Drugs: The General Case

One must start one's consideration of the general case approach to nonclinical safety assessment from some fundamental assumptions about the drug under development or to be developed. The first assumption is that the primary intended route of therapeutic administration is oral, as is indeed the case for the vast majority of both existing and new drugs. Most aspects of nonclinical safety assessment do not depend on route, and in later chapters we consider in detail the situations where the use of other routes influences what is done for nonclinical safety assessment, and why.

A sort of subset assumption in the general case is that drug administration frequency (or regimen) is once daily, though this assumption is less frequently made (in real life) than the oral route assumption. The regimen assumption has its earliest origin mostly in experimental laboratory practice.

The next major assumption in the general case and, indeed a driving force behind the writing of this book is that the International Conference on Harmonization (ICH) process has been quite effective. Indeed, as late as the early 1990s, after Alder and Zbinden (1988) wrote their short text over viewing regulatory safety testing requirements, the situation was that one could not begin to describe a general case. The sole written guidance in the USA was a document authored by Edward Goldenthal and entitled *Total Drug Quality*. Dating to the 1970s (FDA 1971 – also see Goldenthal (1968)) and almost not available in print technology and societal expectations rapidly made its guidance obsolete.

More to the fact, the variation in requirements in other countries was extreme, though in many cases most significant in the details (Mathieu 2000). While they have continued to evolve (and add new testing requirements to the regulatory expectations), it is only ICH which has made the global pharmaceutical market for new drugs as we know it possible. Table 4 lists the current (September, 2007) operative ICH guidances on nonclinical drug safety evaluation.

In late 2008 the specific ICH guidance for oncology (59) the nonclinical safety assessment of oncology products become available in draft form.

Regulations, costs, and risks acceptance along with adherence to the phased process of clinical drug development have caused the task or flow of performances of regulatory nonclinical safety assessment studies to be considered as occurring in three sequential parts.

S.C. Gad, *Safety Evaluation of Pharmaceuticals and Medical Devices: International Regulatory Guidelines*, DOI 10.1007/978-1-4419-7449-5_2,

Table 4 Current operative ICH guidance on nonclinical drug safety evaluation

New codification as per July 2009		Previously coded
Carcinogenicity studies		
S1A	Need for carcinogenicity studies of pharmaceuticals	S1A
S1B	Testing for carcinogenicity of pharmaceuticals	S1B
S1C(R1)	New title: dose selection for carcinogenicity studies of pharmaceuticals and limit dose	S1C
	Previously: dose selection for carcinogenicity studies of pharmaceuticals	
	Addendum to S1C: addition of a limit dose and related notes (in S1C(R1))	S1C(R)
Genotoxicity studies		
S2A	Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals	S2A
S2B (R2)	Genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals	S2B
Toxicokinetics and pharmacokinetics		
S3A	Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies	S3A
S3B	Pharmacokinetics: guidance for repeated dose tissue distribution studies	S3B
Toxicity testing		
	Single dose toxicity tests	S4
S4	Duration of chronic toxicity testing in animals (rodent and non rodent toxicity testing)	S4A
Reproductive toxicology		
S5(R2)	New title: detection of toxicity to reproduction for medicinal products and toxicity to male fertility	S5A
	Previously: detection of toxicity to reproduction for medicinal products	
	Maintenance of the ICH guideline on toxicity to male fertility: an addendum to the guideline on detection of toxicity to reproduction for medicinal products (in S5(R2))	S5B(M)
Biotechnological products		
S6	Preclinical safety evaluation of biotechnology-derived pharmaceuticals	S6
Pharmacology studies		
S7A	Safety pharmacology studies for human pharmaceuticals	S7A
S7B	The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals	S7B
Immunotoxicology studies		
S8	Immunotoxicity studies for human pharmaceuticals	S8
Joint safety/efficacy (multidisciplinary) topic		
M3(R2)	Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals	M3(R2)
E8	General considerations for clinical trials	E8

IND/FIM Enabling

The nonclinical studies required to initiate initial clinical studies of pharmaceuticals in human beings are variously labeled as "IND enables" or "FIM enabling." The initiation of a program to conduct such studies is a major step in the advancement of a therapeutic candidate into actual development. For many drugs, it comprises the only regulatory nonclinical safety work that is ever done as they are not considered for further development after Phase 1 (ICH 1998 and 2008). All the safety studies that are required to be done should be performed in compliance with Good Laboratory Practices (GLPs). This means that certain preparatory steps must be performed before the studies are commenced to achieve such compliance.

1. Sufficiently pure drug substances must be produced and characterized.
2. An appropriate GLP compliant analytical method must be developed and validated to verify the purity of the drug substance.
3. GLP compliant bioanalytical methods (to measure amounts of drug present in plasma or serum of selected test species (typically a rodent and nonrodent) must be developed and validated for the concentration range anticipated.
4. The stability of either the drug substance or Active pharmaceutical ingredient (API) under appropriate storage conditions and in the anticipated animal dosing formulation must be demonstrated.
5. One or more suitable dosing formulations must be developed, such formulations are typically uncomplicated at this point, but tend to channel later efforts to develop more sophisticated formulations.

