes of the regulatory requirements).

RA is participating in the discussion about the trial design regarding the compliance with clinical guidelines as well as the possibility or need for scientific advice.
In scientific advice meetings with CAs questions in drug development, which are not covered by existing guidelines or deviating from them, can be addressed. For a multinational CT usually several CAs are contacted to consolidate the expectations

on the development programme. The briefing documentation for scientific advice, which addresses requests about a special CT, may also include a proposal for a harmonised label, which then can be negotiated and agreed with the CA.

Once the decision for a CT is made, RA collects the necessary information from the involved departments as soon as this is available there and assembles it to a label, which complies with regulatory requirements. By using a standardised questionnaire, (see annex 9.5.1) the RA manager secures that all relevant information is available and appropriately included into the labelling.

An ongoing task during the preparations of the CT is the update of information, the review and consistency check of the labelling with regard to amendments in the trial design, changes of the characteristics of the IMP or choice of participating countries.

The RA manager coordinates the decision process for the labelling of the IMP by providing the consolidated information collected as a basis for the decision. He/she also invites for the meeting (or if necessary several) where the alternatives and the best-balanced choice are discussed. The decision process as well as the resulting labelling will then be archived for transparency, tracability and comprehensibility.

In parallel to the preparation of the labelling, the RA manager is involved in defining the requirements for the submission of the CTA which also includes the labelling as well as in tracking the progress and reviewing the documents for the submission of CTA and/or IND to CA and EC.

5.5.1.2 Clinical Research department

The planning and conduct of CTs is the core competence of the clinical research department.

As early as possible, all involved colleagues have to receive the general information about the trial like the trial code, planned timelines and duration, estimated number of subjects as well as about the IMP to be administered, like the pharmaceutical form, dosage of the active substance, pack sizes, planned application scheme, estimated amount of IMP needed etc.
This information is not only important for the labelling and preparation of the CTA but also for the pharmaceutical quality department.

Early communication about the characteristics of the CT is needed because the feasibility in the pharmaceutical quality departments has to be evaluated and the labelling, which will be part of the protocol, has to be finalised.

It consequently has to be considered that the communication has to be adapted to any changes that may be made to include the results of all discussions during the preparation of all clinical documents like protocol, IB and IMPD which may have an impact on the IMP and its labelling.

The clinical research department contributes to the decision process for the labelling, to provide background knowledge about CTs in general and detailed information about the planned CT. Furthermore the impact of the labelling decision on study logistics is important for their conduct of the CT.
The final label is archived in the trial master file.

5.5.1.3 Pharmaceutical quality departments

The pharmaceutical quality departments, namely the QP, are responsible for pharmaceutical development, manufacture, quality control and release of the IMP and are therefore needed from an early stage of trial preparations on. Their contribution for the labelling of the IMP is only a small part of their responsibilities in the conduct of the CT.

If pharmaceutical development of the pharmaceutical form with the correct amount of active substance is needed for the CT the requirements have to be communicated very early to allow enough time for this task. But depending on the phase of the trial, the pharmaceutical dosage form may already be available. A clear communication is needed, e.g. the dosage of active substance needs to be defined regarding the amount with respect to different salts or esters, if applicable. RA could facilitate this as they usually have an overview over the entire process. This information is also needed for the labelling and therefore the questionnaire for the labelling decision process can also help to support this step of the trial preparations.

For the planning of manufacturing and for the manufacturing of the IMP itself information from the clinical research department is needed about the number of dosage units per package (which is also required for the labelling), the total number of packages needed during the CT etc.

Information about technical feasibility like the size of the IMP package and the size of the label has to be communicated from the pharmaceutical quality departments for the decision process of the labelling. It is important to determine in how many different languages the required information can be printed on the label before the labelling decision can be made.

The input and participation of the pharmaceutical quality departments to the discussion about the best-balanced choice for the labelling is necessary to include in-depths knowledge about the pharmaceutical development including stability, manufacturing, control and release of the IMP and the impact of and on the labelling. Because the QP of the sponsor is the responsible person for the release of the IMP with the final labelling (approved by the competent authorities), the QP has to be closely involved in the decision process of the final English labelling.

