ECETOC Document

No 2

Good Laboratory Practice Standards for Health Effects

August 1979

N° 2 Exp. 19

ECETOC-DOC-2

20.8.79

BEFORE THE

ENVIRONMENTAL PROTECTION AGENCY

COMMENTS OF THE

EUROPEAN CHEMICAL INDUSTRY ECOLOGY AND TOXICOLOGY

CENTRE (ECETOC)

ON

GOOD LABORATORY PRACTICE STANDARDS FOR

HEALTH EFFECTS

Good Laboratory Practice Standards for Health Effects, 44 Fed. Reg. 27362 - 27375 (May 9, 1979).	)))	Docket N° OST-046003

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Pursuant to the instruction given in the Federal Register of 9 May, 1979, page 27334, column 2, please accept the attached written comments from ECETOC on the Environmental Protection Agency's Proposed Good Laboratory Practice for Health Effects which were published in the Federal Register, on May 9, 1979, pages 27362 - 27375.

The European Chemical Industry Ecology and Toxicology Centre (ECETOC) is a non-profit making international association of 40 companies who operate in West Europe, and are engaged in the industrial manufacture of chemicals, and research in this field.

ECETOC was formed to:

a) procure all types of information relevant to the protection of the health of any person who may come into contact with chemicals and to reduce the ecological impact of the manufacture, processing and use of chemicals.

b) coordinate efforts by chemical manufacturers to study and attempt to resolve the ecological and toxicological problems which may result from the manufacture, processing and use of chemicals.

c) cooperate in a scientific context with government, health authorities and all other public institutions concerned with ecological and toxicological problems relating to chemicals.

Commercial questions are excluded from the objectives and concerns of the Centre.

A. INTRODUCTION

Members of ECETOC have a vital interest in the promulgation of good practicable GLP standards. ECETOC therefore appointed a group of responsible practicing scientists from member companies to draw up a set of GLP recommendations based on their experience and ability.

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The group comprised:

L. Durand	GLP Quality Control Officer	Ciba-Geigy (Basle)
H. Fine	Quality Assurance Manager	ICI Central Toxicological Laboratory (Alderly Park).
H. Hulpke	Quality Control Department	Bayer (Wuppertal)
K.H. Leist	Pharma Research, Toxicology	Hoechst (Frankfurt)
R. Millischer	Chief Toxicologist	PCUK(Paris)
S. Paglialunga	Industrial Toxicologist	Montedison (Milan)
J.P. Tassignon	Counsellor, Industrial Medecine and Toxicology.	Solvay (Brussels)
H.G.van Raalte	Consultant Toxicologist	Shell (Den Haag)

This group advised ECETOC in making the present submission, which represents the views of the Center. ECETOC believes that GLP proposals have to meet six criteria :

a) They must be effective in the basic aim of ensuring the quality and integrity of test data.

b) They must be sensible in practice and allow for some differences of laboratory organisation and management between different organisations and countries.

c) They must be necessary and sufficient, ie. detailed enough to be unambiguous and achieve their purpose, but not so over-detailed and constrictive as to prevent the full deployment of scientific initiative, experience, expertise and judgement. Toxicity and ecotoxicity testing are rarely routine operations, and to obtain valid experimental results and conclusions therefrom requires considerable scientific skill and initiative.

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d) The principles must be sufficiently in line with existing proposals to permit future harmonisation or mutual recognition across national boundaries.

e) They must not add unnecessarily to the cost and administrative burden on those responsible for testing, and should impose the minimum of non-productive, bureaucratic work on trained personnel and management.

f) They should be so worded as to cover the measurement of physico-chemical properties and tests on environmental effects as well as health effects, since these are all included in the existing or proposed regulatory requirements for testing chemicals.

The FDA regulations, Federal Register, Vol. 43, N° 247, Dec. 22, 1979, pages 60013 - 60020, offered a good systematic approach to the problem and were taken as a basis. The EPA have also modelled their GLP proposals on those of the FDA and it is therefore important to comment on both documents. To avoid the proliferation of separate GLP regulations for different types of testing, the ECETOC recommendations are worded to cover not only toxicity tests but also those carried out for measuring physico-chemical properties and environmental effects.

