ICH S9: Nonclinical development of anticancer agents – A step in the right direction

Abstract
Since 1990, the International Conference on Harmonisation (ICH) has led the development of guidelines for safety (eg, preclinical toxicity testing, pharmacology and carcinogenicity), efficacy (eg, good clinical practice, clinical safety, clinical trial design) and quality (eg, stability, impurities and analytical validation). These guidelines go through five 'steps' of development and are rigorously discussed and reviewed before being adopted by various national or regional bodies responsible for preclinical and clinical drug approvals.

Prior to the recent update of the ICH S9 guidance (Nonclinical Evaluation for Anticancer Pharmaceuticals), approaches to the preclinical development of new oncology drugs and biologics were not harmonised internationally. Instead, the development of medicines was independently discussed with various competent authorities, including the US FDA, the European Medicines Agency (EMA) and in Japan with the Ministry of Health, Labour and Welfare (MHLW). As a result, any non-consensus of opinion saw delays in bringing promising new therapeutics to cancer patients, as well as being an inefficient use of resources.

To address this issue, industry proposed that the ICH should undertake the development of harmonised guidance. Consequently, in May 2007 the ICH Steering Committee initiated a project to develop a new nonclinical safety guideline to cover both small and large molecules (excluding vaccines, cell and gene therapy products). The existing guidance, ICH S9, was designed to expedite the development of treatments for patients with advanced cancers while maintaining safety regulations. The updated guidance (Step 4 – scientific consensus) was planned for release in early 2010, but was in fact published earlier, in October 2009.

This article offers an overview of oncology drug development legislation to date, and discusses expectations following the release of the new guideline.

Oncology market and trends
Market sales of cancer drugs are predicted to grow by some 20% per annum, with an estimated market total of US$77 billion in 2010.\(^1\) Anticancer agents will be a strong area of R&D growth and a major investment area in the pipelines of many pharmaceutical companies. Oncology is also predicted to become the most common therapeutic focus for biotech companies. The FDA approved fewer small molecules but more biologics in 2009, many of those biologics were antitumour agents.\(^2\) Meanwhile, cancer products will continue to receive the highest share of FDA priority review ratings and FDA/EMA orphan drug designations. However, the cytotoxic/cytostatic class of agents is becoming less popular and newer, non-cytotoxic (signalling pathways) and context-dependent (tumour mutation-specific) mechanisms for the treatment of cancer now make up the bulk of the compounds in development.

History of the ICH S9 guidance
Prior to the recent release of the ICH S9 guidance, various bodies were independently publishing or were drafting their own guidance documents related to the nonclinical development of anticancers. The major concern was that these regional guidances would suggest different approaches, and industry would lean towards following the recommendations of the most conservative agency, in an effort to reduce any duplication of work and thus delay the entry of novel medicines for treatment of life-threatening diseases.\(^3\)

For example, in the US, the FDA’s Center for Drug Evaluation and Research (CDER) had begun drafting an official guidance on the development of small molecule therapeutics. However, this initiative was delayed by the requirement to incorporate biologics into any formal recommendations (previously reviewed and regulated by the biologics centre, the CBER).

Unofficial guidance on the development of anticancers, including the selection of clinical starting doses, was obtained from a publication authored by senior FDA staff.\(^4\) More recently sponsors could also receive guidance on the FDA’s expectations for the development of novel anticancers and biologics from the Oncologic Drugs Advisory Committee (ODAC) meeting.\(^5\) Generally speaking, the advice given was on a case-by-case basis but in order to proceed into first time in human (FTIH – end-stage cancer patient studies) the Committee expected sponsors to conduct Good Laboratory Practice toxicology studies in two species (rodent and nonrodent) and for these studies to follow the clinical schedule, route of administration and formulation as much as possible.