To plan the conduct of the stability study in parallel and – if applicable – to organise the re-labelling of the expiry date information about the planned duration of the CT is necessary. For practical reasons, trial monitors often do the re-labelling of IMP at the sites, but the re-labelling step stays in the responsibility of the QP. Therefore the QP has to give the CT monitors clear and unambiguous instructions for the re-labelling.

The development and/or the production of the IMP can be outsourced to a contract manufacturer, which will then need even clearer and more structured communication and possibly some more time.

The final label of the IMP as well as confirmation that the national CA has approved the labelling is part of the documentation for release of the IMP and archived with it.

5.5.1.4 Marketing

Colleagues from marketing are usually involved in the design of the CT as the profile of the medicinal product to be developed has to reflect the marketing requirements like indication and target patient population.

Input of the marketing on the labelling is especially needed for phase IIIB trials, which can be part of the pre-marketing activities and phase IV studies, which are conducted with a launched medicinal product. It may be important to receive early feedback if the (later) recognition of a marketed product or at least the company is desirable.
At the labelling of IMP, the recognition of corporate identity and the medicinal products may be achieved, for example, by (corporate) design elements, a frame in the company colour or pictograms, which are intended to also be included in the approved labelling of the marketed medicinal product. It is not possible to use the planned trade name on the label of an IMP, which is not (yet) approved.

Of course a marketing colleague participates at the decision process to define the best-balanced choice for the labelling of the IMP, i.e. a company decision reflecting the expertise of all departments relevant for the development of the IMP.

5.5.1.5 Project Management

The project manager is closely involved in the whole process of preparations for the CT. For the decision process of the labelling, he/she will support the RA manager, especially by tracking of the necessary documents (on request and to avoid delays) and by review of documents received from the scientific experts or prepared by RA.

The project management participates in the labelling decision process because, according to their tasks, he/she has an overview over the development process. He/she aims to make the development project as a whole successful and tries to keep the overall timelines. This kind of input is necessary for the best-balanced choice as the final result is more relevant than e.g. any shift of timelines in between.

5.5.1.6 Local representatives

Affiliates (subsidiaries) or CROs are the local representatives, which have to be asked for information about additional or divergent local requirements for CTs and IMP labelling. This request can either be addressed regularly to the affiliates as it is not study-specific or early during the trial preparations at the involved CROs (if any).

The information obtained can be highly relevant for the decision to include or exclude a certain country.

When the countries where the CT is planned to be conducted are determined the local representatives are informed about the upcoming CT with some basic information like the objectives, the phase, the number of subjects and the approximate timelines for the next request for input, the planned submission for the CTA and for the EC opinion as well as the conduct of the CT.

The next request will then ask for an appropriate translation of the English core labelling or correction of a translation respectively. As the translation will include specialised terms it is important to involve local RA to detect deviations from the established expressions.

5.5.2 Summary of labelling process

Initiator of the labelling process is RA who, early during the preparations of the CT, compiles the current regulatory requirements regarding the labelling of the IMP. This also includes national requirements from all possible countries where the trial might be conducted. It seems reasonable to check with the local representatives if the available information needs to be updated.

In a first step regarding a special CT, RA will collect the core information for a labelling draft in English language. This request especially involves the clinical research and the pharmaceutical quality department. The pharmaceutical quality department should also be asked to check issues regarding the technical feasibility like the maximal possible size of the labelling (adapted to the pack size) as this input will be needed for the decision process. Possible marketing requirements, especially about design elements of the labelling, should be asked for already during this early stage of preparations to be able to take them appropriately into account during the decision process.
A questionnaire reflecting the current requirements and a request for any potential problems will either be distributed via email to all involved departments or preferably completed in a meeting, the latter at least as far as possible and already including clarification of inconsistencies. If the questionnaire could only be distributed via email or the information received during the meeting was incomplete the received information will be checked for consistency and completeness by RA. Possible discrepancies need to be clarified with all involved departments; missing information will be collected with update requests.
The project management can support the organisational issues like preparation of the meeting, tracking and reminding as well as the review of information.

