THE PROCESS OF VALIDATION
THE POINT OF VIEW OF THE CRO
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http://www.remanet.net/
The role of contract organization in toxicological development

General trend of industry $\rightarrow$ contract out non-clinical development

Reasons:

- small and mid-size companies (limited experience)
- preference to rely on established techniques
- importance of trained personnel
- assign valuable resources on internal projects
- rare occasions to carry out the methods
Features of the CROs

Industry is not homogeneous

CROs have more knowledge than average industrial companies for their:

- involvement in the safety assessment of a wide range of products
- tendency to deal with different industry segments (different needs, approaches, flexibility, drivers...)
Main functions of CROs

- comply with regulatory requirements
- ensure an updated knowledge of the new method status
- follow both scientific and regulatory points of view
The importance of the CRO experience

Important roles of the CRO in the alternative method validation process:

- ensure laboratory personnel training
- guarantee high quality level and proficiency in a wide variety of techniques

This generally occurs only in laboratories that regularly conduct a wide range of assays
Reasons for an early involvement of the CRO in the validation process

Validation and acceptance process should be as efficient as possible

Possible causes of attrition are:

- lack of rigorous controls
- lack of technical experience
- lack of information on regulatory requirements and industry needs
- design of inappropriate tests or unreliable results

An early involvement of the CRO in the validation process may facilitate its progression
Time of CRO involvement in validation process

- New alternative methods find common ethical driver both in industry and CRO environment

- CROs are rarely involved in the preliminary phase → no real economical incentive (until the method is accepted and requested)

- Industries are often the developers of new alternative methods for economical motivation and law pressure
Importance of independence

Desired attributes of a Reference Laboratory:

- independence from assay developers and manufacturers
- unbiased position in the successful application
- neutral toward scientific and economical interests
Validation process

- Research and Development
- Pre-validation
- Validation
- CRO Industry
- Regulatory acceptance
- Implementation
- Academia Industry
- Industry
- CRO Industry
- Regulators OECD
CRO as the ideal partner for a successful validation strategy

Understanding the needs of industry and regulatory framework is a key factor
CRO in pre-validation phase

CRO as the ideal partner in the pre-validation phase:

- established attitude to work in GLP compliance
- aptitude to facilitate assay transfer
- habit to assess test reproducibility (intra- and inter-laboratories)
- properly trained personnel
CRO in validation phase

CRO as the ideal partner in the **validation** phase:

- ability to analyse a large group of chemicals → test the predictivity of the proposed method

- habit to conduct a significant number of GLP-compliant studies in a timely manner
The point of view of CRO in the validation process

CRO involvement in the validation process represents an excellent occasion to:

- gain experience regarding alternative method opportunities
- get used to the procedural difficulties
- become skilled with the interpretation of results of the new method

CRO must consider balance between immediate investments and delayed payback (rate and time)
# Status of validated alternative methods

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<th>Eye Irritation</th>
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<td>3T3 NRU to estimate starting doses for oral acute toxicity</td>
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<td>In vitro COMET and MN test 3D skin models</td>
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RTC experience - Validation of BCOP

Preamble:
Mainly pushed by the ethical driver, RTC participated in COLIPA validation trial and promoted this test especially as screening method.

Gautheron P; Giroux J; Cottin M; Audegond L; Morilla A; Mayordomo-Blanco L; Tortajada A; Haynes G; Vericat JA
“Interlaboratory assessment of the bovine corneal opacity and permeability (BCOP) assay”
Toxicology in vitro; 8(3); 381-392; 1994
RTC experience - Validation of BCOP

Outcome:

- Few requests at the beginning (lack of regulatory requirements)
- Sponsor requests increased after issue of OECD 437
- RTC method adjusted to comply with the new guideline
RTC Sponsor’s requests for ocular irritation

OECD 405 - Acute Eye Irritation/Corrosion
OECD 437 - BCOP Test

2005

2010 - 2011
RTC experience - Validation of in vitro MNT

Preamble:
RTC participated in the French validation trial and promoted this test as screening method.

