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Special Article

EORTC/CRC/NCI Guidelines for the Formulation of Investigational Cytotoxic Drugs

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INTRODUCTION

THE New Drug Development and Coordinating Committee (NDDCC) of the European Organization for Research and Treatment of Cancer (EORTC), in collaboration with the Cancer Research Campaign (CRC), has recently formalized a procedure for the preclinical development of investigational drugs in Europe. This program is intended to organize the preclinical drug development process and to reduce the lag-time between discovery of promising new agents and initiation of Phase I clinical trials. Through this effort the NDDCC/CRC coordinate a preclinical drug development effort by monitoring the various critical phases of product development. The critical phases include bulk production (or acquisition) of synthetic or natural products, formulation development, and pharmaceutical production. Since the best resources of equipment and expertise are dispersed among the members of the EORTC/CRC, it is likely that the preformulation and production efforts will be conducted at different locations within Europe. It is also likely that the United States National Cancer Institute (NCI) may collaborate on certain chemical and formulation projects. The three organizations have agreed to the formation of a Joint Formulation Working Party and it is our hope that the use of pharmaceutical guidelines will provide some continuity in the development of the investigational product and assure the proper identification, purity and strength of the new drug. Such controls will also provide the necessary documentation for regulatory acceptance and enable the preclinical toxicology and subsequent clinical investigations to be conducted with confidence.

This document is not intended to supersede the established regulatory controls of the various participating countries, but to be used as a benchmark to acceptable practice where guidelines do not exist.

The formulated products developed under the NDDCC/CRC are intended for distribution to those clinical centers registered to participate in the EORTC/CRC Phase I and II clinical trials [1]. It has been the accepted practice for the majority of new investigational agents to be administered in Phase I clinical trials as either an intravenous bolus injection or via intravenous infusion. This route of administration avoids the problems associated with incomplete absorption and the local GI toxicity often seen with oral administration. Consequently, these guidelines and comments mainly address the issues associated with the development of sterile and stable injectable products.

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The new drug substance (NDS)

The acquisition of high quality NDS and other ingredients is essential and may circumvent many formulation problems. Most investigational cytotoxic agents are initially obtained from non-pharmaceutical sources and require a complete chemical and physical assessment prior to initiation of pharmaceutical development. It is always helpful to obtain, if possible, methods of synthesis (or extraction) and purification of the NDS. This information will be used for regulatory documentation and also for analytical purposes to identify possible trace contaminants such as undesirable solvents or unreacted starting materials. The suppliers of the NDS should be informed that their materials are intended for pharmaceutical work and that certain documentation and controls are required. In order to facilitate the documentation and evaluation of the NDS the following minimal information should be provided with each supply:

- Name and address of the supplier
- Manufacture flow sheet
- Certificate of analysis
  - batch control
  - identify and purity analysis
  - date of analysis
- Storage requirements (if known).

Characterization of NDS

On receipt of the NDS the pharmaceutical scientist should verify the identity of the sample and confirm that it is of the highest purity available. In the first stage of development an interim reference standard should be identified. A small proportion of the batch of highest purity should be analytically characterized and set aside as the interim reference standard.

The use of a reference sample greatly facilitates the development of suitable analytical methodology. Chromatographic techniques should be developed, and evaluated, for both qualitative and quantitative purposes. Thin layer chromatography (TLC) is frequently used to detect the presence of impurities. However, it is advisable to use at least two separate chromatographic systems to ensure that the impurity is not masked by the parent NDS. Either liquid (HPLC) or gas (GC) chromatography are usually used as the quantitative analytical procedure. HPLC is often the technique of choice, as the NDS can frequently be analyzed in the aqueous injection diluent without prior extraction.

The analytical technique should be evaluated for its selectivity, accuracy and precision. Once developed the HPLC, or GC, methodology can be subsequently used as the stability indicating assay [2] and adapted for use in the later evaluation of potential formulated products and in pharmacokinetic studies.

Criteria to be applied for characterization of the reference standard and all NDS lots should include:

- spectral analysis such as i.r., u.v., MS, etc.
- chromatographic analysis such as HPLC, TLC
- elemental analysis
- physical description such as color, appearance, odor
- other properties when appropriate such as physical constants, M.P., optical rotation, etc.

A complete analytical profile may not be feasible for certain complex materials especially if they are derived from biological or natural origin; however, every effort should be made to adequately characterize each new bulk substance. The test methods and results of each new batch of NDS should be recorded and compared to acceptable limits previously established with the reference sample. The suppliers of the NDS may be willing to provide some or all of the above information. In such cases only certain tests for confirmation may be required.

Stability and solubility of NDS

If stability data are not available on the NDS, a study should be initiated to provide useful storage and handling information and for projecting expiration dates. The stability should be determined under several storage conditions including elevated temperature, fluorescent light and high humidity (optional). These studies should be carried out over a period of 3–6 months and a stability indicating chromatographic assay used for the quantitation of the drug in the presence of its degradation product(s).

The solubility study should include equilibrium solubility determinations in water, acid, base, and organic solvents such as ethanol, dimethylacetamide, dimethylsulfoxide and other potential pharmaceutical vehicles [3–5].

