Chapter 13
ICH S9: Nonclinical Evaluation of Anticancer Pharmaceuticals: A Perspective from Regulators on the Development of the Guideline*

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Abstract The development of a guideline for nonclinical testing strategies for anticancer drugs and biologicals was initiated by the International Conference on Harmonisation (ICH) in 2007. The rationale for developing this guideline was that separate regional guidelines were being or had been developed. By nature, ICH guidelines tend to describe regulatory recommendations rather than the underlying rationale of the recommendations. The purpose of this chapter is not to discuss the document per se but to describe the perspective of regulators on some of the topics discussed during the deliberations in developing the ICH S9 guideline, focusing on major changes to drug development compared to past practices, and to illustrate the principles underlying the recommendations and alternative views that were considered.

13.1 Background

Over the past decades, approaches to the nonclinical development of anticancer pharmaceuticals have been independently discussed and developed in Europe, the USA, and Japan. The nonclinical approaches were not agreed on across product

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classes such as biologics and drugs. The available disharmonized guideline resulted in inefficient use of animal resources and ineffective drug development in a critical area of human health. In the USA, nonclinical recommendations for cytotoxic drugs were originally developed in collaboration with the US National Cancer Institute in the 1970s and early 1980s (Prieur et al. 1973; Lowe and Davis 1987). At this time, it appeared that there was little commercial interest in developing drugs for this therapeutic area. By the early 1990s, with growing interest in this field, there was recognition that these recommendations needed to be updated, and the FDA's Center for Drug Evaluation and Research (CDER) clarified their regulatory perspective on anticancer drug development (DeGeorge et al. 1998). Subsequently, development of a guideline for nonclinical oncology drug (small molecule) development was initiated in 2001.

The scope of the FDA's developing guideline changed with the merger of some regulatory functions of FDA's Center for Biological Evaluation and Research into CDER and the recognition of different approaches to safety testing for small molecules and biotechnology-derived pharmaceuticals. For example, as discussed by the Oncology Drug Advisory Committee (ODAC 2006), for small molecules, a toxicology study of 1 month duration in rodents and nonrodents was generally sufficient to initiate a phase I clinical trial and allow for continued clinical dosing as long as patients were benefiting and toxicities were considered acceptable. However, for biotechnology-derived pharmaceuticals with long half-lives, a toxicology study of up to 3 months duration or a study based on the proposed duration of clinical dosing (≥1:1 dosing) in nonhuman primates was sufficient to initiate clinical dosing. Longer term toxicology studies may have been needed to be ongoing to continue clinical dosing, and patients could continue beyond the duration of toxicological support on a case-by-case basis. This example highlighted the need to harmonize the recommendations for small molecules and biotechnology-derived pharmaceuticals or to understand the scientific basis for the different recommendations.

In the European Union (EU), the Safety Working Party (SWP) of the Committee for Medicinal Products for Human Use (CHMP) had developed a guideline for anticancer drug development for the European Union (EMA 1998). The guideline was primarily devoted to cytotoxic/cytostatic drugs that are presumed to have a direct effect on tumor cells. While it focused on the development of single drug treatment, studies to support the clinical development of combinations of anticancer drugs, nonclinical testing to investigate pharmacodynamic, kinetic, and toxicological interactions was also encouraged. The guideline aimed at formulating recommendations for pharmacodynamic investigations and the requirements for toxicological studies prior to phases I, II, and III clinical trials as well as marketing applications. This guideline was withdrawn with the adoption of ICH S9.

The Ministry of Health, Labour and Welfare (MHLW) of Japan was developing nonclinical guideline to address various mechanisms of anticancer therapy but did not include biologics in its scope. Thus, there was substantial concern that, when those guidelines would have been completed, there would not have been a harmonized approach in Japan for nonclinical development of drugs for the treatment of patients with cancer.

