An introduction to little-known aspects of nonclinical regulatory writing

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Abstract
Nonclinical evaluation is a key component of drug development. Traditionally, scientists have prepared much of the written regulatory documentation, with dedicated nonclinical writing being a niche profession. This is changing – the demand for nonclinical writers is growing due to the increasing complexity of drug development and regulatory requirements. Yet dedicated resources for nonclinical writers are scarce, and nonclinical health authority guidelines provide little guidance on regulatory writing. In this article, we present an overview of nonclinical development from the perspective of a regulatory writer, highlighting aspects that cannot be discerned from the guidelines. We then give an overview of nonclinical documentation and further describe the distinct challenges of nonclinical regulatory writing and how it differs from clinical regulatory writing. Finally, we discuss key attributes of nonclinical writers.

Introduction
When considering drug development, people naturally think of human clinical trials. And when it comes to preclinical studies, many people assume that these are, as the name implies, conducted and completed before clinical trials are initiated (Figure 1). This reflects the common view that preclinical development is of little importance once human data have been obtained. Indeed, if you ask about the purpose of preclinical development, you will hear that it mostly consists of toxicology studies conducted to ensure a compound's safety before testing in humans.

In this article we will challenge these views. We explain that preclinical evaluations comprise a comprehensive scientific programme that spans the whole lifecycle of the compound (Figure 2, Box 1). To underscore this, we use the term *nonclinical* throughout the article. We then discuss issues specific to nonclinical regulatory documentation and key differences between nonclinical and clinical writing.

The nonclinical regulatory framework and beyond
Nonclinical studies are required for the development of all new pharmaceutical compounds,[1] but the number and type of studies depend on the compound's characteristics, in particular whether it is a small molecule (Figure 2A) or a biologic (Figure 2B). For example, under certain circumstances, biologics are exempt from some pharmacokinetic and safety studies, although they often require additional case-by-case assessments.[2-5]

The regulatory requirements for nonclinical safety evaluation are outlined in the International Conference on Harmonisation (ICH) guideline M3.[6,7] Because this is a fairly broad document, it is supplemented by a large set of specialised guidelines (ICH S1A-S10) detailing the

