International Pre-validation and Validation Studies

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At a symposium that was held on the occasion of establishing ZEBET in 1989, the issue of validating alternatives to animal tests that have to be conducted for regulatory purposes was discussed. To solve this problem we agreed to hold a workshop on the validation of *in vitro* toxicity tests. In 1990 this workshop was held in Amden (Switzerland) and the basic principles of experimental validation that were defined by the participants and published as "report and recommendations of the CAAT/ERGATT workshop on the validation of toxicity test procedures". Later in the same year a second international workshop in Vouliagmeni (Greece) "on the promotion of the regulatory acceptance of validated non-animal toxicity test procedures" was held. Thus even before ECVAM or ICCVAM existed at these two workshops some of the basic principles of experimental validation of *in vitro* toxicity tests were defined.

After the EC/HO international validation study on alternatives to the Draize eye test failed, which was conducted according to these recommendations, at a second validation workshop in Amden in 1995, biostatistically based prediction models were added as essential elements of toxicity tests and also a management structure of validation studies, to ensure that validation studies are conducted as independent and unbiased as possible. Later the same year the pre-validation concept was proposed as result of a cooperation between ECVAM, IIVS and ZEBET.

The specific modules of validation studies that were proposed until 1995 are until today the basis of international documents on experimental validation of toxicity test procedures, e.g. recommendations and guidelines accepted by ECVAM, ICCVAM and finally also by the OECD, which published in 2004 a detailed Guidance Document No. 34 "on the validation and international acceptance of new and updated test methods for hazard assessment".

To speed up the regulatory acceptance of in vitro tests methods that are meeting the requirements of an established test, e.g. to prove that a newly developed skin model meets the requirements of an EU or OECD Test Guideline, in cooperation with ECVAM ZEBET proposed the principle of " catch up validation" and proved that this concept is valid.

Finally ZEBET also contributed to the development of the "weight of evidence" validation concept which was proposed in 2004 under the guidance of Thomas Hartung at ECVAM to speed up the experimental validation process and to reduce costs.

Examples of successful pre-validation and validation studies will be presented to illustrate ZEBET's contribution to establishing *in vitro* toxicology in an "unfriendly environment".