The development of the International Conference on Harmonisation (ICH) guideline ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals was initiated by the ICH, bringing together representatives from the pharmaceutical industries and regulatory authorities from Japan, the EU, and the USA. (Note that the term "pharmaceutical" is used throughout the guideline and in this chapter to denote both drugs and biotechnology-derived products; where necessary, a distinction is made.) The purpose of the ICH is to discuss scientific and technical aspects for development and registration of pharmaceuticals in order to reduce duplicate testing in the research and development of new pharmaceuticals. The first meeting of the ICH S9 Expert Working Group (EWG) was held in October 2007. In addition to ICH members, observers and interested parties to the process included Health Canada, Swissmedic, and the Biotechnology Industry Organization. As described in the concept paper approved by the ICH Steering Committee, the rationale for developing ICH guideline was the existence of an EU guideline on cytotoxic drugs and separate development of broader guideline for anticancer drugs and biologicals in the USA and Japan (Final Concept Paper 2007). After several meetings, a Step 2 draft guideline prepared by the ICH S9 Expert Working Group, and approved by the Steering Committee, was published by regional regulatory authorities. After considering the public comments received, a final document was signed by regulatory authorities and approved for regional publication by the ICH Steering Committee in October 2009. The guideline is available from the ICH Web site and from regional authorities.

Several points need to be made in regard to the actual writing of the guideline. First, each region brought a well-developed perspective to the discussion, which assisted in the discussions, thus reducing the timeline from the first meeting to the final (Step 4) document. Second, a fairly comprehensive document was available to the EWG as an initial working document; initial meetings were devoted to trimming the document to meet the goal of the EWG to produce a guideline outlining recommendations, not an educational guideline. One party in specific (FDA) had noted that some sponsors were not adept in preparing for an Investigational New Drug Application (IND) filing and initially provided a document that included information to assist those sponsors in preparing an IND, such as details in toxicology study design. The EWG removed much of the "educational" aspects of the guideline as not consistent with the approach of other ICH guidelines. In reading ICH S9, it is important to understand that the EWG avoided certain terms as much as possible, such as "need, needed, shall, must, recommend, required," as not appropriate for an ICH guideline. The EWG also sought to avoid the phrase "if feasible" as studies are sometimes feasible but not scientifically justified. Thus, the EWG used other terms such as "warranted" or "not warranted" to reflect the concepts to be communicated by the EWG, and these terms appear frequently in the guideline. Finally, the ICH S9 EWG met several times with the ICH M3(R2) and ICH S6 EWGs that were meeting concurrently with the ICH S9 EWG in order to avoid inconsistencies among documents. To reduce future maintenance of ICH S9, references are made to those documents as appropriate.

13.2 Major Accomplishments and Discussion Topics of the ICH S9 Expert Working Group

13.2.1 Scope of the Guideline

The scope of the guideline as published at Step 2 was similar in concept in many ways to that of the Step 4 document, both in terms of what clinical development programs are included and what is excluded, that is, what products would fall under the scope of ICH S9 or ICH M3(R2). For example, the S9 guideline covers both small molecule drugs and biotechnology-derived pharmaceuticals but excludes radiopharmaceuticals and vaccines. The rationale for the exclusion is that the nonclinical development programs for these types of molecules would be different than those of "traditional" pharmaceuticals and thus unnecessarily complicate an already difficult task of harmonization.

After the completion of the Step 2 document in November 2008, the EWG spent considerable time discussing the wording of the scope based on public comments received at this Step. At this stage, the guidance was to be applied to pharmaceuticals intended to treat cancer in patients with late stage or advanced disease but was not intended for pharmaceuticals used to treat patients with long life expectancy. Public comments requested clarity around the intended population and requested a definition of "long life expectancy," for example, specifying a potential life expectancy of 3 years. A second comment suggested defining long life expectancy as 80% survival at 5 years. Other comments requested a specific reference to the stage of disease, for example, stage III and stage IV metastatic disease, or that the word "incurable" be added. It is perhaps understandable that clarity around these terms was requested in that potential regional differences in the interpretation of the scope could significantly affect drug development timelines.