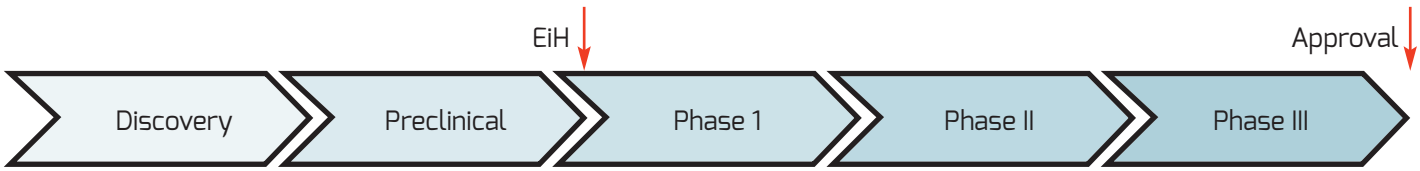
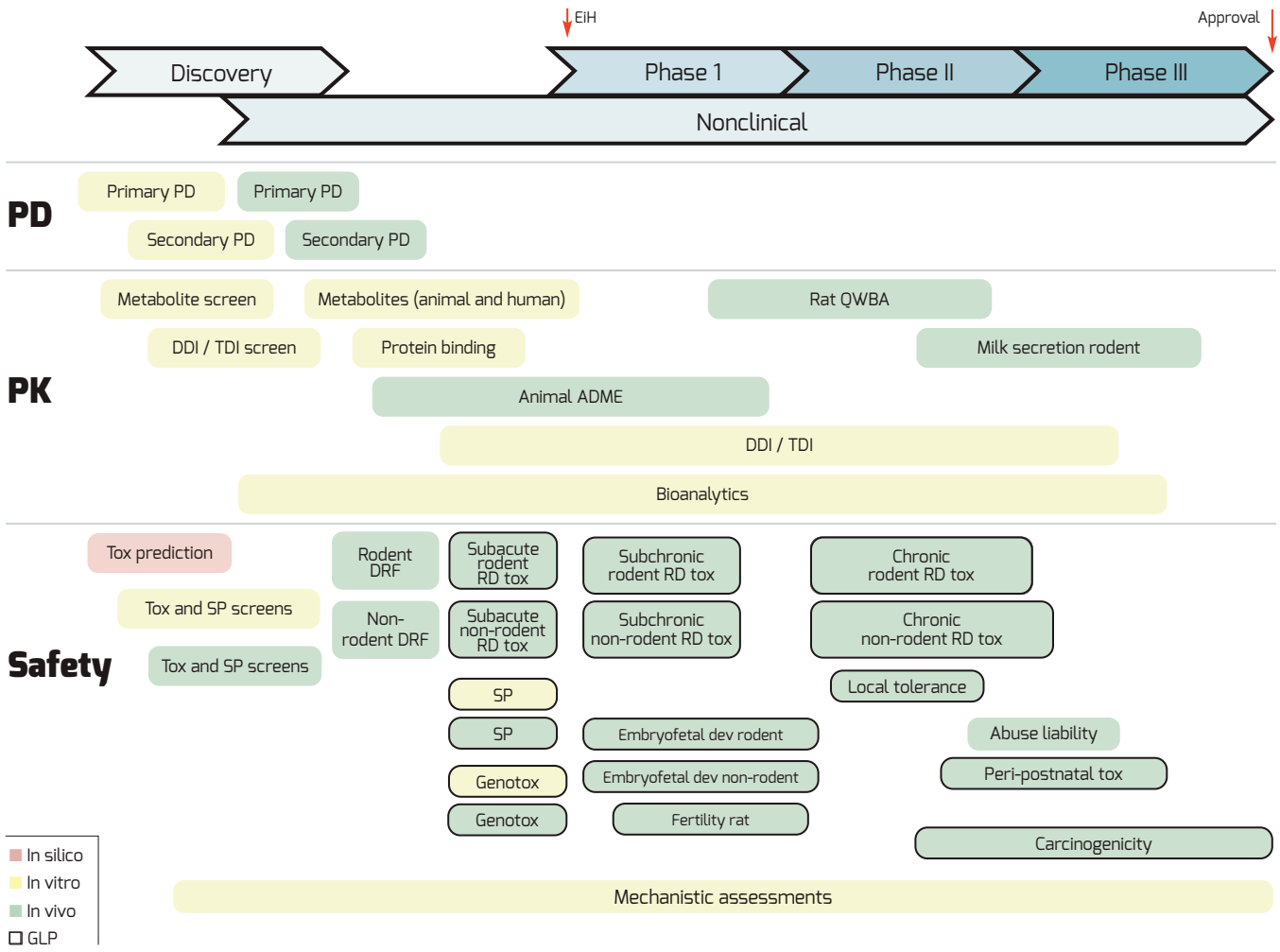


Figure 1. Conventional schema of drug discovery and development. Traditionally, preclinical evaluations have been viewed as an intermediate and isolated step between drug discovery and clinical development (Phase I to III). EiH: entry in human.

Figure 2A. Nonclinical evaluation for small molecules. (See also Box 1.)



Box 1. Nonclinical evaluation for small molecules (Figure 2A) and biologics (Figure 2B).

In practice, nonclinical studies start during the discovery phase and continue until (and sometimes beyond) approval. Nonclinical development covers a number of domains, from the biological research underpinning a compound's mode of action through its disposition in the body (pharmacokinetics) and safety assessment (toxicology).