Another often requested area for guidance was on the duration of nonclinical safety studies relative to the duration of the clinical trial. Again generally speaking, for small molecules, when there is an absence of documented disease progression, an acceptable safety profile and when the agent is administered on an intermittent schedule, the FDA would allow multiple cycles of treatment in a clinical trial. For therapeutics intended to be administered continuously, continuous dosing for 28 days in rodents and nonrodents was generally considered sufficient to support clinical trials of longer than 28 days.\(^6\)

Other examples of ICH regions offering differing approaches or guidelines for the preclinical development of new oncology treatments include Europe and Japan. In Europe, the EMA had official preclinical guidance for the development of cytotoxic cancer treatments\(^7\) and had also issued an addendum addressing paediatric oncology requirements related to the development of drugs.\(^8\) It was generally agreed that

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Keywords
Anticancer; Nonclinical; Preclinical; Safety; Harmonisation; Toxicity; Dose selection; European Medicines Agency (EMA); US FDA

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Regulatory Rapporteur – Vol 7, No 4, April 2010 www.topra.org
nonclinical testing strategies for new agents designed to treat life-threatening diseases such as cancer should be viewed on a case-by-case basis. However, European regulators requested toxicology studies (typically 28 day studies using daily dosing prior to FTIH with patients) in two relevant species (not necessarily rodent and nonrodent as long as justification for species selection was given) for targeted anticancer therapeutics (ie, novel, non-cytotoxic). These studies were required to cover the duration of dosing in the clinic and if treatment in the clinic was to extend past 28 days then the length of nonclinical assessment had to be extended accordingly (which was essentially the same type of nonclinical recommendations for non-oncology agents in the ICH M3 guidance). As a result of these regulatory expectations, chronic animal toxicology studies have been required earlier in the development pathway of novel anticancer agents compared with other disease area therapies.

In addition, the European Organisation for Research and Treatment of Cancer (EORTC) published guidance related to the nonclinical development of novel cytotoxic anticancer agents (although the remit of this organisation is now mainly centred in later stage clinical development).

The MHLW developed a draft preclinical guidance that addressed various mechanisms of anticancer therapy, although it did not include biologics in its scope.

So, as can be seen, even within the ICH member states there was a discord in the guidance given for the preclinical development of anticancers.

In May 2007, the ICH Steering Committee produced a concept paper and business plan, with the aim of discussing the topic at the October 2007 ICH meeting in Yokohama, Japan. Prior to the meeting, members of the Expert Working Group (EWG) from the US, EU and Japan provided guidance documents as a framework for discussion, and developed a unified working document, based on the FDA document -- the most comprehensive document provided to the EWG -- which would serve as the primary basis for discussion. A subsequent meeting of the EWG took place in Portland, US in June 2008 covering topics such as the selection of starting doses in the clinic; the duration and timing of toxicology studies; and the requirement for reproductive and any other toxicology studies to support marketing authorisation whilst adhering to the 3R (reduce/replace/refine) principles for the use of animals in toxicology studies.

Other key areas for discussion was the acknowledgement that toxicology studies should not limit clinical doses studied or the continued treatment of patients receiving benefit from the investigational therapy.

Based on the EWG’s report, there was sufficient agreement on the technical issues for the draft guideline to proceed to the next stage of regulatory consultation. This was released late 2008 (at the EWG meeting in Brussels in November) and the ICH schedule aimed at completion of the harmonised tripartite Step 4 (scientific consensus) guidance by early 2010.

The ICH made progress on its S9 guideline on nonclinical data requirements for late-stage cancer treatments at its most recent steering committee meeting in October 2009 (St Louis, US), with final approval granted by the EMA’s Committee for Medicinal Products for Human Use (CHMP) in November 2009 (coming into operation in May 2010).

Studies to support nonclinical evaluation
The updated ICH S9 guideline allows flexibility on the design and conduct of nonclinical studies, but it is recognised that nonclinical evaluations are conducted to characterise the following:

- Beneficial pharmacodynamic effects
- Potential adverse drug effects (eg, define end organ toxicities and/or reversibility of any toxicity)
- The pharmacokinetic profile.