In response to the public comments, the EWG attempted to provide clarity to the intended patient population identified in the scope. For example, the EWG considered revisions such as pharmaceuticals being studied for "serious and life-threatening malignancies, which have failed available therapy, or for whom no other therapy exists" and "in patients with metastatic or locally advanced disease and serious and life-threatening hematologic malignancies." The latter language was initially the preferred language of the EWG post-Step 2 and was proposed to the Steering Committee at Step 4 in Yokohama in June 2009. However, the Steering Committee rejected this proposal. Some members of the Steering Committee referred to the concept paper and business plan and the possibility that the proposed language could be an expansion of the guidance beyond originally agreed to in those documents. Other members of the Steering Committee expressed concern that some patients with early-stage disease may receive prolonged treatment without adequate toxicological support (e.g., early-stage breast cancer). Some members of the EWG considered this unlikely as clinical trials for anticancer

pharmaceuticals are almost always initially done in patients with advanced disease that has failed available therapy and that clinical safety data could be used with available toxicology data to support trials in patient populations with less advanced disease without the need for additional toxicology studies. The language originally proposed to the Steering Committee is also used in labeling to describe the patient population of some approved anticancer products.

To address the concerns of the Steering Committee, the EWG discussed alternatives to try to reach consensus on the scope. For example, going back to the original Step 2, language was considered, but this could possibly lead to regional disharmony in applying ICH S9. The EWG also discussed proposals to define or limit the scope to pharmaceuticals intended for patients with disease that has failed available therapy, or where no therapy existed, or where clinical development is initially performed in patients whose disease is refractory to available therapy, or have life-threatening disease where no therapy exists. The proposal included a recommendation that when moving investigations beyond this initial patient population, for example, when a drug is studied in patients with curative intent, long expected survival, or as adjuvant therapy, then the need for additional nonclinical studies would depend upon the available nonclinical and clinical data and the nature of the toxicities observed.

Some EWG members thought these proposals lacked flexibility and interpreted these proposals as suggesting that moving beyond the patient population typically studied in phase I, to phase II or phase III, would lead to the need for additional nonclinical toxicology studies as described in ICH M3(R2). The question of what constituted available therapies was raised: If four or five similar therapies existed for a particular disease, would all therapies need to be tried before an investigational pharmaceutical would fall under the scope of ICH S9? In addition, early-stage planning of a nonclinical program of development could be difficult if some of these concepts (e.g., long expected survival) were to be incorporated into the scope.

In the end, consensus was reached at Step 4, using language similar to that of Step 2, replacing "pharmaceuticals that are only intended to treat cancer in patients with *late stage or advanced disease*" with "*serious and life-threatening malignancies.*" Further, the scope outlined in Step 4 refines "long life expectancy." A key question is whether the principles of ICH S9 or ICH M3(R2) would apply to a particular development program. The scope of ICH S9 addresses this question by stating that the recommendations for and timing of additional nonclinical studies depend upon the available nonclinical and clinical data and the nature of the toxicities observed and did not include reference to curative intent. This statement implies that most development programs for anticancer drugs will initially take place in the setting where therapeutic options may be limited. While not providing specific recommendations, the EWG recognized that moving beyond this initial setting may be possible without additional nonclinical studies on a "case-by-case" basis and that information from the clinical program should inform on this decision.

13.2.2 Role of Pharmacology Investigations in Anticancer Pharmaceutical Development

The EWG discussed in some depth the level of detail and type of pharmacology investigations that were needed to support early development and marketing applications. The EWG discussed whether the assessment should include investigations in specific tumor-derived cell lines in vitro and in xenograft models. For example, if a drug is intended for the treatment of patients with lung cancer, would studies in cell lines derived from lung tumors be needed to support an initial investigation or marketing application? In the end, the consensus of the EWG was that with currently available cell lines, there is not a direct one-to-one concordance between the tumor origin of an in vitro cell line and clinical outcome, so such studies would not be specifically needed; hence, the guideline states that "the pharmaceutical need not be studied using the same tumor types intended for clinical evaluation."