The resulting core draft labelling is the basis for the decision process about the labelling of the IMP. The discussion should take place in a meeting (or if necessary several meetings) prepared and chaired by RA.
It allows making the decision about the number of different labels. But a prerequisite for this decision is that the countries where the trial will be conducted are known and

that information about the technical feasibility is available and they can be integrated into the decision.
The decision about the timelines may depend on the company policy and the organisation of the manufacturing process as the involvement of contract manufacturers needs to be taken into account.
It depends on the company's internal processes if the responsible colleagues of the involved departments "only" prepare the presentation of the best-balanced choice for the decision of the upper management (either during a meeting with all of them or by agreement of each line function achieved with the responsible colleague) or if this topic can be decided by them. Of course this has an implication on the timelines of the decision process, which have to be taken into account early.

In parallel to the decision process, a request for any update information on the core draft labelling resulting from changes of the trial design will be sent to the clinical research and pharmaceutical quality departments.
The core draft labelling will possibly be updated to comply with the final protocol, but only minor amendments are expected because otherwise (e.g. when the trial design is changed considerably), the best-balanced choice identified in the decision process might need revision. The resulting English core labelling will be included into the final trial protocol.

The English core labelling will then be sent to the local representatives, and it will be asked for translation and information about necessary amendments (if any). A timeline for the translation as well as information about the planned submission of the CTA and EC vote application should be given.
The translations of the local representatives and the decision about the labelling will then be compiled to the final labelling by RA.

The flow chart of the labelling process, which gives an overview over the activities, is depicted in chapter 4.
In Annex 9.5, a questionnaire is presented with which RA can initiate requests for information in the responsible departments, a checklist to facilitate RA review of the responses regarding consistency and completeness and a draft example of the English core labelling the decision process will be based on. It is based on the current requirements as described in chapter 3 and the annexes 9.2 and 9.3.

5.5.3 Timing of activities

The timing of activities depends on the alternatives (see chapter 5.3). The general necessities for the CT for which the decision will be made are usually available from other meetings with the project team responsible for the NCE/IMP.

RA could therefore early invite for a first labelling meeting during which (possibly among other topics like the preparation of IMPD and CTA or IND) the timing of the next steps is agreed. These clearly are closely related to the alternatives, which are available for the CT.

But because the preparation of the labelling usually does not last as long as the finalisation of protocol and IMPD, there is –for the general case– no time pressure expected. Therefore when requests are sent out they can be given a due date of several days to some weeks, depending on the complexity of the question and the timing during the process.

5.6 Prevention of potential problems

The early consideration of potential problems, which may have an impact on the labelling of the IMP, helps to address these appropriately and even to avoid them. Topics, which could be relevant for all trials, are given below and should be addressed by RA together with study-specific items the involved departments are aware of to define preventive measures. The workflow of the labelling is designed to collect information about potential problems early.

5.6.1 Request for label changes during approval process of the clinical trial

If the labelling is not compliant with current national requirements a request for change of the submitted labelling could be received during the approval process of the CT.

With the request for the CTA respectively also the EC opinion, the competent authorities and in some EU-MS also the EC (in DK, DE, IT, NL) receive the examples of the label in the national language. The detailed requirements given in the regulatory guidance documents for the labelling of IMPs provide some background information regarding their purpose, which underlines the added value, which is intended to be given.

If the labelling does not comply with the national requirements amendments may be needed to receive the CTA and the positive EC opinion. Requests for changes from CA or EC due to lack of regulatory compliance will have an impact on the timelines of the approval and may –in cases where the IMP is already labelled due to the necessity of re-labelling– delay the start of the CT as the IMP is not available as planned.

Regulatory compliance was defined as a must-criterion for the labelling to avoid this potential problem, which might delay the start and consequently also the finalisation of the CT.

5.6.2 GMP compliance – delay in release of IMP

The labelling of medicinal products is a part of the product, which has to be checked for compliance before release. According to GMP, the release of the IMP is only possible with an approved labelling.

