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 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

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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 toxicity screening test

Long Term Toxicology
451 Carcinogenicity studies
452 Chronic toxicity studies
453 Combined chronic toxicity/carcinogenicity studies

The following three are newly drafted guidelines.

Percutaneous absorption–in vitro method
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, including guidelines, policy statement, recommendations and points to consider.

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

Step 3; Comments are collected by the regulatory 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 carcinogenicity studies for pharmaceuticals (Step 2)
S1B Species for carcinogenicity studies (Step 1)
S1C Dose selection for carcinogenicity studies of therapeutic agents (Step 4)

S2 Genotoxicity
S2A Genotoxicity: Specific aspects of regulatory tests (Step 3)
S2B Genotoxicity: Standard battery tests (Step 1)

S3 Toxicokinetics
S3A Toxicokinetics: A guidance for assessing systemic exposure (Step 4)
S3B Pharmacokinetics: Guidance for repeated 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)