The EWG discussed level of detail or investigations in understanding the mechanism of action of a pharmaceutical was the company's responsibility, but that some rationale should be put forward to justify the clinical trial. It was recognized that a complete understanding of a pharmaceutical was unlikely at early stages of development or even at the time of submission of the marketing application; thus, the level and timing of investigations were left mostly to the discretion of the sponsoring company. However, for biotechnology-derived products, the importance of pharmacology studies in selecting a relevant model, as discussed in ICH S6 (since replaced by ICH S6(R1) 2011), should also be considered.

13.2.3 Duration of Nonclinical Studies to Support Clinical Development

In a significant departure from past practice, the duration and timing of chronic toxicology studies for anticancer pharmaceuticals has evolved. The practice of submitting long-term toxicology study of 6 months' duration in rodents and nonrodents with the marketing application was changed to 3 months to be submitted prior to phase 3. FDA had collected data for about a 6–7-year period to understand how findings from 6-month studies were used; for example, did findings inform clinical monitoring and affect approval recommendations or subsequent clinical investigations in other patient populations? The FDA reported to the EWG that it had no examples to support the need for 6-month studies. Prior to accepting this recommendation, all parties in the EWG consulted with their members and discussed the utility of the current approach of requiring 6-month studies with a marketing application, looking for specific examples where such studies affected clinical development or recommendations. From the response of the EWG, few examples were provided, and it was obvious that long-term toxicology studies submitted with the marketing application had little utility in the course of clinical development and thus the proposal was accepted.

Table 13.1 Examples of treatment schedules for anticancer pharmaceuticals (drugs and biologicals) to support initial clinical trials

Clinical schedule	Examples of nonclinical treatment schedule[a–d]
Once every 3–4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5–7 days, alternating weeks	Daily for 5–7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	Once a week for 4–5 doses

[a]Table 13.1 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

[b]For further discussion regarding flexibility in the relationship of the clinical schedule and the nonclinical toxicity studies, see Sect. 3.3 (of the S9 guideline)

[c]The treatment schedules described in the table do not specify recovery periods (see Sect. 2.4 of the ICH S9 guideline and Note 1 regarding recovery)

[d]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 (ICH guidelines: S6)

The EWG discussed possible scientific rationales that would indicate that a difference in duration of toxicity testing for small molecules and biotechnology-derived pharmaceuticals might be warranted either to initiate a clinical trial or to support marketing. The EWG concluded that the same principles be applied to small molecules and to biotechnology-derived pharmaceuticals. For example, it was noted that some small molecules have a long half-life (e.g., liposome-encapsulated drugs, drugs that bind tightly to serum proteins). Thus, the types of studies needed to support pharmaceutical development programs should be based on sound scientific judgment, taking into account the general recommendations as outlined in Table 1 of the guideline (see Table 13.1).

13.2.4 Dosing Levels in Nonclinical Safety Studies

In general, anticancer drugs developed to date do not have a safety margin, and usually some toxicity in clinical use is anticipated and needs to be managed. For this reason, and since the start dose is based on toxicity, the EWG concluded that defining a No Observed Adverse Effect Level/No Observed Effect Level (NOAEL/NOEL) was not considered essential. Resources should not be dedicated, and toxicology studies repeated, simply to define the NOAEL/NOEL. The rationale behind this concept is another distinguishing feature of anticancer pharmaceutical development.

13.2.5 Defining a "Cytotoxic" Compound by Function

It is recognized that most anticancer therapeutics are "cytotoxic" to one degree or another, and as such, in this context the term is not specific. For this reason, the ICH S9 guideline avoids the use of the term "cytotoxic." The guideline instead refers to a functional capacity of a pharmaceutical to target rapidly dividing cells (e.g., crypt cells, bone marrow) and that are genotoxic; pharmaceuticals in this class are exempt from the need for embryofetal developmental (EFD) toxicity studies as these compounds are either teratogenic or lethal to the developing fetus. The EWG did not address other situations, for example, when pharmaceuticals targeted rapidly dividing cells but were *not* genotoxic, as there was no database to support a conclusion that pharmaceutics in this class are, or are not, teratogenic.