The impact on the timelines may differ depending which alternative was chosen concerning the time when the labelling is attached to the IMP; but to avoid

unnecessary delays of IMP delivery to the sites the communication concerning CTA/positive EC opinion between RA and QP as well as with clinical research and the investigators needs to be clearly defined in advance. This includes the responsibilities of all functions as well as the contact persons and their substitutes (for the case of illness, business trips, …).

5.6.3 Manufacturing

The feasibility of the manufacturing with the labelling resulting from the decision process needs to be checked concerning potential technical problems and timing.

A potential technical problem can be the size of the label compared to the amount of information, which can be printed on it in a still readable type size (usually 6 point is the smallest type size allowed). This therefore is already included as technical feasibility in the collection of information for the decision process.

But also the availability of special types (symbols or foreign language with different script like Cyrillic, Greek or Japanese, but even some special letters in French, Spanish or Swedish) may –depending on the equipment– cause difficulties or delays.

Concerning the timing of the manufacturing, the potential problems depend on the alternative chosen during the decision process. The labelling part of the manufacturing can be done some time between soon after the manufacturing of the pharmaceutical form (requiring re-labelling in case of requests) and after receipt of the national approval (or even approvals in case of multinational labelling).
If the labelling (or re–labelling) should take place immediately after receipt of the approval this might have a considerable impact on the manufacturing department as capacities need to be shifted from other (possibly also urgent) manufacturing processes to avoid further delay of the start of the CT.

Clear communication about the possibilities and the associated problems as well as about the expected timelines can help to limit the associated difficulties.

5.6.4 Clinical trial logistics – concerning supply with correctly labelled investigational medicinal product

Smooth trial logistics concerning delivery of correctly labelled IMP to the sites require a sufficient amount of IMP with the national labelling of all countries participating in the multinational CT.

The decision about the number of different labels to be used therefore has major consequences on trial logistics.
In case of only one labelling for the whole amount of IMP the number of packages to be manufactured can be easily summarised from the amount for the trial and the pharmaceutical quality department (quality control, stability study, retain samples etc.).
But the larger the number of different labels the more IMP is needed as a reserve to avoid lack of correctly labelled IMP for certain countries that might require more IMP

than estimated. The expectation concerning recruitment of subjects in a certain country can be exceeded for example due to earlier approval and resulting in earlier beginning of the trial or faster recruitment of subjects.

It is therefore important to estimate correctly the amount of needed IMP for all countries and to manufacture some more IMP than planned to avoid lack of medication. If the IMP is very expensive this could be considered when making the choice about the number of different labels to avoid unnecessary costs.

5.6.5 Request for label changes during GMP or GCP inspection

An inspection is a review of the internal documentation of the company like SOPs or files of a CT or a certain batch by inspectors from an authority. GMP inspections already are well known, the possibility of GCP inspections was introduced by the Directive 2001/20/EC (implementation due in 2004), and currently, the first experiences have been gathered.

Possible questions of inspectors may concern the regulatory compliance of the labelling. Usually, only the national version of the labelling and no samples are submitted to authorities. Therefore the inspector might wish to confirm the identity of submitted labelling with the printed version, the choice of an appropriate type size or compliance with special topics like the German requirement to give the same information in all languages on the label.

An inspection usually takes place when the trial is being conducted. Therefore requests to change the labelling might require a recall of IMP, which definitively has a major impact on the conduct of the CT.

This might be one more reason to regard the relevant regulatory requirements and their detailed provisions –which facilitates compliance with them– as an added value for the conduct of the CT.

6 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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8 LIST OF ABBREVIATIONS

AT	Austria
BE	Belgium
CA	Competent Authority (= Regulatory Authority)
CFR	Code of Federal Regulations (US)
CH	Switzerland
CRO	Contract Research Organisation
CT	Clinical Trial (= clinical study)
CTA	Clinical Trial Authorisation
CZ	Czech Republic
DE	Germany
EC	Ethics Committee (EU; corresponds to IRB in US and JP)
EC	European Commission (in this text only in the context of the number of a Directive)
ES	Spain
EU	European Union
EU-MS	Member States of the European Union
FR	France
FSI	First Subject In
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier (part of the documentation needed for a CTA application in EU)
IND	Investigational New Drug
IRB	Institutional Review Board (US and JP; corresponds to EC)
IT	Italy
JP	Japan
LSO	Last Subject Out
MAA	Marketing Authorisation Application
NCE	New Chemical Entity
NL	The Netherlands
QP	Qualified Person (according to article 48 of Directive 2001/83/EC as amended)
RA	Regulatory Affairs
SmPC	Summary of Product Characteristics
SE	Sweden
UK	United Kingdom
US	United States of America