The required solubility is dependent on the projected Phase I starting dose and the estimated human maximum tolerated dose (MTD). The estimated human starting doses is calculated from the available animal screening data and other pharmacological indicators. The initial starting dose is then increased, in the Phase I protocol, via a modified Fibonacci escalation scheme [6], or by further utilization of the relevant pharmacokinetic data [6, 7]. These early dosing estimates are critical in determining the solubility requirements of the new agent and the approach to formulation development.

Formulation

An evaluation of the solubility and stability profile of the NDS assists the pharmaceutical scientist

in assessing the complexity of the formulation problem. The lack of adequate aqueous solubility, relative to the estimated dose requirement, is the most frequently encountered formulation problem for injectable products.

Injectable products can be classified as either sterile liquids or sterile solids. The sterile liquids may be injected directly or may require further dilution before injection depending on the manufacturers' recommendations. The sterile solids all require some form of reconstitution and may require further dilution for infusion administration. Most products are sterilized by membrane filtration with the exception of those products of sufficient stability to withstand terminal autoclaving. Membrane filtration has an additional advantage of removing undissolved particulates. It is generally less expensive to prepare injectable liquids than the sterile dry products which usually involves freeze drying. However, freeze dried products provide a method for formulating substances that are stable in the solid state but lack the necessary stability in solution. The manufacturing controls and tests for injectable products follow similar approaches of evaluation.

Once an acceptable dosage form has been developed in the laboratory a small pilot batch should be prepared to ensure stability and compatibility of the product with the equipment and conditions of manufacture. The pilot batch product may then be used for additional stability studies, efficacy testing in the tumor screen (if considered necessary), and other pre-clinical studies such as in pharmacology and plasma compatibility. The information obtained in the pilot run can then be used for the batch manufactured for preclinical toxicology.

Manufacture and control documentation

Manufacturing documentation should be prepared with each lot of finished product appropriately detailing the formulation procedures and recording such details as order of mixing, solution times, temperatures, filtration methods, etc. This documentation is extremely important for regulatory control and for retrieval of historical data in the event of questionable product problems.

The preparation of product specifications for postmanufacture release of finished dosage forms is essential. The specifications for new products are often stated as tentative specifications allowing for adjustments as more experience is gained in the manufacture of subsequent batches. The following is a list of suggested tests and specifications that may be included in a certificate of analysis:

Test	*Specification*
Appearance	(colour)
Assay (minimum 3 vials)	±10% of label potency
Weight variation	compendia
Moisture	determine (set limits)
pH	determine (set limits)
Completeness and clarity of solution	compendia
Particulate matter	compendia
Sterility	compendia
Pyrogen	compendia
Conformance to labelling	conforms

The compendia refers to European Pharmacopoeia tests and procedures. The pH and moisture values can be established during product development. The release documents for the formulated material should include all batch production and quality control records.

Packaging and labelling

All investigational products should be fully labelled to provide proper product identification and information to the pharmacist and clinical investigator. The following details should be provided on the label:

- Drug name (state salt or free base)
- Strength and potency
- Other ingredients
- Storage conditions
- Name and address of manufacturer
- Batch (or lot) number
- Expiration date—and/or manufacture date
- Investigational use statement (if applicable)
- Reconstitution instructions (if applicable).

If a sterile solution is to be used only as an additive to infusion fluids a warning such as 'to be diluted before intravenous injection' should be placed on the label. Details on the storage and stability of the reconstituted product and infusion solution should be given in either the package insert or the clinical brochure. All stability statements should be supported by laboratory trials and documented in the product history records.

Shelf life studies

Following the release of the manufactured batch sufficient vials should be set aside for long term shelf-life evaluation of the product. The shelf-life date will support the products integrity under various storage conditions. The information obtained will allow for future adjustments to the label storage recommendations and provide necessary information for assignments of expiration dates.

New products should be evaluated under at least three storage conditions; the recommended storage temperature, one level above the recommended storage temperature, and one level below the recommended storage temperature. The study should run for 24 months or longer depending on the number of samples that can be put aside and the long range goals for the clinical trial. The following are suggested storage conditions and test intervals that may be considered for new product evaluation:

Storage temperature (°C)	Testing interval (months)							
−10	3	6	9	12	18	24	36	48
4	3	6	9	12	18	24	26	48
25	3	6	9	12	18	24	36	48
50	3	6	9	12	18	24	36	48

The tests are performed frequently during the first year, then biannually, then annually. The tests performed at each interval include: potency, color, appearance, clarity of solution, pH and constitution time (if applicable).

Storage and distribution

A product storage and distribution system should be established to ensure proper storage of the investigational drug products and to assure that only authorized investigators receive the products for specific clinical protocols. The distribution system should contain sufficient historical documentation that all investigators holding stocks of the drug could be contacted in the event of a product recall. The system should be written or computerized and should contain the following lot-specific information.

Product storage file

- Name and description
- Potency
- Amount and date received
- Manufacturer and lot number
- Expiration date
- Storage conditions

Product distribution file

- Clinical trial number
- Participating investigators
- Amount and date shipped
- Manufacturer and lot number

DISCUSSION

The guidelines described above are intended to be neither exhaustive nor inflexible. Each NDS can present unique problems for the pharmaceutical scientist and in solving these problems certain liberties may have to be taken. These guidelines are intended to be used as a check-list for the pharmaceutical aspects of new investigational anticancer drugs. It is the intention of both the EORTC/CRC and the NCI that data generated within either facility should be acceptable to the regulatory authorities in all the participating countries.

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