13.2.6 Basis for Reproductive Toxicology Testing

While available information is limited, there is some indication that for some cancers, first detection is at the time of pregnancy diagnosis. For this reason, the ICH S9 guideline focuses on the need for embryofetal development studies of the core battery described by ICH S5(R2) (2002) guideline. The rationale for this approach was to understand the risk to the fetus from unintended exposure if a diagnosis of cancer occurs during early pregnancy. While the entire battery provides important information, for patients with cancer, the EWG consensus was that providing the EFD study alone was sufficient for this patient population. Fertility and pre- and postnatal development studies are not recommended. If pharmaceuticals are to be used in other patient populations, or in the adjuvant setting, then other guidelines would become relevant.

The rationale for not requesting a second embryofetal toxicity study is that if the first is positive, there is no need to confirm a positive finding. In some non-oncology therapeutic areas, there may be a need for a second study to get some idea of a toxic dose and therapeutic dose. Since anticancer drugs are dosed to toxicity in nonclinical studies, and to a maximum tolerated dose in clinical studies, a safety margin is unlikely. Thus, a study in a second species is "not warranted."

13.2.7 Clarifying the Need for Stand-Alone Safety Pharmacology Studies

Safety pharmacology studies investigate functional effects on vital organ function, primarily cardiovascular, central nervous system, and respiratory. Of particular importance is the effect on cardiovascular due to the potential for life-threatening consequence from impairment of this system. The EWG discussed the importance of these studies and concluded that stand-alone studies are not essential to initiate clinical studies as sufficient patient protection is in place with clinical monitoring of cardiovascular function (see ICH E14).

13.2.8 Setting the Start Dose for First Administration in Humans

The EWG discussed several approaches to setting the first in human start dose and concluded that many approaches could be acceptable. The EWG agreed that while it is not likely that most patients will receive a therapeutic benefit while in a phase 1 trial, subtherapeutic dosing should be minimized. In the past, the standard approach for setting a start dose for small molecule drugs was using 1/10th the STD_{10} or that dose that is severely toxic to 10% of rodents (DeGeorge et al. 1998; EORTC 1985). In this case, severely toxic does not necessarily equate to lethality. The EWG agreed that this approach was and could still be useful. Other approaches considered by the EWG were less formulaic, using all the available data, an approach that is common with biotechnology-derived products. This approach was considered more challenging to adopt for small molecules, perhaps leading to greater uncertainty in preparing an initial clinical plan, and it remains to be determined how this will work in practice. Thus, it was thought best by the EWG to provide as much flexibility to sponsors while maintaining patient safety, the approach reflected in the guidance.

13.2.9 The Need for Recovery Groups in All Toxicology Studies

The Step 2 document included language in the General Toxicology Section regarding the need for a recovery (non-dosing) period at the end of the study. In this draft document, the expectation for inclusion of recovery groups to support the initial phase 1 clinical trial was rather definitive. There was also an expectation that progression of toxicity be evaluated. A complete reversibility of findings was not expected; for example, testicular toxicity may not recover within the usual time frame of a 2-week recovery period often used for 1-month toxicology studies.

The EWG had extensive discussion on this topic in responding to public comments while preparing a Step 4 guideline. The EWG noted that there were few, if any, examples of a novel toxicity appearing after the dosing phase. The EWG also decided to provide more flexibility on the inclusion of recovery animals, providing examples where these groups may not be necessary. It was noted that toxicological pathologists were not in complete agreement on the ability to identify lesions that may not recover and that the public literature on this topic was sparse, making the ability to scientifically justify noninclusion of recovery groups difficult. It is clear that findings such as necrosis are not reversible, even if this is not reported upon histopathological examination after the recovery period. It was also reported that some parties do use this data in clinical trial design to determine whether dose interruption or dose decrease may be more appropriate if a particular toxicity is observed. The lack of consensus on this topic was considered a serious deficiency but was included to give sponsors the ability to make a justification. It was also recognized that at some point in the future, a consensus may be reached as to which lesions are reversible and which may require further study.

