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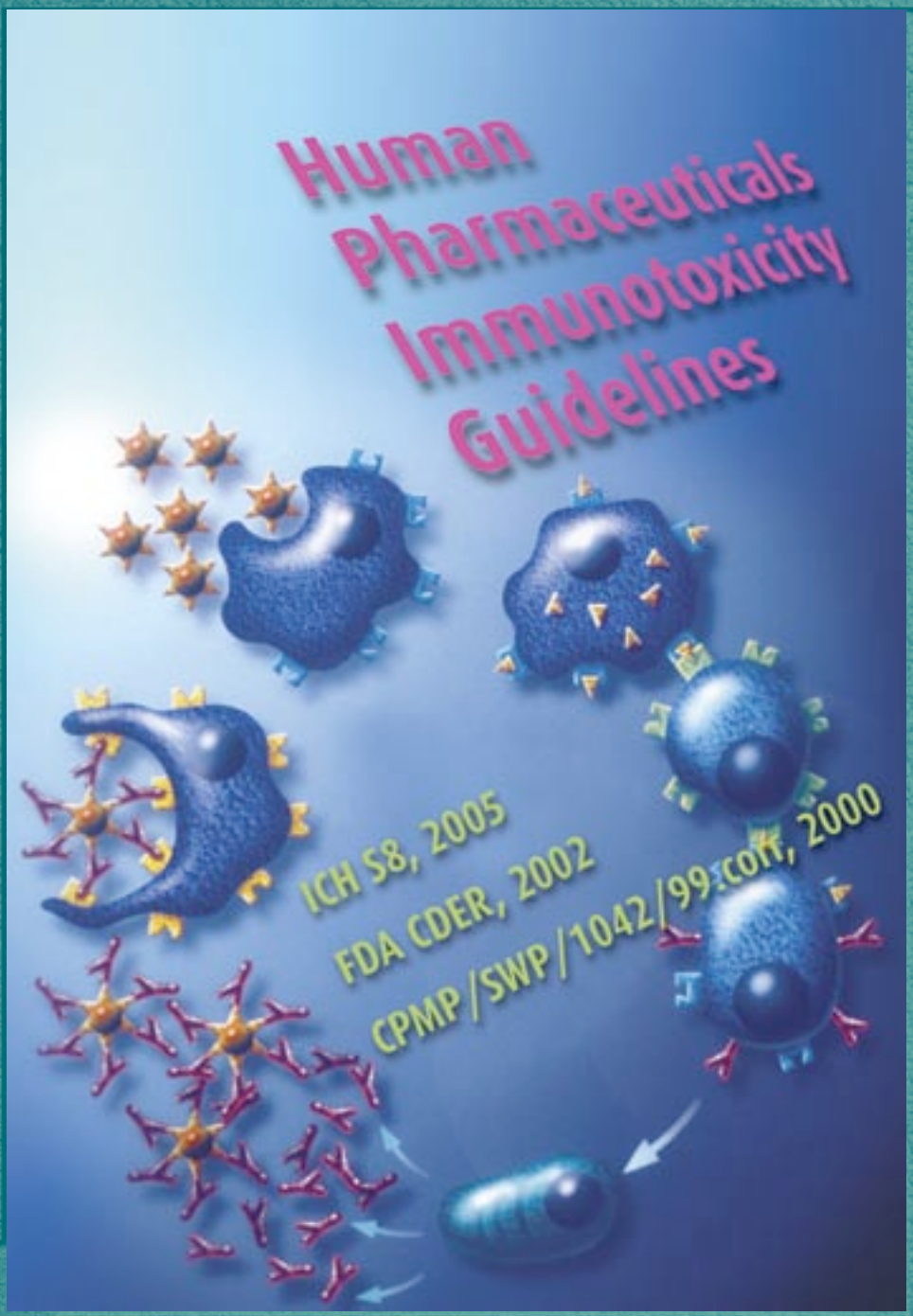
Regulatory Rapporteur

TOPRA – THE ORGANISATION FOR PROFESSIONALS IN REGULATORY AFFAIRS



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Cover illustration:

ICH, EU and US guidelines on immunotoxicity are compared in an overview beginning on page 2.