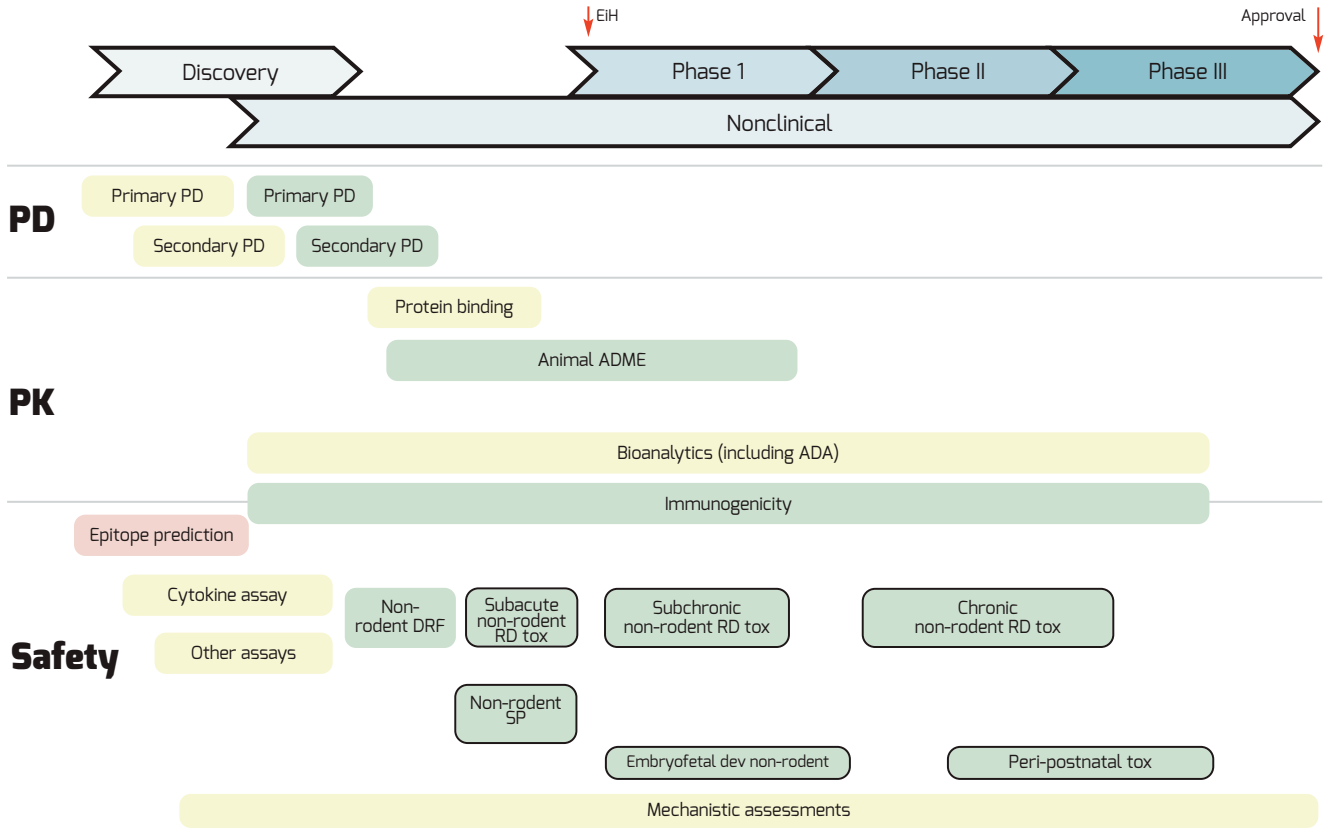
(A) For small molecules, early studies, including in silico predictions and in vitro/in vivo screens, provide a valuable feedback for compound optimisation during the discovery phase. They also form the basis for managerial decisions to advance molecules into Good Laboratory Practice (GLP) safety assessments. GLP studies, if successful, enable the conduct of the first human trials. Larger scale and longer clinical trials in Phases II and III require more toxicological evidence, including longer (subchronic and chronic) repeated dose toxicity studies. Nonclinical studies required for marketing approval, such as carcinogenicity studies, should be initiated well in advance of the submission (usually during Phase III).

(B) For biologics, although nonclinical evaluation requires fewer studies, it may still become complex due to limited experience with new molecules and modes of action or to a lack of relevant species. In many cases, the only relevant species may be a non-rodent, and so rodent studies may be omitted. However, health authorities may also request that the non-rodent studies are supplemented with data generated in transgenic mouse models. Another challenge is immunogenicity, which can lead to unwanted pharmacodynamic (lack of efficacy) or pharmacokinetic (high variability, fast clearance) effects or cause adverse reactions. Immunogenicity testing can therefore constitute a large portion of a nonclinical programme for biologics.