Once these steps are performed suitable studies (as described in Chapter "IND Enabling Toxicology Programs") need to be conducted to support the filing of an IND (in the USA), CTA (in the EU), or equivalent. These studies typically include acute and repeat dose systemic toxicity studies in a rodent and nonrodent species, genetic toxicity, and safety pharmacology studies.

With these in hand, after a regulatory review period initial (Phase 1 and perhaps early Phase 2) clinical studies may be conducted.

To Support Continued Clinical Development

The IND enabling studies typically support repeat dose clinical studies up to a couple of (four at most) weeks in duration. Drugs more often than not require longer term than four weeks of dosing clinical trials than there to reach market (ICH, E8) which means that longer term (than the typical 28-day IND enabling repeat dose toxicity studies) must be conducted in both selected rodent and nonrodent

species. Additionally developmental and reproductive toxicity studies are usually required to allow the inclusion of a broader range of patients in clinical trials. Such longer term repeat dose studies are generally conducted in incremental steps so that Clinical studies through Phase 3 can be conducted. Chapter "Nonclinical Safety Evaluation Studies Conducted to Support Continued Clinical Development" addresses this part of the safety assessment process.

To Support Marketing Approval

The last distinct part of the nonclinical safety assessment study package generally consists of studies, which are not required until a marketing application (in the USA, a New Drug Application (NDA) or Biological License Application (BLA)) is submitted. This group is usually limited to carcinogenicity studies (if required) and the final parts of the reproductive toxicity package.

Though there may be some special requirements that arise in specific situations Chapter "Supporting Marketing Applications" presents the general approach to this part of the safety package.

Subset: Special or Hazard Studies

All that has been presented so far are appropriate and required for almost all new therapeutics. By the routes other than oral, however, there are additional expected studies which address issues of local tissue response to administer clinical dosage form (or drug product).

What is to be tested is the clinical formulation about to be evaluated in humans. As said, formulation may change several times over the course of clinical development; these tests may need to be repeated several times (for each new formulation). The tests are truly hazard tests – they are generally performed with a strictly defined protocol, with results being evaluated using a set in accordance with subjective preclinical scale, against which it is determined to be pass or fail.

The tests include such studies as hemolysis (for *iv* products), pyrogenicity (for parenteral products), sensitization (for dermal products), and route specific irritation assays (eye, skin, muscle, mucosal, nasal, and so on).

These studies are expected but the expectations are not clearly spelled out in any single guidance indeed. To some degree they are desirable not in a regulatory guidance at all, but rather in the appropriate pharmacopeia (in the USA, this is the *USP – United States Pharmacopeia*).

ICH Requirements: The Global General Case

The ever changing and growing number of ICH guidelines[1] provides the conceptual starting point for assessing the safety of new medicines, whether they are small molecules or proteins, while a review of Table 5 makes it clear that these two sets of structures remain viewed as vastly different and raising different concerns (ICH 2004).

Continued revisions of guidance should be taken as an exception, for in no other way the growth of knowledge of therapeutics and of means and mechanisms of therapeutics producing adverse events are accommodated.

So from these and associated requirements (such as USP), our general case arrives.

Table 5 Comparison of protein therapeutic agents with small-molecule drugs

Parameter	Proteins	Small Molecules
Drug substance	Heterogeneous mixture; broad specifications during development; specifications may change during development	Single entity; high chemical purity; exception; racemic mixtures; specifications well defined early in development
Drug product	Usually intravenously or subcutaneously	General oral; few formulations during development
Impurities	Difficult to standardize	Purity standards well established
Bridging requirements	Significant for drug substance	Bioequivalence procedures
Biological activity	May mimic naturally occurring molecules; primary mechanism of toxicity; predictive based on mechanism	Less predictive
Nonspecificity	Variable significance	Usually significant; drug—drug interactions
Chronic toxicity	Lack of models because of species-determined biological specificity and antigenicity	Models sometimes relevant
Impurities	Toxicity not a major issue; may impact immunogenicity	May be significant; purity standards well established

G.C Gad (2009) Drug Safety Evaluation (2nd ED)

[1] Always remember that these are not regulations, and such allow for flexibility – particularly on the part of regulation.

The First Rule

Presented above and throughout this volume is the general case, what usually is expected to be done (and is prescribed in the guidelines). Only – rarely in the case of any specific drug that such a general case applies. This book seeks to point out the exceptions and exclusions that apply, but undoubtedly has missed some.

So *Caveat emperator* – The reader should always remember the first rule is *that the general case never fully applies.*

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