Editorial

Welcome to the first 2006 issue of *Regulatory Rapporteur!*

Dr Paolo Biffignandi, VI.REL Pharma S.r.l., Turin, Italy
Chairman, TOPRA Information Services Business Unit

Last year all members of TOPRA noticed the great efforts that have been made to improve the quality and usefulness of the information contained in the journal. Indeed, a high standard of authors and topics has been reached, to parallel the high standard of membership audience. The introduction of "focus issues" greatly enhanced the availability of updated "hot topics", and we are planning to repeat this experience this year.

Warm, friendly, and grateful thanks go to Axel Wenzel, who chaired our Information Services Business Unit since the creation of TOPRA. Axel is now TOPRA's President-elect and I am sure I am representing all members' feelings in wishing him all the best for his new and exciting appointment.

I am taking over responsibility for chairing this Unit, hoping that this journal, our website and *InTouch* will become even more useful to us members of TOPRA, as tools of regulatory intelligence, information, professional enhancement and friendship.

Several new projects are under discussion for the journal (you may notice the inclusion of abstracts and key words for each original article, starting from this issue), the website is constantly improving and *InTouch* is becoming appreciated like a phone call from an old good friend, telling us about the past and present.

Past and present are also the spirit of the article of John Taylor about the development and current status of immunotoxicity guidelines. It is an honour that Dr McBlane from the UK MHRA is sharing with us his opinions about such a complex scenario in which a new chemical entity is being developed for a clinical indication in which a carcinogenicity assessment would be expected, but where a meaningful carcinogenicity study cannot be performed. Michael F O'Neill reports again on the EMEA's activity for anti-dementia treatments (a topic I sometimes think closer to me than expected, after the efforts to understand the new medicines legislation in Europe!). Even for those whose memory is still working, there is the need of finding sources of regulatory information. Several different options (websites, gateways, regulatory journals, commercial database products, and cooperation between regulatory professionals) are discussed in details by Sally Cox and John Poland. And since New Year's Day is still close, we finish with an "exotic" touch provided by Neil Armstrong and Roberto Latini on regulatory affairs in Brazil, the second largest healthcare market in the Americas (second only to the USA).

Finally, on behalf of the Management Team, our deepest thanks to all present and future contributors, members, and correspondents, without whom the *Regulatory Rapporteur* would not exist. Read it and rely on it.

Focus

An overview of immunotoxicity guidelines – past to present

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Introduction

On September 15, 2005, the *ICH S8 Immunotoxicity Studies for Human Pharmaceuticals* guideline was recommended for adoption at Step 4 of the ICH process. This important harmonisation step for immunotoxicity guidance was the culmination of more than quarter of a century of a range of international initiatives (conferences and guidelines) on this important component of human risk assessment. It is useful therefore to provide a brief overview of some of the most important initiatives over the years and give a more detailed account of contemporary guidelines (including ICH S8) for pharmaceuticals.

Immunotoxicology regulatory guidelines have evolved from the 1980s, during which time there have been a number of significant international conferences on immunotoxicity testing and risk assessment. An overview is provided in Table 1 on the chronology of key programmes and guidelines which have influenced the development of the science of immunotoxicology, and the development of more recent guidelines for pharmaceuticals. The US Environmental Protection Agency and the US National Toxicology Program were particularly involved in the formative years in the development of tiered immunotoxicology testing guidance, which has since been adopted for chemicals, pesticides and pharmaceuticals. Separate efforts were made in the 1980s in Europe to provide guidance on the prospective assessment of the immunotoxicological potential of chemicals including pharmaceuticals.

Table 1: Some Key Immunotoxicity Programmes and Guidelines Prior to Contemporary Immunotoxicity Guidelines for Pharmaceuticals

