Appendix V: USING THE INVESTIGATIONAL MEDICINAL PRODUCT

Dispatch certificate and acknowledgement of receipt

To be able to recover a batch of test drug (for example, if it is decided to terminate a trial), it should be possible to know where it is at all times and who has it. To do this, one of the rules to be followed is that a dispatching certificate should be attached to each shipment and an acknowledgment of its receipt obtained.

In addition, there is a section to be filled out by the addressee:

- parcel received intact;
- contains the expected product;
- in good condition.

Resupply

For periodic resupply (for example, every month, patient by patient), it is wise to place on-site at the study center the first two packages corresponding to the first two treatment periods.

Other types of resupply

- a patient has lost his supply of test drug;
- an investigator recruits more cases than initially planned.

Shelf Life

Parallel to the development of a product and, in particular, during the first clinical trials phase, information on the expiry date of the pharmaceutical formulation progresses step by step.

- **Initial expiry date**

  A consensus exists between the European Union, the USA and Japan on recommendations for studies on stability necessary in a registration file. They do not involve test drugs for clinical trials and make use of large quantities of products, but they can be a guide.

  Tests on storage under “normal” and “accelerated” conditions are undertaken on the active substance, dosage units, alone or in contact with the immediate packaging most commonly used for clinical trials. Controls are made at regular intervals. In this way, one obtains an initial expiry date whose duration is approximately six months.

  Concomitantly, as soon as the initial shelf-life is known, a second identical batch is manufactured. This results in being able to ensure a 6-month period of drug stability. In the European Union the duration should take into account the nature of the product, its immediate packaging, and conditions for storage.

- **Extension of an expiry date**

  When a clinical trial is conducted, it is desirable that the expected duration of the study (duration of patient enrollment and time necessary for treatment of the last patient enrolled) be less than the known duration of product shelf-life.

Breaking the Blind

- Randomization code envelopes
- Circumstances for decoding and documentation
    - In the European Union, the name, address and phone number of the contact point where emergency decoding can be obtained are provided with test medications, either written on the product label or on a card or a booklet given to the patient, to be kept on him.

Recovery and Destruction

At the end of the trial, all clinical drug supplies recovered must be destroyed.

- Destruction

In compliance with the procedure and following regulations for protection of the environment, the remaining test drug supplies are destroyed at the sponsor's and a dated and signed certificate of destruction is written and filed.

The European Union recommends that remaining test drug supplies used in a clinical trial be destroyed only when an evaluation of the quantities shipped, dispensed and recovered is completed and documented, after resolution of any discrepancies, and after obtaining the sponsor's written approval.

Appendix VI: ADVERSE EVENTS AND MANAGEMENT ISSUES

Non-serious Adverse Events

- A description of several events;
- And for each of them:
    - Severity (mild, moderate, serious);
    - Frequency in case of multiple episodes;
    - Dosage of the study drug (unchanged, decreased, terminated)
    - Possible re-challenge
    - Possible corrective therapy.

The investigator's opinion on the causal relationship is added in the form of a multiple choice question which may have a highly variable number of replies:

- Often in four grades (probably, possible, unlikely, excluded);
- And up to eight: excluded, unlikely, doubtful, conditional, possible, probable, definite, unknown.

Considering the uncertainty of these replies, it is preferable not to increase the shades of meaning.

This form is part of each visit in the CRFs.

Serious Adverse Events

A standard page for collection of a serious adverse event is inserted only once in each CRF because, most commonly the occurrence of such an event results in discontinuation of the study drug and specific follow-up.

Phone Numbers

Phone numbers of persons to be contacted in case of emergency may be listed in the protocol, for example, the study monitor's office phone number (and home phone if possible).

On-call rotation
Medical Decisions

- Withdrawal from the studied treatment;
- Code-breaking;
- A request for further appropriate laboratory tests;
- Administration of corrective therapy;
- Collection of additional information aimed at determining the causal relationship with therapy in the case involved;
- Reporting the event to the competent authorities, the ethics committee, and to other investigators, depending on modalities stipulated by local regulations.

Causal Relationship

- The Bégaud et al method
  This method is based on the combination:
  - of chronological criteria
  - clinical signs or investigations suggesting the role of the suspect medication
  - The conclusions are the causal relationship
    - I_0 appears excluded;
    - I_1 doubtful;
    - I_2 possible;
    - I_3 probable;
    - I_4 very probable.

- The Karch and Lasagne method
  This method, developed in the US, but not required by the US Food and Drug Administration (FDA), is based on a decision-tree consisting of five criteria (timing, previously known event, other possible cause, outcome following discontinuation of treatment and rechallenge). This method results in six ratings: definite, probable, possible, conditional, doubtful, or excluded relationship.

Reporting by the Sponsor

- International Regulations
  According to the recommendations of the International Conference on Harmonisation, an adverse event is one that has to be reported to the competent authorities (and the ethics committee if local legislation stipulates this) if it is:
  - **Serious**, i.e. significant enough to justify within a short time period a noteworthy change in dosage, monitoring or consent. In particular, this includes death; a real life-threatening risk (and not merely a potential risk) for the subject, hospitalization induced or prolonged by the event, a major or persistent or significant disability or incapacity, a congenital anomaly or birth defect, but also all other cases considered of concern based on medical judgment, in particular, if a treatment initiated to remedy it has had the effect of preventing its worsening to one of the cases mentioned in

the above. It is necessary to differentiate a “serious” case from one that is “severe”;
    - **Unexpected,** i.e. whose nature or severity do not correspond to the available information, in particular in the investigator’s brochure;
    - **Possibly having a causal relationship** with the studied treatment, a suspected reasons sufficient for this.

In the European Union

- All **suspected unexpected serious adverse reaction**;
- Expected cases whose **outcome may be unexpected**;
- Any **increase in the frequency** of an expected serious adverse event, which may be clinically significant;
- Cases that have occurred **after the end of the trial**.

In the USA

The time frame within which cases must be reported can be negotiated ahead of time with the FDA, possibly for grouped reporting of case. The sponsor can at his convenience use either the US “Medwatch 3500A” form, or the international CIOMS-1 form. In every report, the sponsor should review previously reported, similar cases and analyze the new case in light of the previous ones.