Federal **A**gency for **M**edicines and **H**ealth **P**roducts (FAMHP)

Regulatory Acceptance and Use of *in vitro* Methods for Non-Clinical Testing of Human Medicinal Products

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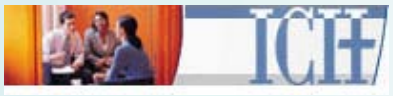
Regulatory background

Non-clinical guidelines, recommendations by:

UE: EMEA (European Medicines Agency; www.emea.europa.eu)

European Medicines Agency

ICH: International Conference on Harmonisation
(www.ich.org)



JAPAN: Japanese Ministry of Health and Welfare (www.mhlw.go.jp)

Ministry of Health, Labour and Welfare

厚生労働省

The 3R's and medicinal products

EU level:

CPMP Position Paper on Replacement of Animal Studies by *In Vitro* Models (CPMP/SWP/728/95 - adopted 1997)

- Feasibility of replacing *in vivo* animal studies
- Procedure for validating *in vitro* tests
- Procedure for incorporating *in vitro* tests into the regulatory requirements
- Areas for which the acceptance of *in vitro* tests can be considered

Criteria of acceptance of *in vitro* methods

- Early tox / compound screening:
  in-house validation by companies, NO regulatory involvement

- Exploratory/mechanistic studies for regulatory decision-making:
  based upon demonstrated "scientific validity"

- Pivotal (guideline-driven) studies:
  different routes of „formal (?)" validation
  - "historically" introduced *in vitro* models: NO formal validation
  - transition from exploratory/mechanistic screening models to pivotal studies based on accumulating experiences (review of data bases)
  - targeted replacement of established animal study by *in vitro* model requires formal validation

Recently accepted new *in vitro* methods for standard regulatory safety testing of medicinal products

- Phototoxicity testing

CPMP Note for Guidance on Photosafety testing (CPMP/SWP/398/01 - adopted 2002)

- Recommends the use of the *in vitro* 3T3 NRU phototoxicity test
- 3T3 NRU PT results from a formal validation procedure driven by the cosmetic sector
- OECD Guideline Number 432
- EU-only, no ICH initiative yet

Recently accepted new *in vitro* methods for standard regulatory safety testing of medicinal products

- Genotoxicity testing

Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (ICH S2 (R1): Revision of ICH S2A/B - Step 2 February 2008)

- Recommends the use of the *in vitro* micronucleus test as part of the standard testing battery
- *In vitro MN test* results from a formal validation procedure (ECVAM), an OECD Guideline 487 is in preparation
- Ames assay and the mammalian cell systems *(in vitro metaphase CA assay and mouse lymphoma L5178Y cell tk gene mutation assay)* are widely use and considered sufficiently validated (historically introduced models!)
- + REDUCTION!: integration of *in vivo* genotoxicity assay in repeat dose toxicity study

Recently accepted new *in vitro* methods for standard regulatory safety testing of medicinal products

- Safety Pharmacology testing

Note for guidance on the nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (ICH S7B - adopted October 2005)

- Recommends the use of *in vitro* and *in vivo* assays as complementary approaches
- Study results are used to elucidate mechanism of action and estimate risk for delayed ventricular reporlarisation and QT interval prolongation
- NO formal validation , but selection of test system based upon:
  - scientific validity and robustness of method and endpoints
  - standardisation of assay and cell preparations
  - reproducibility of the results
  - endpoints/parameters relevant for assessment of human risk

Recently accepted new *in vitro* methods for standard regulatory safety testing of medicinal products

- Hepatotoxicity testing

Non-clinical guideline on drug-induced hepatotoxicity (CHMP/SWP/150115/2006 - draft adopted February 2008)

- Recommends the use of *in vitro* assays as mechanistic approaches to elucidate drug-related adverse liver reactions
- NO formal validation , but selection of test system based upon:
  - scientific validity and robustness of method and endpoints
  - Standardisation of assay and cell preparations
  - reproducibility of the results
  - endpoints/parameters relevant for assessment of human risk

Conclusions

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- There is no clearly defined process for acceptance and the implementation of *in vitro* methods for regulatory safety testing of medicinal products

- However, multiple and flexible approaches are possible in response to the range of specific objectives and regulatory requirements

- Implementation via ICH process has the highest impact

And the future … ?

- The development of more strict acceptance criteria is currently not under consideration
- The integration of 3R expertise in the ICH process is ongoing (collaboration with CVAMs has started)
- A proactive identification of areas where new *in vitro* methods might be appropriate (and necessary!) is desirable
- Communication with other sectors (chemicals, cosmetics etc) via EPAA is a step forward but should be increased