Key Immunotoxicology Programme/Guideline	Main Features of Programme/Guideline
US Environmental Protection Agency Office of Pesticide Program guideline for the immunotox. evaluation of pesticides (Subdivision M; Pesticide Assessment Guidelines), 1982	New pesticides should be evaluated according to Tier I and Tier II immunotoxicology evaluation.
Council of the European Communities, *Official Journal*, no. L332/11, 1983	Recommendation for assessment of immunotoxicity of new medicinal products, with particular emphasis on histopathological assessment of immune system.
National Institute of Public Health and Environmental Protection (RIVM) in the Netherlands (Vos and van Loveren, 1987)	Tiered approach for testing based essentially on OECD Guideline 407 at Tier I. Tier II testing (cell-mediated immunity, humoral immunity, macrophage function, NK function, host resistance) performed where required to further define immunotoxic effects.
US Environmental Protection Agency proposal for first draft revision of 1982 guideline (Sjoblad, 1988)	New pesticides should be evaluated by repeat dose (>30 days) toxicity testing at Tier I (includes functional assays). Tier II would be performed if positive or uninterpretable immunotoxicity results were obtained from Tier I or if other sources indicate immunotoxicity.
US National Toxicology Program (Luster *et al.*, 1988; Luster *et al.*, 1992; Luster *et al.*; 1994)	Inter-laboratory immunotoxicology (repeat dose) validation study in mice of five test substances (including diethylstilboestrol and cyclophosphamide). The study later included over 50 test substances. Tier I testing: general toxicity, pathology and functional endpoints. Tier II testing: to further define immunotoxic effects.
Organisation for Economic Development and Cooperation (OECD), Revised Guideline 407, 1995	Repeat dose toxicity guideline, including revised specific guidance on immunotoxicity (pathological) investigations.
US Environmental Protection Agency Toxic Substances Control Act (TSCA; Federal Register, 1997)	Update of the pesticides guidelines on immunotoxicity testing covering histopathological and functional endpoints. Tier I testing was for general toxicity and pathology and humoral immunity. Innate immunity (NK assay) may be performed. Tier II testing to further define immunotoxic effects.

The spirit of the above immunotoxicology programmes and guidelines has been adopted for subsequent testing guidelines issued in the pharmaceuticals sector, as detailed later in this overview. In particular, tiered approaches to testing have been used for many years, and recent developments for immunotoxicity testing of pharmaceuticals have focused particularly on optimising tiered testing strategies.

Current developments for pharmaceuticals

The developing awareness of possible unwanted immunomodulating effects of pharmaceuticals has resulted in the release of a number of regulatory guidance documents for immunotoxicity testing in all three ICH regions in the more recent past. Within the various guidelines that have been developed, it is emphasised that evaluation of the potential adverse effects of human pharmaceuticals on the immune system should be incorporated into standard drug development.

Final guidelines for identifying the potential immunotoxicity of new chemical entities have been released by the European Union (EU) Committee for Proprietary Medicinal Products (CPMP) in 2000 and the US Food and Drug Administration Center for Drug Evaluation and Research (CDER) in 2002.

The current immunotoxicity guidelines focus on immunosuppression by small chemical entities and exclude biotechnology-derived pharmaceuticals. The latter are presently covered by the final *ICH S6 Pre-clinical Safety Evaluation of Biotechnology-Derived Pharmaceutical* guideline, released in 1997. This guideline considers both the immunogenicity and immunotoxicity of biotechnology-derived pharmaceuticals, many of which are intended to stimulate or suppress the immune system thus potentially modulating humoral and cell-mediated immunity.

ICH guideline S6 excludes immunotoxicity testing of vaccines which is covered by a number of specific guidelines released in the three ICH regions, focusing on the testing of vaccines or adjuvants. In the EU, guidelines for adjuvants and vaccines are included in the Guidance Documents section of the Human Medicines part of the EMEA website. The World Health Organisation (WHO, 2003) has published comprehensive guidelines on the non-clinical evaluation of vaccines, with detailed information on immunotoxicity assessments.

There is still much debate about the best approach for assessing the immunotoxicity potential of new chemical entities. Much of this debate is focused on subtle differences between the FDA (2002) and CPMP (2000) guidelines with regard to the best approach for determining the immunotoxicological risk.

Efforts to harmonise immunotoxicity testing programmes have culminated in development of the *ICH S8 Immunotoxicity Studies for Human Pharmaceuticals* guideline, which reached Step 4 of the ICH development process on September 15, 2005. As a Step 4 guideline, this final draft document is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

The following Table 2 compares the guidelines for immunotoxicity testing issued by the ICH, US (FDA CDER) and EU (CPMP).

Table 2: Comparison of Current ICH, EU and US Immunotoxicity Guidelines

	ICH S8 Step 4 2005	US FDA CDER 2002	EU CPMP 2000
Specific immunotoxicity guideline	Yes.	Yes.	No, included in guidance on repeated dose toxicity.
Drug-induced hypersensitivity, immunogenicity and autoimmunity excluded	Yes.	No, these categories are included in the guideline.	Yes (Note: skin sensitizing potential addressed in CPMP Note for Guidance on Non-Clinical Local Tolerance Testing, 2001).
Screening study(ies) required	Yes, the initial screen for potential immunotoxicity involves Standard Toxicity Studies (STS) from short-term to chronic repeat dose studies in rodents and non-rodents.	Yes, including all standard repeat dose toxicology studies that have been performed.	Yes, screening required for all new active substances in at least one repeated dose toxicity study (duration ideally should be 28 days). Rats or mice are species of choice.