Of note, the figure only presents key nonclinical evaluations, which may consist of several separate studies. For example, carcinogenicity assessment typically consists of a 2-year rat study and a 6-month transgenic mouse study, both preceded by dose-range finding studies.

In general, the need for nonclinical studies should be assessed on a case-by-case basis; a real nonclinical programme is thus always tailored to the compound being developed.

Figure 2B. Nonclinical evaluation biologics. (See also Box 1.)



Abbreviations: ADA, anti-drug antibody; ADME, adsorption, distribution, metabolism and excretion; DDI, drug-drug interactions; Dev, development; DRF, dose range finding [study]; EiH, entry in human; Genotox, genotoxicity; GLP, Good Laboratory Practice; QWBA, quantitative whole-body autoradiography; PD, pharmacodynamics; PK, pharmacokinetics; RD, repeat dose; SP, safety pharmacology; TDI, time-dependent inhibition; Tox, toxicity

requirements for particular types of nonclinical studies or specifying programmes for certain compound classes or patient populations (Table 1). The guidelines for the first-in-human clinical trials provide additional details on the nonclinical programme, including more precise requirements for assessing pharmacodynamics[8] and determining the starting dose.[8,9] Nonclinical evaluation is further guided by a variety of cross-disciplinary documents.[10] For example, many nonclinical pharmacokinetic in vitro evaluations are mandated by drug-drug interaction guidelines.[11,12]

The methodology of nonclinical studies overlaps significantly with that of industrial toxicity testing. Hence, regulatory agencies expect Organisation for Economic Co-operation and Development (OECD) guidelines to be considered if applicable. These not only include the well-known OECD GLP guideline,[13] which is the nonclinical sister to the Good Manufacturing and Good Clinical Practices, but also many internationally agreed-upon and validated toxicity testing methods.[14]

Although all of these guidelines are extensive and appear comprehensive, they cover, in fact, only a subset of the nonclinical studies included in submission packages. Additionally, they do not provide a general overview of how the nonclinical programme fits into the full drug development programme. To fill this gap, we address below four key points about nonclinical development.

Nonclinical studies vary greatly

Although nonclinical development is often associated with animal tests, like rat or monkey toxicity studies, in reality, the nonclinical programme is much more diverse. Apart from in vivo toxicity studies, nonclinical investigations also include in silico, in vitro, and in vivo assessments of pharmacological effects and pharmacokinetic properties, as well in silico and in vitro toxicity tests. Although safety testing must be conducted in two species (rodent and non-rodent), an overall nonclinical programme can involve more than two species because certain nonclinical questions may require special animal models. For example, our group has even worked on studies using woodchucks, one of the rare suitable animal models for hepatitis B. For biologics, the only relevant species may be a non-rodent, usually non-human primate, and thus the requirement for rodent studies can be waived. In addition to these in vitro and in vivo animal evaluations, many nonclinical in vitro tests are performed using human samples, such

as primary cell cultures or blood. Some nonclinical studies may be purely physicochemical, for example, X-ray crystallography of a ligand-receptor complex.

Nonclinical programmes are also closely linked with medicinal chemistry and manufacturing. At the discovery stage, nonclinical data drive compound optimisation.[15] During nonclinical development, the formulation and even the molecular structure of the compound can change, necessitating bridging nonclinical studies. As manufacturing scales up, assessing impurities becomes an additional nonclinical issue.[16] For complex manufacturing processes, more genotoxicity testing may be needed than for the original active compound – we have seen as many as 30 studies for impurities.

Nonclinical methods are largely influenced by innovation. Pharmaceutical companies constantly seek to reduce both the attrition rate and the need for animal studies in nonclinical development by introducing new in vitro screening methods, such as human organs-on-a-chip.[17] Thus, novel methods are consistently being tested and presented to the appropriate regulatory bodies. The rise of biologics and other new types of pharmacological intervention[18] has also prompted rethinking of the traditional approaches to nonclinical evaluation used for small molecules.[3,4,19] Following advances in understanding carcinogenicity and the increasing demand for early access to paediatric drugs, new ICH nonclinical safety guidelines (S1 and S11; see Table 1)[20-22] are in preparation.

