

The Regulations and Regulatory Practices in the US and EU for Amendments During Drug Development

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- Amendments are changes in a drug development program and its components (e.g. protocols, manufacturing)
- They are a normal part of drug development and are very difficult to avoid
- They must be managed well and carefully
- Managing amendments is a form of **risk management**

- Routine processes
 - Add clinical investigators to the clinical plan
 - Modify clinical protocol slightly
- Evolving commercial environment, competition, other drugs on the market, pricing, cost of goods
 - redesign clinical trial (e.g. add comparator arm, change dose regimen, change endpoints, etc.)
 - change manufacturing process (e.g. to improve yield)
 - change formulation (e.g. new excipients)
 - Change dosage form (e.g. from tablet to capsule)
- Drug Safety
 - change safety monitoring plan
 - Modify or even discontinue the trial

- Justify the amendments rigorously on scientific or commercial grounds
- Develop arguments why amendments are necessary and beneficial
- Develop communication plan of the amendments to Authorities; identify pros and cons of amendments
- Communicate amendments to the Authorities; explain that they are necessary but will not invalidate the drug development program

- Establish a regulatory framework for accepting and reviewing Amendments
- Establish a process for accepting and reviewing Amendments, and for communicating decisions to Sponsor
- Require Sponsor to submit detailed, specific documentation on Amendments, including timelines for implementation of Amendments

Code of Federal Regulations TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Subpart B--Investigational New Drug Application (IND)

Sec. 312.30 Protocol amendments.

Sec. 312.31 Information amendments

- Amendment Types:
 1. New Protocol
 2. Changes in a Protocol
 3. New Investigator
 4. Content and Format

- Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study.
- Such study may begin provided two conditions are met:
 1. The sponsor has submitted the protocol to FDA for its review; and
 2. The protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study
- The sponsor may comply with these two conditions in either order.

- A sponsor shall submit a protocol amendment describing:
 - any **change in a Phase 1 protocol** that significantly affects the safety of subjects or
 - any **change in a Phase 2 or 3 protocol** that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

- Examples of changes requiring an amendment under this paragraph include:
 - Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol,
 - Any significant increase in the number of subjects under study
 - Any significant change in the design of a protocol (such as the addition or dropping of a control group)
 - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety

- A protocol change may be made provided two conditions are met:
 1. The sponsor has submitted the change to FDA for its review; and
 2. The change has been approved by the IRB with responsibility for review and approval of the study.
- The sponsor may comply with these two conditions in either order
- A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified

- A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol
- Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study.
- The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

- A protocol amendment is required to be prominently identified as such (*i.e.* , "**Protocol Amendment: New Protocol**", "**Protocol Amendment: Change in Protocol**", or "**Protocol Amendment: New Investigator**"), and to contain the following:
 - In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.
 - In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.
- In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study

- Reference, if necessary, to **specific technical information in the IND** or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.
- If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

- A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation.
- Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals.
- When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

- *Requirement for information amendment.*
A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report.
- Examples of information requiring an information amendment include:
 1. New toxicology, chemistry, or other technical information; or
 2. A report regarding the discontinuance of a clinical investigation.

- *Content and format of an information amendment.*
An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: **Chemistry, Manufacturing, and Control**", "Information Amendment: **Pharmacology-Toxicology**", "Information Amendment: **Clinical**"), and to contain the following:
 1. A statement of the nature and purpose of the amendment.
 2. An organized submission of the data in a format appropriate for scientific review.
 3. If the sponsor desires FDA to comment on an information amendment, a request for such comment.
- *When submitted.* Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

Practical Examples - US



Planned Change	How to Inform FDA
Increase patient number from 800 to 1200	Protocol Amendment: Changes in a Protocol
Add 8 study sites to facilitate additional patient enrollment	Information Amendment: Clinical
Change age range in inclusion criteria from 35-64 years to >13 years of age	Protocol Amendment: Changes in a Protocol
The sponsor's Medical Monitor has left the company and another physician has been appointed as Medical Monitor.	Information Amendment: Clinical
Manufacturing scale-up difficulty: eliminate talc from the formulation and increase the amount of magnesium stearate	Information Amendment: CMC
The first carcinogenicity study report is complete	Information Amendment: Nonclinical

- The Amendments process has been in place in the US since 1987 and in general it works well
- What can go wrong?
 - FDA may not agree with the Amendment
 - Sponsor changes the protocol or manufacturing process very frequently, causing FDA to doubt the sponsor's focus
 - Sponsor implements the Amendment, but later FDA responds and objects to the amendment (suggestion: check with FDA about acceptability of amendment)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS,
BODIES, OFFICES AND AGENCIES
EUROPEAN COMMISSION

**Communication from the Commission –
Detailed guidance on the request to the
competent authorities for authorisation of a
clinical trial on a medicinal product for human
use, the **notification of substantial amendments**
and the declaration of the end of the trial (CT-1)
(2010/C 82/01)**

- 27 Member States
- A clinical trial may be conducted only in one Member State or in more than one Member State
- Each Member State where the trial is conducted has jurisdiction over its CTA and has a national Ethics Committee

- After the commencement of the clinical trial, the sponsor may make amendments to the approved protocol.
- If those amendments
 - are **substantial** and
 - are likely to have an impact on the **safety** of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or
 - if they are otherwise significant,

the sponsor shall notify the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned
- Notification/submission of information (1) is only obligatory if the amendment is a **substantial amendment**.