13.2.10 Integrating Clinical and Nonclinical Data into a Safety Assessment to Support Changes in the Clinical Schedule

Industry representatives to the EWG, and some regulatory parties, thought this topic would be very valuable in clarifying the need, or lack thereof, for additional nonclinical studies to support changes in the clinical dosing schedule, including the clinical dosing schedule proposed during drug development before the first patient had been treated. The rationale for including Sects. 3.3 (initial clinical trials) and 3.4 (continued clinical development, i.e., where some clinical data exist) in the ICH S9 Guideline to address this topic was the lack of clarity and uncertainty in regulatory acceptance of a change in clinical schedule without supporting nonclinical data. This lack of clarity could possibly lead to unnecessary studies and likely increased animal use for little additional information. All parties agreed that the ideal nonclinical program would use a schedule in nonclinical studies similar to that proposed clinically. However, as many of the industry representatives to the EWG pointed out, the complicated nature of pharmaceutical development does not often lend itself to the ideal and that development programs may often change. For example, a drug may be considered for intravenous administration, but new formulations may make oral dosing feasible. After discussion by the EWG, specific factors are provided for consideration in the guideline (Sect. 3.3) to assist in whether additional nonclinical studies would be useful.

13.2.11 Addressing Photosafety Testing

The topic of photosafety testing was incorporated after the Step 2 document was published, in response to public comments received about the Step 2 document in order to address this emerging topic. The ICH S9 EWG discussed various approaches to photosafety testing from “no studies were needed” to “follow the recommendations outlined in ICH M3(R2).” The EWG discussed the predictive value of photosafety testing in terms of possible risks to patients in phase 1 clinical trials and the potential recommendations that might result from a potential risk. There was also some discussion that an evaluation could be better collected as part of the safety assessment in a phase 1 trial. The FDA noted that phototoxicity was not thought to be a major observation in early clinical trials and thus did not warrant additional nonclinical testing. Ultimately, the EWG concluded that at the minimal, an assessment should be conducted. The EWG recognized that this was likely to become a topic of a future ICH guideline and for that reason decided not to incorporate more detailed recommendations.

13.2.12 Evaluation of Drug Metabolites

This topic needed to be addressed primarily because of the FDA guideline on the topic (Safety Testing of Drug Metabolites 2008). The FDA guideline states that a separate guideline would be coming out for anticancer drugs and this topic was being incorporated into the FDA draft guideline. When the ICH S9 topic was adopted by the Steering Committee, FDA participants argued that addressing drug metabolites then needed to be addressed by the ICH EWG.

In light of the FDA guidance on this topic, the EWG spent considerable time discussing this topic both before and after Step 2 and received extensive public comments. The Step 2 guideline stated that if the drug was positive in EFD or genotoxicity evaluations, then separate studies of the "disproportionate metabolite" might not be warranted. Several public comments stated that the intent was confusing; further, a definition of "disproportionate" could not be provided, and this could lead to different interpretations and disharmony. The EWG provided a more definitive conclusion in the Step 4 guideline, stating that a separate evaluation of metabolites identified in humans that may not have been qualified in animal studies was generally not warranted for patients with advanced cancer. The rationale for this approach is that for anticancer drugs, a maximum tolerated dose is usually studied nonclinically and clinically. For qualification purposes, the contribution of a metabolite to overall toxicity relative to the drug substance is generally expected to be low, and/or separate nonclinical studies with the metabolite alone are unlikely to provide additional value or change a clinical recommendation.

13.2.13 Evaluation of Combination of Pharmaceuticals

In the context of the guideline, combinations generally refer to coadministration of two or more pharmaceuticals. Some members of the EWG felt the combination toxicity data were needed, while others felt that it could be addressed by just automatically lowering combination doses in clinical studies. It was recognized that this later approach may not be optimal as it possibly could lead to under dosing of humans with cancer hoping for treatment, thus the recommendation to collect information of significant concern from combination pharmacology studies, even though these studies are not usually conducted according to good laboratory practice (GLP) regulations. The consensus opinion was that conducting an expanded pharmacology study should be the first step in understanding whether there is an increased risk of the combination compared to the individual compounds. This study would be particularly important for combinations in which at least one of the compounds was in early-stage development. To some parties, "early-stage development" generally referred to a pharmaceutical where the phase I study has not been completed (the human toxicity profile has not been characterized), although the EWG chose not to specify phase I in order to allow flexibility. This EWG affirmed that this study, as is typical for many

pharmacology studies, need not be GLP compliant. Of critical interest is whether there is significant change in severe toxicity that can be detected in combination pharmacology studies as it was recognized that the sensitivity of detecting small changes in toxicity in the expanded pharmacology studies was limited.