In short, nonclinical studies vary greatly, and the nonclinical landscape continues to evolve.

The nonclinical package includes early investigations

Nonclinical evaluation lacks a definitive starting point, unlike the clinical programme, where first clinical trial approved marks the beginning of clinical development. The start of pivotal (GLP) toxicity studies is a significant milestone, yet it is preceded by many other investigations reaching back to the early discovery stage. These early studies are not specifically mandated by the guidelines but are driven by scientific and practical reasoning: No company would run an expensive GLP toxicity study without an extensive screening for possible toxicities, including in silico,[23] in vitro, and smaller-scale non-GLP in vivo investigations. Similarly, early assessment of pharmacokinetic properties informs both the discovery programme (e.g., compound optimisation) and the design of the safety evaluations (e.g., safety-relevant human metabolites). If the compound progresses, almost all of these early studies will become part of the nonclinical package.

Nonclinical studies continue after entry into human

Although many nonclinical studies are completed before the first human clinical trials, nonclinical development continues far beyond. Some of these later studies are aimed at supporting late clinical phases (e.g., chronic repeated-dose toxicity studies), while others are required for marketing approval (e.g., carcinogenicity studies). Planning nonclinical studies to be run in parallel to clinical development is a challenge because nonclinical results must be delivered in time for applications for next clinical trials or marketing approval. In some situations, nonclinical studies may be conducted post-approval, either as part of post-approval commitments or to support post-marketing safety evaluation. Thus, nonclinical documentation support is usually needed throughout the whole lifecycle of the compound.