9 ANNEXES

9.1 Tabular overview on definitions

ICH: Chapter 1 of Guideline E6 (R1)	EU: Article 2 of Directive 2001/20/EC	Japan: CPAC-GCP Advised to MHW from CPAC (CPAC Notification No. 40)	US: CFR Title 21 Chapter I D Part 312 A § 312.3	US: Federal Register, Vol. 62, No. 90, pp. 25691-95709
1.12 Clinical Trial/Study Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmaco-dynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.	(a) clinical trial: any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmaco-dynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites,	2-20 Clinical Trial Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmaco-dynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy, and to collect documents for submission for approval applications for manufacturing or import of drugs or that for partial changes in the approved	Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.	1.12 Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmaco-dynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

ICH: Chapter 1 of Guideline E6 (R1)	**EU: Article 2 of Directive 2001/20/EC**	**Japan: CPAC-GCP Advised to MHW from CPAC (CPAC Notification No. 40)**	**US: CFR Title 21 Chapter I D Part 312 A § 312.3**	**US: Federal Register, Vol. 62, No. 90, pp. 25691-95709**
	whether in one or more than one Member State.	items.		
1.40 Multicentre Trial A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.	(b) multi-centre clinical trial: a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries.	2-19 Multicenter Trial A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.	-/-	1.40 Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.
1.33 Investigational Product A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used	d) investigational medicinal product: 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	2-35 Investigational Product A pharmaceutical form (whether or not related to be approved) of an active ingredient or placebo being tested or used as a reference in a clinical trial.	Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part.	1.33 Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used

ICH: Chapter 1 of Guideline E6 (R1)	**EU: Article 2 of Directive 2001/20/EC**	**Japan: CPAC-GCP Advised to MHW from CPAC (CPAC Notification No. 40)**	**US: CFR Title 21 Chapter I D Part 312 A § 312.3**	**US: Federal Register, Vol. 62, No. 90, pp. 25691-95709**
to gain further information about an approved use.	to gain further information about the authorised form.			to gain further information about an approved use.
1.53 Sponsor An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.	e) sponsor: an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.	2-21 Sponsor An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.	Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.	1.53 Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

9.2 Labelling requirements of Annex 13

TABLE 1. SUMMARY OF LABELLING DETAILS (§26 to 30)

a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;

(c) the batch and/or code number to identify the contents and packaging operation;

(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the trial subject identification number/treatment number and where relevant, the visit number;

(f) the name of the investigator (if not included in (a) or (d);

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product

(h) “for clinical trial use only” or similar wording;

(i) the storage conditions;

(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

(k) “keep out of reach of children” except when the product is for use in trials where the product is not taken home by subjects.

GENERAL CASE
For both the outer packaging and immediate container (§26)

Particulars
a [1] to k

IMMEDIATE CONTAINER
Where immediate container and outer packaging remain together throughout (§29)[5]

a [2] b [3] c d e

IMMEDIATE CONTAINER
Blisters or small packaging units (§30)[5]

a [2] b [3,4] c d e

[1] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times (§ 27).
[2] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.
[3] Route of administration may be excluded for oral solid dose forms.
[4] The pharmaceutical dosage form and quantity of dosage units may be omitted.
[5] When the outer packaging carries the particulars listed in Article 26.