It should be noted that the phrase "specific cause for concern" is not found in the Step 4 document. The EWG noted that this phrase is somewhat vague and it would be more useful to provide clarity around what constituted concern. In the case of studying combinations, for example, concern generally refers to studying pharmaceuticals in which one compound of the combination is still early in development. In this case, a remedy is the expanded pharmacology study.

13.2.14 Flexibility in Qualification of Impurities

For potentially genotoxic impurities in genotoxic drug substances, it makes little sense to follow a threshold of toxicological concern approach to qualification. In addition, the threshold for toxicological concern approach addresses lifetime risk of cancer, and this is not considered appropriate for patients with advanced cancer. This would be particularly true if the genotoxic impurities arise late in development (e.g., as the commercial process becomes finalized) and the pharmaceutical has demonstrated a known survival advantage. Thus, the approach as outlined in the ICH guidelines Q3A and Q3B for determining levels for qualification may be more appropriate, although it should be noted that the EWG did not provide specific recommendations.

13.2.15 Examples of Treatment Schedules for Anticancer Pharmaceuticals to Support Initial Clinical Trials (Table 13.1)

For many participants, this table was thought to be one of the most useful parts of the document. This was also reflected in comments to the Step 2 document. The examples provided were not meant to take the place of rationale scientific judgment but to serve as a guide. The rationale for a single dose supporting a once-every-3–4-week schedule is that the experience is that this was the schedule for the traditional cytotoxic drugs that suppressed bone marrow, and full recovery took approximately 3 weeks. Otherwise, the rationale is that animals should be exposed to several doses of a compound at least but close as possible to the clinical schedule. It was recognized that the proposed clinical schedule may change during development so that some flexibility was needed to avoid repeating animal studies and delaying clinical trials. However, the EWG recognized that it was the sponsor's obligation to provide some justification that any proposed schedule would be safe for patients.

Table 13.2 Expected reduction in animal use by adoption of ICH S9

Study	Before S9	After S9	Effect
General toxicology	6 months' duration concurrent with drug development	1 month sufficient to initiate development; 3 months sufficient to support pivotal clinical trials	Long-term toxicology studies are not needed early in development, eliminating the need for many 3- and 6-month studies
General toxicology—change in clinical schedule	Need to conduct additional nonclinical studies (2 species?) to support a change in clinical schedule	Evaluate nonclinical and clinical data (if available) to see if available data is sufficient to support the proposed clinical schedule; if not, then a study in one species is usually sufficient	Reduction in the default requirement that studies in 2 species (rodent and non rodent) would normally be needed. Reduction in the use of nonrodents
General toxicology—recovery	Usually included in every study in 2 or more dose groups	Need based on scientific justification	Possible reduction in use of nonrodents; full effect remains to be determined
General toxicology—acute studies	Usually needed in every application	Not generally needed	Reduction in use of rodents
"Cytotoxic" drugs	2 species for initiating clinical development	1 species to initiate clinical development	Eliminated the need for the study in nonrodent to initiated clinical trials for "cytotoxic" drugs
Reproduction toxicology	Embryofetal studies needed in 2 species; studies needed fertility and pre- and postnatal development	Embryofetal study in one species only if positive	Eliminated the need for a second positive embryofetal toxicity study; no requirement for the fertility and pre- and postnatal development studies
Safety pharmacology	Follow ICH S7A and B	Cardiovascular safety and other endpoints could be incorporated into general toxicology studies	Minimized the need for stand-alone safety pharmacology studies
Photosafety testing	In vitro studies needed with possible in vivo follow-up	An assessment needed	No specific requirement for in vivo follow-up

13.2.16 The Role of 3Rs

Throughout the course of developing the ICH S9 guideline, the 3Rs, reduction, refinement, and replacement of animal testing had been kept in focus by the EWG to ensure that the goals outlined in the concept paper were realized. In this, the guideline was successful, eliminating or delaying some animal testing (Table 13.2). For example, recovery groups may not be needed if adequate scientific justification can be provided; acute toxicity studies are not needed; general toxicology studies are limited to 1 month to support initial clinical development, and 3 months should be sufficient to support phase III and in most cases the marketing application; and reproduction toxicology studies can be provided at marketing and are limited to studying embryofetal development.