The studies employed should guide safe use in human clinical trials, determine a safe and reasonable starting dose and provide sufficient data to conclude that patients are not exposed to unreasonable risks.

It is recognised that, in the development of anticancer drugs, clinical studies often involve cancer patients whose disease condition is progressive and fatal. In addition, the dose levels in these clinical studies are often close to or at the adverse effect dose levels. For these reasons, the type, timing and flexibility called for in the design of nonclinical studies of anticancer agents can differ from those elements in nonclinical studies for other pharmaceutical compounds.

An area of scope in the guidance that remained consistent with previous versions of the ICH S9 guideline was that if healthy volunteers (or patients with a long life expectancy) are to be included in the early clinical trials then the ICH M3 guideline should be followed.

Pharmacology
Prior to Phase I clinical studies, preliminary characterisation of the mechanism(s) of action, resistance and schedule dependencies, as well as anti-tumour activity, should have been made. Appropriate models should be selected based on the target and mechanism of action, but need not be studied using the same tumour types intended for clinical evaluation. These studies can provide proof of principle; guide schedules and dose escalation schemes; provide information for selected test species and aid starting dose selection.

Safety pharmacology
An assessment of vital organ function should be available before the initiation of clinical studies. Detailed clinical observations are generally considered appropriate, and stand-alone safety pharmacology studies (as detailed in ICH S7A and S7B guidelines) need not be conducted to support studies in patients with late stage cancer or advanced disease.

Pharmacokinetics
The evaluation of limited kinetic parameters, eg, peak plasma levels, AUC and half life in the animal species used for nonclinical studies can facilitate dose escalation during Phase I. Any further characterisation can be conducted in parallel with subsequent clinical development.

General toxicity
The primary objective of Phase I clinical trials in patients with cancer is to assess the safety of the pharmaceutical. This can include dosing to a maximum tolerated dose (MTD) and dose limiting toxicity (DLT). Therefore, determination of a no observed adverse effect level (NOAEL) or no observed effect level (NOEL) in the toxicology studies is not considered essential to support clinical use of an anticancer pharmaceutical. The requirements on recovery have now been reduced in the guideline prior to Phase I to a single species and the need for its inclusion (or not) in the study design should be based on scientific justification. If there is severe toxicity at approximate clinical exposure, and if recovery cannot be predicted by scientific assessment, at least one nonclinical study should incorporate a recovery period at the end of the study. This should assess for reversibility of toxicity findings or the potential that toxicity continues to progress after cessation of drug treatment. Demonstration of complete reversibility is not required.
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Table 1: Example schedules for anticancer pharmaceuticals to support initial clinical trials

<table>
<thead>
<tr>
<th>Clinical schedule</th>
<th>Examples of nonclinical treatment schedule&lt;sup&gt;1,2,3&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Once every 3-4 weeks</td>
<td>Single dose</td>
</tr>
<tr>
<td>Daily for 5 days every 3 weeks</td>
<td>Daily for 5 days</td>
</tr>
<tr>
<td>Daily for 5-7 days, alternating</td>
<td>Daily for 5-7 days, alternating weeks (2-dose cycles)</td>
</tr>
<tr>
<td>Once a week for 3 weeks, 1 week off</td>
<td>Once a week for 3 weeks</td>
</tr>
<tr>
<td>Two or three times a week</td>
<td>Two or three times a week for 4 weeks</td>
</tr>
<tr>
<td>Daily</td>
<td>Daily for 4 weeks</td>
</tr>
<tr>
<td>Weekly</td>
<td>Once a week for 4-5 doses</td>
</tr>
</tbody>
</table>

<sup>1</sup>The table describes the dosing phase. The timing of the toxicity assessment(s) in the nonclinical studies should be scientifically justified based on the anticipated toxicity profile and the clinical schedule. For example, both a sacrifice shortly after the dosing phase to examine early toxicity and a later sacrifice to examine late onset of toxicity should be considered.