9.3 Tabular overview on labelling requirements – some examples

Annex 13	AT	BE	CZ	DE	FR	IT	NL	ES	SE	UK	CH	JP	US
(a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding)		X	name of the sponsor	X; sponsor and CRO	X	sponsor	name of sponsor	X	X	X	X (without tel.no.)	X	
(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, name/identifier and strength/potency		X	X	X	X	Pharm. form	X	X	X	X	Denomi-nation of product, amount or volume	Chem. name or identi-fication code	Quantity of contents
(c) batch and/or code number to identify the contents and packaging operation	X	X	X	X	X	X	X	X	X	X	X	X	X
(d) trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere	X	X	X	X	X	Protocol no.	X	X	X	X	X		
(e) trial subject identification number/treatment number and where relevant, the visit number		X	X	X	X		X	X	X	X	X		

Annex 13	**AT**	**BE**	**CZ**	**DE**	**FR**	**IT**	**NL**	**ES**	**SE**	**UK**	**CH**	**JP**	**US**
(f) name of the investigator (if not included in (a) or (d)		X			X	X, incl. address	X	X	X, princi-pal investi-gator	X			
(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)		X	X in Czech	X	X		X	X	X	X	X		
(h) "for clinical trial use only" or similar wording	X	X	X in Czech	X	X	X	X	X	X	X	X	X	X
(i) storage conditions	X	X	X	X	X	X	X	X	X	X	X	X	
(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity	X	X	X	X	X	X	X	X	X	X	X	X	
(k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects		X	X	X	X	X	X	X	X	X			
	Name of the manu-facturer			EudraCT number		Address of clinical centre							Name and place of business of manufacturer, packer, or distributor.

Annex 13	AT	BE	CZ	DE	FR	IT	NL	ES	SE	UK	CH	JP	US
				Precautions for disposal									Proprietary and established name of the drug and its quantity
				Information given in other languages identical to German info									

9.4 Decision Analysis Matrix for the number of labels in a special CT

		Alternatives	One label for all countries		One label for each country		Some labels for several countries each			
							Including US label		Special label for US	
Criteria	**M / W**	**Weight for Criterion**	**Score**	**Weight**	**Score**	**Weight**	**Score**	**Weight**	**Score**	**Weight**
Regulatory Compliance	M	5	*1*	*5*	*2*	*10*	*3*	*15*	*4*	*20*
Optimisation of timing	M	4	*1*	*4*	*4*	*16*	*2*	*8*	*3*	*12*
Facilitation of CT logistics	W	3	*4*	*12*	*1*	*3*	*2*	*6*	*3*	*9*
Facilitation of IMP manufacturing	W	2	*4*	*8*	*1*	*2*	*2*	*4*	*3*	*6*
Consideration of costs	W	1	*4*	*4*	*1*	*1*	*2*	*2*	*3*	*3*
Sum	**-**	**-**	**-**	***33***	**-**	***32***	**-**	***35***	**-**	***50***

In this example for a *fictive* CT the decision analysis matrix was filled to elucidate the process described in chapter 5.4.
The preferred choice for this fictive CT would be to create some labels for several countries each, one of them being a special label for the US. The other alternatives have a nearly equal score sum indicating that they can be all considered to be a second-best choice but with different strengths and weaknesses.

A decision analysis matrix for a special CT would evaluate more concrete alternatives.

9.5 Templates for labelling decision process

9.5.1 Questionnaire and checklist regarding information for the core labelling

Trial reference code: _____
Substance code: _____

	1. Questionnaire for responsible departments		2. Checklist for RA	
Required information	**Responsible department**	**Information**	**Clarification necessary ?**	**Description of required clarification**
General information about this clinical trial				
Trial design [1]	Clinical research		☐ no ☐ yes	
Planned countries	Clinical research		☐ no ☐ yes	
Planned number of subjects	Clinical research		☐ no ☐ yes	
Planned FSI	Clinical research		☐ no ☐ yes	
Planned LSO	Clinical research		☐ no ☐ yes	
How many batches of the IMP will be needed ?	Pharmaceutical quality		☐ no ☐ yes	
When is the final labelling needed at the latest ? [2]	Pharmaceutical quality		☐ no ☐ yes	

[1] Information like type of blinding, comparator/placebo, parallel/cross-over, …
[2] give relative (weeks before planned FSI) or absolute timeline (date)