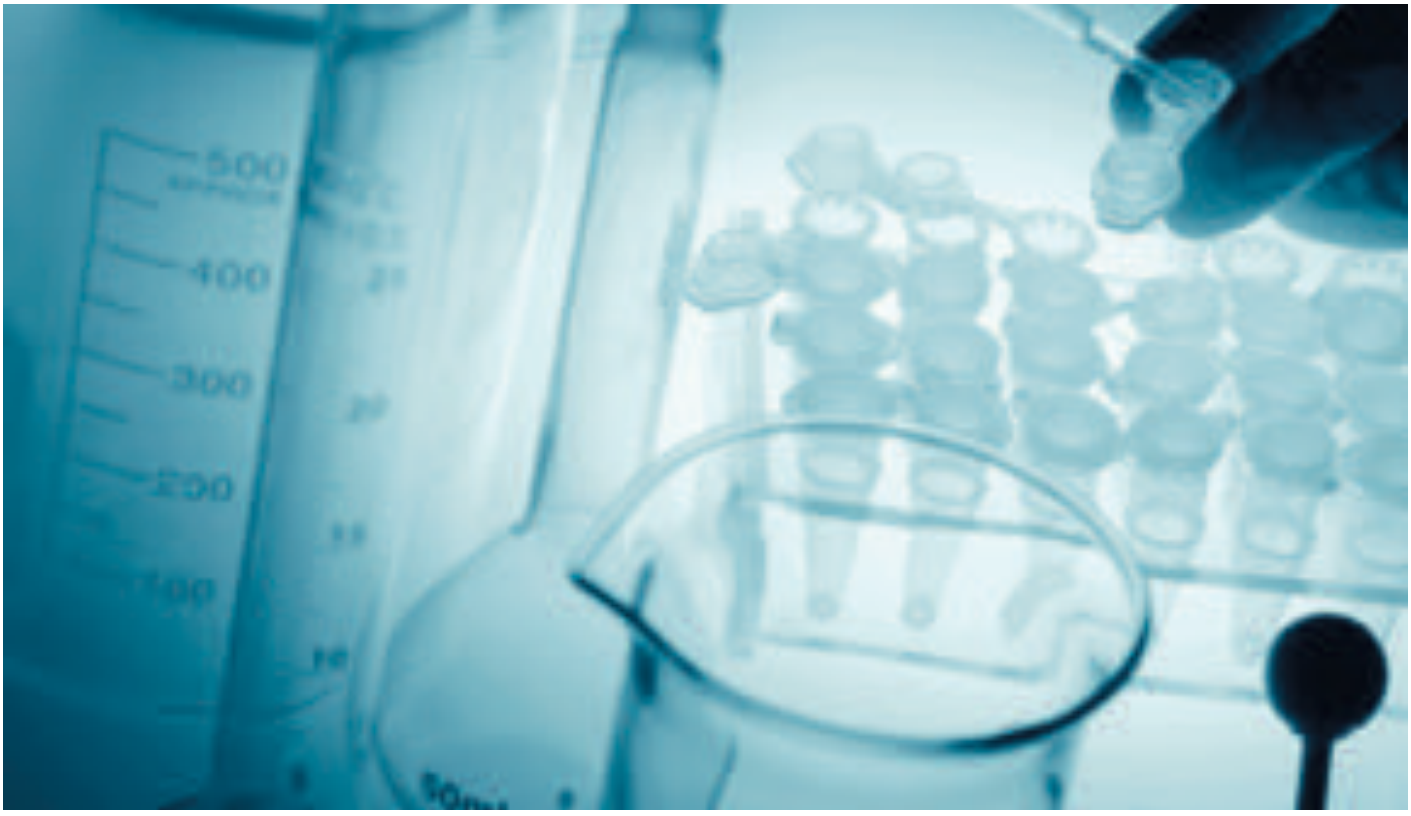


Table 1. Key guidelines for nonclinical evaluation

Guideline	Name	Description
ICH M3	Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals.	The key guideline, which describes the general principles, timing and standards for nonclinical safety evaluation.
ICH S1A	Guideline on the need for carcinogenicity studies of pharmaceuticals.	These three guidelines will be replaced by a single comprehensive guideline (ICH S1) on rodent carcinogenicity testing for human pharmaceuticals.
ICH S1B	Testing for carcinogenicity of pharmaceuticals.	
ICH S1C	Dose selection for carcinogenicity studies of pharmaceuticals.	
ICH S2	Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.	The guideline describes the standard test battery for genotoxicity of small molecule compounds and provides recommendations for individual tests.
ICH S3A	Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies.	The guideline describes the assessment of systemic exposure in toxicity studies. It does not provide guidance for nonclinical pharmacokinetics and metabolism testing.
ICH S3B	Pharmacokinetics: Guidance for repeated dose tissue distribution studies.	Specific guideline for tissue distribution studies within the nonclinical pharmacokinetics programme.
ICH S4	Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing).	This small guideline sets out the minimal duration of chronic toxicity studies that is acceptable for submission (6 months for a rodent and 9 months for a non-rodent study).
ICH S5	Detection of toxicity to reproduction for medicinal products and toxicity to male fertility.	The key guideline for reproductive toxicity testing. It is currently under revision.
ICH S6	Preclinical safety evaluation of biotechnology-derived pharmaceuticals.	This guideline outlines the nonclinical safety evaluation for biologics. It is a supplement to ICH M3.
ICH S7A	Safety pharmacology studies for human pharmaceuticals.	The two guidelines provide recommendations for studies that examine unwanted pharmacological effects on physiological functions (so-called "safety pharmacology" studies). Safety pharmacology studies may be considered part of toxicological programme and summarised in the toxicology written summary.
ICH S7B	The non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals.	
ICH S8	Immunotoxicity studies for human pharmaceuticals.	The guideline describes nonclinical testing for immunosuppression and immuno-enhancement. It does not cover allergenicity or drug-specific autoimmunity.
ICH S9	Nonclinical evaluation for anticancer pharmaceuticals.	The guideline describes specific requirements and certain toxicology study exemptions for nonclinical testing of anticancer compounds.
ICH S10	Photosafety evaluation of pharmaceuticals.	The guideline describes in detail phototoxicity testing of new compounds, excipients of dermal formulations and photodynamic therapy products and illustrates situations that do not require experimental evaluation in biological systems.
ICH S11	Nonclinical safety testing in support of development of pediatric medicines.	This will be a new guideline for nonclinical evaluation of compounds for paediatric use ("paediatric first" or "paediatric only").
GLP	Good Laboratory Practice.	The quality standard for nonclinical studies. The OECD GLP is a common reference point, however, regional legal implementations can vary significantly. Studies conducted in a country that is not included in the OECD Mutual Acceptance Data system may be not accepted by some health authorities.
EMEA/CHMP/SWP/28367/07 Rev. 1	Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.	The cross-disciplinary guideline from EMA, which provides additional details for nonclinical programme intended to support entry in human.
ICH M7	Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.	A new cross-disciplinary guideline that complements the existing ICH Q3A and ICH Q3B guidelines. It contains considerations for the risk assessment for potentially mutagenic impurities.