B. COMMENTS ON FDA REGULATIONS

There are various reasons why certain changes, omissions or additions were made to the FDA document in arriving at the ECETOC proposals. Some of the FDA proposals were too elaborate and burdensome, and were not necessary in achieving the desired aim. Others would impose a too-detailed organisation and structure on a laboratory. Some of the subject-matter was specific to the US, or was inappropriate for GLP since it would normally be the prerogative of other government authorities. Finally, the FDA regulations are concerned only with health effects, and in order to cover the measurement of physico-chemical properties and environmental effects many changes of wording and additional words or phrases were necessary.

a) Major differences

- Quality Assurance. The FDA section 58.35 a) calls for a "QA Unit composed of one or more individuals" to monitor the compliance of the study with GLP regulations. The obligatory creation of such an entity would impose an organisational structure on a laboratory which may not be suitable. Smaller laboratoires would find this particularly difficult, expensive and wasteful of skilled man-power.

  ECETOC prefers to concentrate on meeting the aims of QA, and not on the organisational mechanism for achieving them, by requiring a set of procedures and controls for this purpose, designed and operated as best fits the particular laboratory - see ECETOC GLP sections A.2.h and B.4 below.

- Periodic inspection. In section 58.35 3), FDA requires inspections by the QA Unit "at intervals adequate to assure the integrity of the study" for studies lasting less than 6 months. For studies of over 6 months it requires inspection every 3 months. ECETOC prefers the former approach for all studies, since the periodicity of inspection, to be adequate, depends very much on the type of study and developments within it - see ECETOC GLP, section B.4 a),.i).

- Master schedule sheet. In section 58.35 b.i) the FDA requires the maintenance of a "master schedule sheet of all studies in the testing facility".
  ECETOC agrees that this is good practice in planning and managing a laboratory, but is also aware that such sheets have been asked for during inspections by regulatory authorities. It is not proper that one inspecting authority should be entitled to know of work being carried out for another authority, and we have therefore avoided the term "master schedule sheet" and have adopted a form of words (see B.1.a) which has no implications regarding the inspection process.

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- Synthesis and process details. The FDA in section 58.105 a) requires documentation of methods of synthesis or fabrication of the test substance, for the purpose of characterising it. ECETOC believes that it is not necessary to reveal such information, since the substance will be adequately characterised by other information called for, eg. source, identity, composition, etc.. Impurities arising from the laboratory synthesis or plant manufacture will normally be identified as required, without having to divulge the method of synthesis or manufacture.

- Study Director's Responsibility. In FDA section 58.33, the Study Director is to have overall responsibility for "...the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting." In such multi-disciplinary studies as are necessary in this field no one person would be expert enough to carry immediate responsibility for the detailed interpretation, analysis, documentation and reporting, and ECETOC prefers a more realistic description ie. "responsible for the overall conduct and reporting of a study..." (see section II, B.3.b).

b) Minor differences

These are too numerous to list in full. They often involve careful wording and the avoidance of repetition to produce a shorter, clearer text. In a few instances the obligatory nature of a requirement has been softened by making it "as necessary", where a mandatory requirement is not necessary to achieve the aim of Good Laboratory Practice.

One example of a simplification which removes a cumbersome requirement concerns signature of the final report. The FDA in section 58.185 a) 12), requires that the final report shall contain "the signed and dated reports of each of the individual scientists or other professionals involved in the study". In a multi-disciplinary study this would involve a large number of people. The ECETOC proposal recognises normal line-management responsibilities and requires only "the principal scientist from each of the cooperating disciplines" to report and sign - see ECETOC GLP J.1 a) v).

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c) Omissions

The FDA sections on inspection (58.15) and disqualification (sub-part K) of testing facilities have been omitted since these will presumably be regulated by national authorities. FDA section 58.33 dealing with office space, showers, toilet, etc... is also governed by existing national legislation and is not appropriate to GLP rules.
Finally the requirement (58.29 f) that sick personnel report their health or medical condition to their immediate supervisors is not proper practice in many European countries, and has been omitted.

C. COMMENTS ON EPA PROPOSALS

1. General. While the EPA have copied the FDA regulations in general, they have incorporated a number of additional proposals which reduce the flexibility of the FDA requirements. EPA also intend to issue further GLP requirements eg. for environmental effects and chemical fate. ECETOC disagrees strongly with this proliferation of GLP regulations. Studies required for risk evaluation have common needs in study design, conduct, documentation and evaluation, and ECETOC suggests that all requirements should be in a single GLP document.