Clare MG; Lorenzon G; Akhurst LC; Marzin D; van Delft J; Montenero R; Botta A; Bertens A; Cinelli S; Thybaud V; Lorge E.
“SFTG international collaborative study on in vitro micronucleus test II. Using human lymphocytes”
Mutat. Res. 2006 Aug 4;607(1):37-60
RTC experience - Validation of *in vitro* MNT

**Outcome:**

- Immediate success of this kind of study as genotoxicity screening
- Sponsor requests increased following EU regulatory acceptance and rapid integration into REACH legislation
- RTC method adjusted to comply with the new versions of OECD guideline
RTC experience - Validation of *in vitro* MNT

- Economical driver
- Improvement of *in vitro* test battery predictivity → limitation of animal testing
- Ethical consequences: Intelligent Testing Strategy
RTC experience in promoting alternative methods

RTC position with other alternative methods

- EpiOcular assay
- Inflammatory cytokine measurement in 3D skin models
- Genotoxicity tests in 3D skin models

CRO plays a central role to encourage the use of promising methods as preliminary screening
CRO strategy in the selection of alternative tests

- business area (Cosmetic, Pharmaceutical, Chemical)
- CRO technical and scientific vocation
- white or position papers which foresee regulatory requirements
- number of Sponsor enquiries
- possibility to apply the new test as a stand-alone substitute of conventional method
- expectations of economical return after investments for internal implementation and demonstration of proficiency
RTC experience in the alternative test selection – OECD 425

Preamble:

- OECD 401 (LD50) guideline deleted in December 2001
- Alternative test methods introduced in the mid 1990’s
- RTC implemented the 3 OECD guidelines
  - OECD 423 (Toxic class)
  - OECD 420 (Fixed dose)
  - OECD 425 (Up and Down)
- OECD 425 is the most complex, difficult to manage and requires more time to carry out the test
RTC experience in the alternative test selection – OECD 425

Distribution of RTC Sponsor’s requests for acute toxicity studies
RTC experience in the alternative test selection – LLNA

Radioactive LLNA

- included in RTC services following issue of OECD 429 guideline
- offered as sensitization test alternative to M&K and Buehler tests
- high costs of disposal for radioactive waste → test poorly profitable
RTC experience in the alternative test selection – LLNA

BrdU LLNA

- OECD guideline did not present radioactive method as the only acceptable one

- Sponsors did not trust “cold” alternatives until the specific guideline was issued in 2010 (OECD 442B).
Importance of regulatory position on reliability of alternative methods

Industry may have a conservative approach driven by the risk avoidance

- non-chemical industry (skin sensitization tests) → M&K or Buehler still requested in place of LLNA

2005

2010 - 2011
Importance of regulatory position on reliability of alternative methods

- non-chemical industry (skin irritation tests) → *in vivo* study requested instead of Intelligent Testing Strategies (QSAR, pH, alternative *in vitro* methods)

- pharmaceutical industry (photosafety assessment) → requests of complete battery in presence of negative results in *in vitro* phototoxicity assay
Toxicology is a conservative science

Often toxicologists rely on previous experience of dossier acceptance

- fear that results from alternative studies might be not easily accepted
- rare requests for methods abolished for ethical reasons

Role of CRO in updating sponsors on validation progress

- promote acceptance of methods
- facilitate quick adoption in routine use
RTC experience in the alternative test selection – Episkin

RTC in the recent years witnessed an increasing number of requests for *in vitro* skin studies, in particular for skin irritation tests.

- **2005**
  - OECD 404

- **2010 - 2011**
  - OECD 431, 435, 439
  - OECD 404
RTC experience in the alternative test selection – Episkin

Reasons:

- predictivity comparable to *in vivo* conventional studies
- good reliability as screening assay (e.g. pharmaceutical formulations)
- regulatory driver (Cosmetic and REACH regulation)
- costs
Conclusion

CRO an ideal reference laboratory during the validation process

- independence from assay developers and manufacturers
- GLP-compliance
- experience in routine use of *in vitro* assays
- understanding of scientific and regulatory needs of industry
- knowledge of regulatory agencies requirements
- aptitude to meet programmed deadlines
Conclusion

- Promotion of alternative tests may be challenging
- CRO may find economic benefit if involved in the validation process and subsequent application of alternative methods

CRO plays a central role to encourage the use of new tests and overcome the natural cautious aptitude of industrial sponsors
Responsive
Thorough
Competent

Reactive
Tailored
Cost effective

Reliable
Team focused
Committed

Receptive
Timely
Capable

Respected
Trustworthy
Collaborative

Right size
Toxicology
CRO

Thank you