13.3 Summary

The S9 EWG met between October 2007 and November 2009 and in that time developed a consensus as to what to include and not include in the tripartite guideline and incorporated public comments into the document. In reaching consensus, the EWG kept three principles in focus: patient safety; harmonizing requirements; and reduction, refinement, and replacement of animal use. The EWG met its timelines as set out in the business plan, and the guidance represents a significant step forward in harmonization. However, during the discussion and since publication, the guidance has raised several topics that may require additional discussion, including: what scientific data are needed to justify inclusion or noninclusion of recovery groups into a toxicology study; the number of dose levels to include in a nonrodent study; a more complete discussion surrounding the start dose of biologics, including antibody drug conjugates; and a more robust discussion of what would constitute an appropriate photosafety evaluation. Inclusion of this latter topic has resulted in some confusion as to what is needed. An interesting topic that could be included if the guidance were being written today is the development of dried blood spots for pharmacokinetic and toxicokinetic evaluation, as this could have the potential to reduce the need for satellite groups in rodent studies. The translation of the animal data into a clinical start dose still remains a challenge, particularly for biologics. In addition, while the EWG did have some discussion regarding the circumstances where a carcinogenic evaluation might be necessary, as this topic is addressed for anticancer drugs in ICH S1A, this topic did not receive as complete a discussion as warranted. As time progresses and more investigators gain experience with the guidance, other topics requiring clarification are sure to become evident. However, as one member of the EWG pointed out toward the end of the discussions, the EWG should not let a perfect guidance delay the good.

A legitimate question would be what effect the S9 guidance has had so far. From the regulatory perspective, by far the biggest impact of the guidance is anticipated

to be the reduction in the length of studies, from 6–9 months to 13 weeks to support product registration. One of the 10 new anticancer drugs approved since the beginning of 2011 was approved with 3-month-only studies for rodents and nonrodents. The toxicology studies for this drug were conducted in 2009. Of the remaining drug approvals, most of the toxicology studies for these programs date from the mid-2000s or before. Because of the lead time needed to conduct studies for development programs prior to filing for registration, it is premature to conclude that the reduction in the duration of the toxicology studies has made a major impact. However, sponsors are including questions relating to ICH S9 in meetings with FDA, including whether toxicology studies of 3 months duration would be sufficient to support further clinical development for drugs for patients with less advanced disease. Second, there has been some movement to 13-week-only studies for nonrodents to initiate clinical development of biologics, but this remains rare. In the past, 13-week study was often provided for initiating clinical development of a biologic to be studied in patients with cancer, perhaps due to an interpretation of ICH S6. The S9 guidance clearly states that studies of much shorter duration are acceptable for this purpose. The FDA has seen some toxicology studies without recovery groups, but most studies submitted still contain these add-on groups. Finally, the discussion in the guidance on combination of products provided much-needed clarity to this topic, especially with the growing clinical interest in trials using multiple drug combinations. Basically, the FDA is not seeing combination toxicology studies but well-designed pharmacology studies if needed, demonstrating the success of the guidance. Taken together, it is clear that another major impact of the guidance has been a reduction in animal use, a trend that is likely to continue.

The ICH Steering Committee signed off on the ICH S9 *Step 4* guideline in St. Louis following the recommendation of the ICH S9 EWG, after the EWG addressed the comments received after public consultation. Having produced a Step 4 harmonized guideline, the EWG accomplished its primary goal, but the task of implementation remains, a task made easier if the scientific rationale behind the recommendations is transparent.

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