Note: The EMA has a dedicated page containing a comprehensive list of nonclinical guidelines.[10]

Nonclinical studies support labelling

For marketing approval submissions, nonclinical information is traditionally seen as corroborating clinical evidence. Safety assessments can provide mechanistic explanations of adverse reactions observed in humans, and pharmacokinetic evaluations can inform decisions on clinical pharmacology studies, but it is the clinical trial results that actually support labelling claims. However, some data cannot be intentionally obtained in clinical trials, most notably data on carcinogenicity and reproductive toxicity. Thus, labelling is directly influenced by the results of these nonclinical investigations, along with some nonclinical pharmacokinetic data (e.g., drug-drug interaction or transporter studies).

Nonclinical regulatory documentation

Nonclinical regulatory documentation can be divided into three major domains:

- Summary documents for regulatory submissions
- Study reports with original data
- Various regulatory documents presented during the life cycle of a compound

The common documents with nonclinical content are summarized in Table 2.

Summary documents for regulatory submissions

For clinical regulatory writers, the Investigator's Brochure (IB) is likely the most familiar document with nonclinical content. The IB contains a summary of all clinically relevant pharmaceutical, nonclinical and clinical data about a compound.[24,25] The IB is first prepared for the initial, first-in-human trial and is then updated at least annually and before any clinical trial application. The nonclinical section may be written by the scientists or by nonclinical writers. The first few versions are usually fairly extensive, but the section is usually condensed as clinical trials advance and clinical knowledge increases.

Along with the IB, the nonclinical Common Technical Document (CTD) Module 2 documents are the only nonclinical documents with clear guidance about their content (ICH M4S;[26] for more detail, see Debbie Jordan's overview of the CTD.[27]) These include three written summaries, for pharmacology, pharmacokinetics, and toxicology (sections 2.6.2, 2.6.4, and 2.6.6), which present an integrated summary of findings; three corresponding tabulated summaries (sections 2.6.3, 2.6.5, and 2.6.7), which present the data in tabulated form with no interpretation; the nonclinical introduction (section 2.6.1), which contains a brief summary of pharmaceutical structure, pharmacological properties and intended clinical use; and the nonclinical overview (section 2.4), which provides an integrated assessment of the safety, pharmacokinetics, and pharmacology data in the context of the proposed clinical trial or label. Module 2 documents are submitted with marketing approval applications and with FDA Investigational New Drug applications (INDs), which are mandatory for initiating clinical trials in the US.[28] Similar, though less detailed, documents are required for clinical trial applications outside the US, such as the nonclinical sections of the Investigational Medicinal Product Dossier in Europe[29, 30] and Part 3 of the Australian Clinical Trial Exemption application.[31]

Importantly, the argumentation in the nonclinical documents changes as the compound advances in clinical development. Early submissions, such as FDA INDs, focus on nonclinical evidence for safety and pharmacological activity, including justification for the chosen nonclinical program and the adequacy of the safety precautions set in the clinical protocol. For marketing approvals, the writing task is different because nonclinical data must be discussed in the context of available human data with an emphasis on how they align with the effects observed in humans (e.g., pharmacological mechanism or adverse reactions) and labelling claims. The summary documents also become more extensive because the number of studies to include generally grows following the first-in-human trials.

A rarely discussed aspect of these submissions is the health authority responses and questions. Unsurprisingly, given their overall complexity, submissions do not elicit straight yes or no responses from the health authorities! Frequently, health authorities have questions about the submission data and their interpretation that must be answered within a limited timeframe – anywhere from one day to several months, depending on the country, submission, and number and type of questions. These may include, for instance, technical queries (e.g., a missing report signature), proposed alternative interpretations of findings, or requests for additional data to support a particular claim. These questions often require delving deeper into the original study data or scientific literature and sometimes even planning a new study.

