

*Delayed Adverse Effects of Drugs and Toxicological Risk Assessment (T. Fujii and T. Yanagita, eds.)
Session II. Educational Lecture*

CURRENT STATUS OF THE INTERNATIONAL TOXICOLOGY GUIDELINES, FOCUSING ON THE OECD AND ICH GUIDELINES

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The OECD Council Recommendation was announced to establish guidelines for “Procedures and Requirements for Anticipating the Effects on Chemicals on Man and in the Environment”, and was adopted in 1977 as the “OECD Chemicals Programme”. These guidelines show the framework for assessment of new chemicals, including : (1) determination of their physical-chemical properties, their potential hazards to human health, and their potential to reach the natural environment ; and (2) determination of their potential hazards to the environment.

Since 1982, OECD Member countries have developed and updated the OECD “Guidelines for Testing of Chemicals” intended to harmonize the international standards for safety testing of chemicals. The purpose of the guidelines is to enhance the validity and international acceptability of test data, to make the best use of available resources in both government and industry, and also to avoid non-tariff trade barriers. The test guidelines reflect the current state-of-the-art for chemical safety testing and are an invaluable reference for toxicologists working in industry, government, and academia on the testing and assessment of chemicals.

In 1995, guidelines concerned with health

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effects, including those on short term toxicology (22), long term toxicology (3) and genetic toxicology (31), were adopted as follows :

Short Term Toxicology

- 401 Acute oral toxicity
- 402 Acute dermal toxicity
- 403 Acute inhalation toxicity
- 404 Acute dermal irritation/corrosion
- 405 Acute eye irritation/corrosion
- 406 Skin sensitization
- 407 Repeated dose oral toxicity–28-/14-day study in rodents
- 408 Subchronic oral toxicity–90-day study in rodents
- 409 Subchronic oral toxicity–90-day study in non-rodents
- 410 Repeated dose dermal toxicity–21-/28-day study
- 411 Subchronic dermal toxicity–90-day study
- 412 Repeated dose inhalation toxicity–28-/14-day study
- 413 Subchronic inhalation toxicity–90-day study
- 414 Teratogenicity
- 415 One-generation reproductive toxicity study
- 416 Two-generation reproduction toxicity study
- 417 Toxicokinetics
- 418 Acute delayed neurotoxicity of organophosphorus substances
- 419 Subchronic delayed neurotoxicity of

- organophosphorus substances
- 420 Acute oral toxicity–fixed dose method/
acute toxic class method
- 421 Reproductive/developmental toxicity
screening test
- 422 Combined repeat-dose toxicity study
with reproduction/developmental toxic-
ity screening test

Long Term Toxicology

- 451 Carcinogenicity studies
- 452 Chronic toxicity studies
- 453 Combined chronic toxicity/carcinogenic-
ity studies

The following three are newly drafted guide-
lines.

- Percutaneous absorption–*in vitro* meth-
od
- Percutaneous absorption–*in vivo* method
- Neurotoxicity

The ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) was started in 1991 (as “ICH-1”) in order to promote harmonization of regulatory requirements for the three major world markets, i.e. the United States, Europe and Japan. The ICH is jointly sponsored by the EU, the FDA, the MHW, and the IFPMA (International Federation of Pharmaceuticals Manufacturers Association); the last organization consists of pharmaceuticals industries associations of three regions like PhRMA (US), EFPIA (EU) and JPMA (Japan). They are collectively called the 6-pack. Industry and regulatory experts from the 6-pack organize the EWG (expert working group) with respect to quality (Q), safety (S), efficacy (E) and multidisciplinary (M) topics on pharmaceuticals. Since the ICH-1, EWGs have been frequently opened in different regions, and the ICH-3 will be in Yokohama in November 1995. The steering committee (SC), which consists of delegates from the 6-pack and the IFPMA (a total of 14 persons) oversees the whole ICH process. Topics to establish harmonized tripartite guidelines are selected by the SC and EWGs are asked to develop them according to the following steps:

Step 1; Preliminary discussion of topics by the relevant EWG, which is mandated by the SC, followed by preparation of the first draft, includ-

ing guidelines, policy statement, recommenda-
tions and points to consider.

Step 2; On recommendation by the SC, the draft is transmitted to the three regional regula-
tory authorities for formal consultation in accord-
ance with their normal internal or external con-
sultation processes. The comment period should
normally be six months.

Step 3; Comments are collected by the regula-
tory authorities and exchanged among the other
regulatory bodies. The designated regulatory
rapporteur analyses the comments and amends
the draft. The revised draft is referred to the
EWG to be “signed off” by the experts before
being referred to the SC for adoption.

Step 4; The final draft is endorsed by the SC,
which recommends it for adoption to the three
regulatory bodies.

Step 5; The recommendations are incorporated
into domestic regulations or other appropriate
administrative measures, according to national or
regional internal procedures.

At present, “safety” is divided into six areas,
and eleven tripartite guidelines are being or have
been established as follows:

S1 Carcinogenicity

- S1A Conditions which require carcinogenic-
ity studies for pharmaceuticals (Step 2)
- S1B Species for carcinogenicity studies (Step
1)
- S1C Dose selection for carcinogenicity stud-
ies of therapeutic agents (Step 4)

S2 Genotoxicity

- S2A Genotoxicity: Specific aspects of re-
gulatory tests (Step 3)
- S2B Genotoxicity: Standard battery tests
(Step 1)

S3 Toxicokinetics

- S3A Toxicokinetics: A guidance for asses-
sing systemic exposure (Step 4)
- S3B Pharmacokinetics: Guidance for repea-
ted dose tissue distribution studies
(Step 4)

S4 Single-and repeat-dose toxicity testing

- (Step 5 for single-dose toxicity and Step 1 for
repeat-dose toxicity)

S5 Reproductive toxicity

- S5A Detection of toxicity for reproduction in
medicinal products (Step 5)
- S5B Reproductive toxicity: Male fertility

study (Step 2)

S6 Safety studies on biotech products (Step 1)

The following four guidelines are not included in the “safety” area, but they contain safety issues :

M3 Timing of preclinical studies in relation to clinical trials (Step 1)

Q3A Impurities in new drug substances (Step 4)

Q3B Impurities in dosage forms (Step 1)

Q3C Impurities : Residual solvents (Step 1)