	1. Questionnaire for responsible departments		2. Checklist for RA	
Required information	**Responsible department**	**Information**	**Clarification necessary ?**	**Description of required clarification**
Labelling information				
Allows the trial reference code identification of the trial, site, investigator and sponsor ? [3]	Clinical research		☐ no ☐ yes	
trial subject identification number / treatment number [4]	Clinical research		☐ no ☐ yes	
Is the visit number relevant ? [5]	Clinical research		☐ no ☐ yes	
name, address and telephone number of the sponsor	Clinical research		☐ no ☐ yes	
name, address and telephone number of the CRO or investigator[6]	Clinical research		☐ no ☐ yes	
quantity of dosage units per package	Clinical research		☐ no ☐ yes	
Is the name of the investigator included in the contact address [7] or the trial reference code ? [8]	Clinical research		☐ no ☐ yes	

[3] if not: give elsewhere
[4] which one should be stated?
[5] depending on trial design
[6] the main contact for information on the product, clinical trial and emergency unblinding
[7] "name, address and telephone number of the CRO or investigator (main contact for information on the product, clinical trial and emergency unblinding)"
[8] if no: to be stated on the label

	1. Questionnaire for responsible departments		2. Checklist for RA	
Required information	**Responsible department**	**Information**	**Clarification necessary ?**	**Description of required clarification**
directions for use [9]	Clinical research		☐ no ☐ yes	
Do subjects take IMP home ? [10]	Clinical research		☐ no ☐ yes	
pharmaceutical dosage form	Pharmaceutical quality		☐ no ☐ yes	
route of administration	Pharmaceutical quality		☐ no ☐ yes	
name/identifier and strength/potency[11]	Pharmaceutical quality		☐ no ☐ yes	
batch and/or code number [12]	Pharmaceutical quality		☐ no ☐ yes	
storage conditions	Pharmaceutical quality		☐ no ☐ yes	
period of use [13]	Pharmaceutical quality		☐ no ☐ yes	
{Additional country specific information[14]}	Depending on required information		☐ no ☐ yes	

[9] reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product, please specify if this is an option

[10] if yes: “keep out of reach of children”

[11] only in the case of open trials

[12] to identify the contents and packaging operation

[13] to be given as use-by date, expiry date or re-test date as applicable, in month/year format and in a manner that avoids any ambiguity, please specify the desired way of stating the period of use

[14] to be specified by RA for already known countries before distribution of the template

	1. Questionnaire for responsible departments		**2. Checklist for RA**	
Required information	**Responsible department**	**Information**	**Clarification necessary ?**	**Description of required clarification**
Additional information for the labelling				
Maximal still possible size of the label [15]	Pharmaceutical quality		☐ no ☐ yes	
Please indicate any desirable additions on the labelling[16]	Clinical research		☐ no ☐ yes	
	Pharmaceutical quality		☐ no ☐ yes	
	Marketing		☐ no ☐ yes	
	Project management		☐ no ☐ yes	
Please indicate any potential problems[17]	Clinical research		☐ no ☐ yes	
	Pharmaceutical quality		☐ no ☐ yes	
	Marketing		☐ no ☐ yes	
	Project management		☐ no ☐ yes	

[15] depends on size of the planned package

[16] for example additional information to optimise conduct of the CT, compliance of the subjects or corporate identiy elements to facilitate later recognition of the approved product

[17] either trial specific or general

9.5.2 Example of the draft core labelling

To be completed by RA based on the information received from the involved departments in the questionnaire from annex 9.4.1.

for clinical trial use only

{trial reference code} {visit number}
{trial subject identification number / treatment number}

{pharmaceutical dosage form, quantity of dosage units}
{name/identifier and strength/potency}
{route of administration, directions for use}
{storage conditions}

{keep out of reach of children}

{batch and/or code number} {period of use}

{name of the investigator}
{name, address and telephone number of the sponsor, CRO or investigator}

Additional information	
Number of countries	
Countries	
Size of the final label	
Final label needed until	
Planned FSI	
Duration of CT	
Number of IMP batches expected	

RA will distribute the core draft labelling for revision to all involved departments.
In parallel it will be subject to the IMP labelling decision process.

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Frankfurt, den

Dr. Astrid Weyermann