- Amendments to the trial are regarded as ‘substantial’ where they are likely to have a significant impact on:
 - the **safety** or physical or mental integrity of the clinical trial participants, or
 - the **scientific value** of the trial.
- It is up to the sponsor to assess whether an amendment is to be regarded as ‘substantial’. However, care has to be taken to avoid over-reporting.
- In particular, not every change to the clinical trial application form is by default to be considered as a ‘substantial’ amendment.

- The sponsor should assess also whether the combination of substantial amendments lead to changes of the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would then be subject to a new authorisation procedure.

Amendments that are typically “substantial”



- Change of main objective of the clinical trial;
- Change of primary or secondary endpoint which is likely to have a significant impact on the safety or scientific value of the clinical trial;
- Use of a new measurement for the primary endpoint;
- New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk/benefit assessment;
- A change in the definition of the end of the trial, even if the trial has in practice already ended;
- Addition of a trial arm or placebo group;

Amendments that are typically “substantial”



- Change of inclusion or exclusion criteria, such as changes to age range, if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial;
- Reducing the number of monitoring visits;
- Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the clinical trial;
- Withdrawal of an Independent Data Monitoring Board;
- Change of IMPs (Investigational Medicinal Products);
- Change of dosing of IMPs;
- Change of mode of administration of IMPs;
- A change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or **the risk/benefit assessment.**

- Changes to the identification of the trial (e.g. Change of title, etc.);
- The addition/deletion of exploratory/tertiary endpoints;
- A minor increase in the duration of the trial (< 10 % of the overall time of the trial);
- An increase in duration of > 10 % of the overall time of the trial, provided that:
 - the exposure to treatment with the IMP is not extended,
 - the definition of the end of the trial is unchanged, and
 - monitoring arrangements are unchanged;

- A change in the number of clinical trial participants in the member state concerned, if the total number of participants is identical or the increase/decrease is insignificant in view of the absolute number of participants;
- A change in the documentation used by the research team for recording study data (e.g. Case report form or data collection form);
- Additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis;
- Minor clarifications to the protocol;
- Correction of typographical errors.

- New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator;
- Changes to the reference safety information for the annual safety report.
- A change of sponsor or the sponsor’s legal representative;
- The revocation or suspension of the IMP’s marketing authorisation.

- Any change of persons other than the sponsor or his legal Representative, for example applicant, clinical research associates (CRAs) who monitor the clinical trial for the investigator, and clinical research organisations (CROs) (note that the responsibility vis-à-vis the national competent authority for the clinical trial is always with the sponsor or his legal representative);
- Any change in the contact details of persons referred to in the documentation (see, however, section 3.2 as regards contact details of the contact person);
- Changes to the internal organisation of the sponsor or of the persons to whom certain tasks have been delegated;
- Changes in the logistical arrangements for storing/transporting samples;
- Change of technical equipment;
- Addition or deletion per se of another member state or third country concerned.

Who in EU should be notified about substantial amendments?



- The Member State(s) where the trial is conducted
and/or
- The Ethics Committee(s) with jurisdiction over the trial
- It is essential that the Member State(s) and the Ethics Committee(s) communicate with each other
- The EU Commission Guidance 2010/C 82/01 specifies the content and format of communicating substantial amendments

- Sponsor must
 - Document all nonsubstantial amendments and keep them on file
 - Update the Clinical Trial Application Form when submitting a substantial amendment
 - Update the Form with the nonsubstantial amendments when updating the Form with a substantial amendment

- The Ethics Committee(s) and/or the Member State(s) must respond to the applicant within **35 days** –either approving or not approving the substantial amendment
- Up until then, the trial can continue on the basis of the original documentation
- Upon approval, it is the sponsor's responsibility to ensure communication of the changes to the investigators.

EU Member States View Amendments Differently: Some Examples



Type of Amendment	Treated as “Substantial”	Treated as “Notification”	Approval required
Increase N of patients total trial	Belgium, Czech, Denmark, Finland, France, Romania, Slovakia	Poland	Estonia, Latvia, Lithuania
Enrollment halt	Austria, Belgium, Finland, France, Germany, NL, Romania, UK	Czech, Estonia, Lithuania, Poland, Slovakia	Latvia
Sponsor name change	Belgium, NL, UK	Check, Denmark, Estonia, Finland, France, Germany, Estonia, Lithuania, Poland, Slovakia, Sweden	Romania

- Urgent safety measures (e.g. to protect the safety of trial subjects) may be taken without prior notification to the national competent authority.
- However, the sponsor must inform the national competent authority and the Ethics Committee of the Member State concerned of the new events, the measures taken and the plan for further action as soon as possible.
- Where the initial contact is by telephone, this should be followed up, for reasons of traceability, by fax or e-mail. It should be followed by a written report.

- **Recommendation to Sponsors:** align regulatory and commercial strategies from the start in detail, to try and minimize the need for Amendments that are driven by commercial considerations
- **Recommendation to Regulators:** the regulatory framework must allow flexibility and acceptance of amendments without necessarily stopping the trial, because drug development is fluid and sometimes needs to be adjusted
- The common goal is to promote innovation, rapid development and affordability of innovation for all patients who need therapeutic products

- A Drug Development Plan should be agreed by Sponsor and Regulator up-front, including CMC, nonclinical and clinical aspects
 - The goal: make no changes to the plan
- But “events“ happen during development, and changes (Amendments) to the Drug Development Plan often become necessary. This is life.
 - Justify any Plan changes very rigorously – first internally within the Sponsor, then to the Authorities
- Establish a framework for clear, detailed and transparent communication between sponsor and regulator regarding amendments – based on regulations but also on **earned trust**

Thank You

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