Focus continued…

Table 2: Comparison of Current ICH, EU and US Immunotoxicity Guidelines *(Continued)*

	ICH S8 Step 4 2005	US FDA CDER 2002	EU CPMP 2000
Screening study(ies) immunotoxicity parameters	Changes in hematology, lymphoid organ weights, histopathology of immune system, serum globulins and increased incidences of infections and tumours should be evaluated for signs of immunotoxic potential in the STS.	Changes in hematology, lymphoid organ weights, gross pathology and histopathology of immune system, serum globulins and increased incidences of infections and tumours should be evaluated for signs of immunotoxic potential.	Hematology, lymphoid organ weights, histopathology of lymphoid tissues, bone marrow cellularity, distribution of lymphocyte subsets and NK cell activity (if latter two unavailable, primary antibody response to T-cell dependent antigen).
Other factors to consider in evaluation of potential immunotoxicity and the need for additional immunotoxicity studies	Pharmacological properties of drug; patient population; structural similarities to known immunomodulators; drug disposition; clinical data.	Patient population; known drug class effects (including SARs); drug pharmacokinetics; clinical data. If drug intended for HIV, immune function studies required.	None specifically included in the guideline.
"Follow-on"/"Additional" immunotoxicity studies	"Additional" studies may be required depending on the "weight-of-evidence review" of STS and "other factors". "Additional" studies addressed in 3.2, 3.3 and Appendix of guideline.	"Additional" immune function studies (sections III.B and III.C of guideline) may be required depending on "weight-of-evidence review" of effects in toxicity studies and "other factors".	"Follow-on" functional immunotoxicity studies (Appendix B of guideline) warranted on a case-by-case basis.
Timing of "Follow-on"/ "Additional" immunotoxicity testing in relation to clinical studies	"Additional" immunotoxicity testing, if required, should be completed before clinical Phase III, or earlier depending on the effect or the patient population.	Not specified.	Not specified.

The US Food and Drug Administration CDER (2002) publication also covers developmental immunotoxicity, which should be addressed where a drug has shown immunosuppressive potential in adult animal studies. More recently, a group of immunotoxicology experts from the US and EU has proposed a testing frame work for developmental immunotoxicity (Holsapple MP *et al*., 2005). The major conclusions are that the rat is the preferred model and that validated developmental immunotoxicity methods should be incorporated into standard developmental and reproductive toxicity protocols where possible.

The common spirit of regulatory immunotoxicity guidelines

All current immunotoxicity guidelines for new drug entities are based on a tiered testing approach with a basic set of parameters to be assessed during standard toxicological studies (STS), and "Additional"/ "Follow-up" investigations initiated by alerts from basic toxicological studies.

As outlined in the ICH S8 Step 4 guideline (2005) and in the US FDA CDER guideline (2002), in addition to the alerts from the STS, other causes for concern that might prompt additional immunotoxicity studies include the pharmacological properties of the drug, the intended patient population, known drug class effects, the disposition of the drug and clinical data.

All guidelines from the different ICH regions request that basic immunotoxicity screening should encompass hematology, lymphoid organ weights and histopathology of the lymphoid organs. All of these parameters are assessed in standard repeat dose toxicity studies.

Discrepancy remains in the ICH regions on the need for a functional assay. Currently, only Europe requests functional assays in routine screening. In Europe (CPMP, 2000), the routine screening of every compound should include distribution of lymphocyte subsets (by phenotyping) and natural killer cell activity. If these are not available, primary antibody response to a T-cell-dependent antigen may be assessed as an alternative.

The FDA CDER (2002) document advocates a case-by-case approach to the need for functional assays. This approach is similar to the position taken by the ICH S8 Step 4 guideline (2005). Irrespective of whether a functional assay for immunotoxicity was already integrated into the basic toxicological tests (as in Europe), a decision whether additional immunotoxicity follow-up studies are appropriate should be determined by a weight of evidence review of cause(s) for concern. It is generally agreed that a follow-up immunotoxicity testing programme must be designed on a case-by-case basis to allow for sufficient flexibility reflecting the different effects a drug may exert on the immune system.