<sup>2</sup>The treatment schedules described in the table do not specify recovery periods.

<sup>3</sup>The treatment schedules described in this table should be modified as appropriate for molecules with extended pharmacodynamic effects, long half-lives or potential for anaphylactic reactions. In addition, the potential effects of immunogenicity should be considered (see ICH S6).

For small molecules, rodent and nonrodent species should be used. However, in certain circumstances, determined case-by-case, alternative approaches can be appropriate (eg, for genotoxic drugs targeting rapidly dividing cells, a repeat-dose toxicity study in one rodent species might be considered sufficient, provided the rodent is a relevant species). For biologics (eg, monoclonal antibodies), reference is made to ICH S6<sup>11</sup> for the selection of species to be studied. Toxicokinetic evaluation should be conducted as appropriate.

Reproduction and developmental toxicology
Embryofoetal studies are not considered essential to support clinical trials intended for the treatment of patients with late stage or advanced cancer. However, embryofoetal data should be available prior the submission of a marketing application. These studies are also not considered essential for pharmaceuticals which target rapidly dividing cells or belong to a class of agents which has been well characterised in causing developmental toxicity. Biopharmaceuticals are now included in this section of the guideline, and it states that an assessment in one pharmacologically relevant species should be sufficient. This assessment may be done by evaluating the toxicity during the period of organogenesis or study designs as described by ICH S6. Alternative approaches might be justified, including a literature-based assessment, an assessment of placental transfer and the direct or indirect effects of the biopharmaceutical. Generally no fertility study is warranted to support the treatment of patients with late stage or advanced cancer. Studies in juvenile animals are not usually conducted in order to support inclusion of paediatric populations for the treatment of cancer. Conducting studies in juvenile animals should be considered only when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group.

Genotoxicity
Genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with late stage or advanced cancer; however, these studies should be performed to support a marketing authorisation application (MAA).

Carcinogenicity
Carcinogenicity studies are not required to support marketing applications for therapeutics intended to treat patients with advanced cancer.

Immunotoxicity
For anticancer pharmaceuticals the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support an MAA.

Phototoxicity
Phototoxic potential should be assessed prior to Phase I, based on photochemical properties of the drug and information on other members in the class. If there is an indication of a potential risk, appropriate protective measures should be taken during patient trials. If the photosafety risk cannot be adequately evaluated based on nonclinical data or clinical experience, a photosafety assessment consistent with the principles described in ICH M3 should be provided prior to marketing.

Other considerations
The guideline goes on to describe how you can use the preclinical data in designing your clinical trial: starting dose for first administration in man, dose escalation and the highest dose in clinical trials. The guidelines also provide guidance on the duration and schedule of toxicology studies to support initial clinical trials (see Table 1); the duration of toxicology studies to support continued clinical development and marketing (generally a 3-month study is considered sufficient); how to manage combination pharmaceuticals and, finally, the nonclinical studies to support trials in paediatric populations.
Briefly, after defining a relatively safe dose in an adult population, initially agents can then be investigated in paediatric patients with some fraction of that adult dose. Other considerations addressed in the guidelines include conjugated agents, liposomal products, evaluation of drug metabolites, and evaluation of impurities.

Conclusions

Considerable effort has been made to develop the harmonised ICH S9 nonclinical guidance on oncology therapeutic development so that it will cover both small molecules and biotech products. The guidance will undoubtedly reduce the inconsistencies in approaches experienced when conducting clinical trials and seeking marketing authorisation in the various regulatory jurisdictions, with the added bonus of reducing the number of animals used (by reducing the type and the number of studies required) and, most importantly, reducing the time for the therapies to get to the patients.

References

8 ICH M3(R2). Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, December 2009.