If the EPA issue a series of GLP's, international harmonisation will be made more difficult. ECETOC draws attention to the work of the OECD group on GLP which is working towards one set of proposals for legislatory purposes.

2. Diets. On page 27364 EPA specifies diet(s) to be used.
This is not appropriate to GLP, which ECETOC believes should be concerned with how tests should be carried out, not with the specification of the scientific details.

3. Storage. On page 27374, para. J.2, EPA set out in great detail the requirements for storing material, data and records. ECETOC believes that it is sufficient to specify that management be responsible for the security and integrity of such storage.

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There are adequate penalties against the failure to store properly. For example, the failure to produce records, etc... from storage may lead to a submission being rejected.
The requirements concerning access to the archives, on page 27374, J.2.iv) are unnecessarily burdensome, and security arrangements should be left as a normal prerogative of management.

4. Reporting format, page 27366, h i). Insistence on a detailed lay-out for reporting results will make reporting difficult and less than optimally effective. EPA should limit the requirement to general guidance about the structure of the report.

5. Removal of sick animals to guarantine page 27366, f.2.
This is not a generally accepted practice. Removal to another area can increase the spread of disease, and many laboratories kill small animals as soon as they are found to be sick. Good practice depends on circumstances, and should not be detailed in GLP regulations.

6. Labelling reagents, page 27373, f.2. The requirement to label all reagent bottles with the expiry date is an unreasonable and excessive burden on a laboratory. Probably around 90% of chemicals and solutions are indefinitely stable. This requirement should be "as necessary".

7. Correspondance as raw data, page 27364, column 2. The proposal that correspondence relating to planning, conduct and interpretation of a study be classed as raw data is most objectionable.

Much correspondence regarding a study consists of transient thoughts, ideas, suggestions, etc.. exchanged between scientists, and also ephemeral matters of no permanent value to the final factual report. Speculation should form no part of raw data, which by definition is a record of data, i.e. facts. The proposal will inhibit the freedom of scientific discussion by written notes, memos, etc... Where such correspondence deals with matter relevant to a number of topics, burdensome duplication of copies to each study file would be necessary.

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8. Inspection of quality assurance reports, page 27365, c.2).
ECETOC believes that the FDA are correct in not requiring the inspection of QA reports. These reports are merely a part of the tools whereby the Study Director ensures that the study is in compliance with GLP, and actions arising from such reports are incorporated in the study and the factual record.

9. Submission of study plan, page 27338, column 1. This requirement to submit a study plan 90 days before the study should not be obligatory. The notifier's responsibility is to submit information obtained in compliance with GLP and relevant to risk evaluation. It is in the interest of the notifier to submit acceptable information and he may wish, voluntarily, to submit a study plan to the authority.
An undesirable effect of the requirement will be to delay the start of a study by up to 90 days, leading to further delay in the eventual manufacture and marketing of a new chemical. This is unreasonable since the amount produced and marketed in the first 3 months of the life of a new chemical is likely to be very small.

10. Submission of quarterly reports, page 27339, column 2.
This would impose an unreasonable burden, of little value in furthering the purposes of the study, on staff conducting the study. Interim results of toxicological studies are always treated with great caution by the scientists involved, and premature disclosure of such results is a dangerous practice. Under many national laws there is a responsibility to report confirmed adverse effects. If this practice were followed, scientists would not need to waste time writing quarterly reports and could spend the time saved in useful experimentation.

11. Retention of samples of substances with carrier, page 27370, b) 3.B.ii), col. 3. The retention of samples of substances with carrier is not a valuable practice for the purposes of the study since analyses will already have been carried out, and the stability will have been measured. It would represent an enormous additional cost to the study.
This requirement should be omitted.

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12. Determination of stability, page 27370 b) 1.ii). The requirement to determine the stability of each test or control substance before initiation of a study is unreasonable, since for example in a 2-year study the duration of the whole would be prolonged to 4 years. It is in the sponsors' interest to obtain stability data at a time early enough that the whole study is not ruined by the unforseen decomposition of the tested materials. The EPA requirement should be omitted.

13. Responsibility for quality assurance, page 27365, column 1.
The EPA propose that the Study Director be responsible for assuring that QA procedures are followed. This conflicts with the requirements that QA personnel are not responsible to the Study Director. ECETOC is in agreement with the FDA position that the Study Director should not be responsible for ensuring that QA procedures are followed.

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