All relevant guidelines only recommend testing methods for follow-up assessment of immunotoxicity. It is at the discretion of the investigator to choose appropriate models, test methods, and protocols for follow-up immunotoxicity studies.

Non-clinical programmes designed to assess adverse effects of new drugs on the immune system should be based on generally accepted, as well as technically and biologically validated methods. The programme should furthermore follow the general rules of toxicology by reflecting the following parameters, as outlined in ICH S8:

- Statistical and biological significance of the changes
- Severity of the effects
- Dose dependency
- Safety factor above the expected clinical dose
- Study duration
- Number of species and endpoints affected
- Changes that may occur secondarily to other factors, eg, stress
- Possible cellular targets and/or mechanism of action
- Doses which produce these changes in relation to doses which produce other toxicities
- Reversibility of effect(s).

Conclusions

The science of immunotoxicology has been developing for more than a quarter of a century. The issue of the Step 4 ICH S8 guideline is a landmark for immunotoxicology in that an international harmonized approach to immunotoxicity assessment and testing strategies has been achieved. This is especially important since the availability of biomarkers for evaluating the immune system in clinical trials is limited. Therefore, emphasis must be placed in every new non-clinical development programme to identify potential immunotoxicological risks. Toxicity data support the design of clinical trials and may, depending on findings observed, trigger enhanced screening for certain immune related effects in clinical trials.

Focus continued…

3rd Annual TOPRA Symposium

2–4 October 2006

Hilton, Amsterdam, The Netherlands

Make a note in your diary now, for the most important TOPRA meeting in 2006!

Those of you who came to the 2nd Annual Symposium in Berlin will know that TOPRA attracts excellent high-level speakers and provides a forum for detailed discussion of all the most important regulatory issues of the day. The TOPRA Symposium is an opportunity to get right up to date with latest information and to network with industry and agency colleagues.

For 2006 we are delighted that with the agreement of TOPRA Advisory Council member, Dr Aginus Kalis, the Dutch Medicines Evaluation Board (MEB) will be assisting with the organisation of the programme and this meeting will be an ideal opportunity to get to know this key agency better.

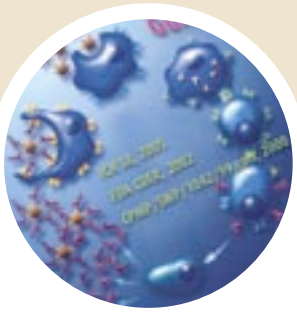
Also in 2006 the programme will be expanded to include sessions covering medical technologies and veterinary matters, amongst others.

The 2006 Symposium will also be the venue for the 2006 AGM and the 2006 Graduation Ceremony for the TOPRA MSc in Regulatory Affairs.

As always there will be a trade exhibition showcasing companies with products and services to assist the regulatory professional, and a social event for informal networking.

Look out for further announcements during the coming months.

In the meantime, if you would like to be part of the planning team for this or any other TOPRA meeting, please e-mail our Conference and Training Programme Manager, Christopher Bailey (christopher@topra.org)



Conclusions *(Continued)*

The importance of immunotoxicity risk assessment should not be underestimated, since the findings may affect the indication, patient management and the labelling of the medicinal product. Long-standing examples of small molecules that have such an impact given their immunotoxicity include immunosuppressive agents such as cyclophosphamide and methotrexate. A more recent example has been the use of TNF-α inhibitors in the treatment of autoimmune diseases. While showing significant efficacy, the potential to exacerbate infections has been observed through inhibition of TNF-α, since this cytokine is an important mediator of inflammation and cellular immune responses.

The ICH, EU (CPMP) and US (FDA CDER) guidelines, as discussed above, produced over the last five years support rational development of medicinal products using tiered approaches to testing. Crucially, the most recent guidelines emphasise the need to utilise all relevant information, and that requires harnessing the expertise of non-clinical experts and of other disciplines (including clinical and regulatory) to achieve optimal immunotoxicity testing strategies and clinical risk: benefit assessments for patients.

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Key Words

Immunotoxicity, ICH.

Abstract

This overview discusses the ICH, EU (CPMP) and US (FDA CDER) guidelines produced over the last five years which support rational development of medicinal products using tiered approaches to testing immunotoxicity. Differences between the three approaches and the common spirit of regulatory immunotoxicity guidelines are outlined.