Nonclinical study reports

Nonclinical study reports are included in CTD Module 4 of marketing approval applications and INDs. In Europe and other regions, a summary of the nonclinical findings is usually sufficient for a clinical trial application,[29, 30] but agencies may request study reports during the review. For a first-in-human clinical trial application, on average, 20 to 50 reports will be prepared, and even more reports are usually needed for a marketing approval submission. These reports, anywhere from 5 to 3,000 pages long, range from early pharmacology work to complex toxicity studies conducted under GLP. The reports may have been prepared in-house, at a contract research organisation, or even by another pharmaceutical company in the case of purchased compounds. Complex studies, most notably GLP general toxicity studies, include several substudies, so-called "phase" studies, which are ultimately incorporated into the final report. Coordinating the preparation and delivery of the phase reports can be complicated because they often come from different departments or contract research organisations. This can also be a challenge if submitting draft GLP toxicology reports to the FDA because they must contain a signed pathology phase report and must be followed within 120 days by the final report with a detailed list of changes.

In addition to the nonclinical studies, nonclinical writers support some studies in the clinical domain (CTD Module 5). These include in vitro and ex vivo pharmacokinetic evaluations with human biomaterials, as well as certain parts of clinical studies. Nonclinical writers also frequently support method validation and bioanalytical reports because analyses for both nonclinical and clinical studies are often performed by the same bioanalytical laboratory. Other examples include biomarker analysis and population pharmacokinetics studies, which are often conducted by nonclinical or cross-functional units.

There is a high turnover of nonclinical reports due to the relatively short duration and large number of studies. Reports are produced on an ongoing basis to inform regulatory and managerial decisions, with new findings sometimes leading to additional investigative studies. Writing activities must be coordinated

Table 2. Common documents with nonclinical content

Document	Nonclinical content	Content/Writing Guidelines	CTD Module	Submission package or Timepoint
Investigator's Brochure	This comprehensive document contains a summary of all clinically relevant pharmaceutical, nonclinical and clinical data about a compound.	ICH E6[24]	Module 1 (IND)	Clinical trial application (CTA), IND
Investigational Medicinal Product Dossier	A high-level summary of the nonclinical programme. Usually, however, the dossier simply refers to the corresponding sections of the IB.	EU Guideline[29] EU Regulation[30]	–	CTA
Nonclinical Overview	The nonclinical overview provides an integrated analysis of the nonclinical programme, which includes justification for the nonclinical testing strategy and conclusions for the safety for the intended clinical trial or therapeutic use. Similar summary documents are submitted with clinical trial applications in some regions (e.g. in Australia).	ICH M4S[26]	Module 2, Section 2.4	IND, Marketing approval
Nonclinical Introduction	A small document (few pages) that contains a brief summary of pharmaceutical structure, pharmacological properties and intended clinical use of a compound.	ICH M4S[26]	Module 2, Section 2.6.1	IND, Marketing approval
Nonclinical Written Summaries	The documents contain high level summaries of pharmacology, pharmacokinetics and toxicology data, including a brief summary of the principal findings and a concise discussion and conclusion.	ICH M4S[26]	Module 2, Sections 2.6.2, 2.6.4, 2.6.6	IND, Marketing approval
Nonclinical Tabulated Summaries	The documents summarise pharmacology, pharmacokinetics and toxicology data in tabulated form with no interpretation. Similar tables are prepared for clinical trial applications in China.	ICH M4S[26]	Module 2, Sections 2.6.3, 2.6.5, 2.6.7	IND, Marketing approval
Nonclinical Study Reports	The reports are included in the CTD Module 4 of marketing approval applications and INDs. In Europe and other regions, a summary of the nonclinical findings is usually sufficient for a clinical trial application, however, all cited study reports must be available on request. Nonclinical regulatory writers can also support some reports included in the clinical CTD Module 5 (e.g., in vitro and ex vivo pharmacokinetic evaluations with human biomaterials).	No single guideline available, some scientific guidelines contain high level requirements for study reports.	Module 4, Module 5	CTA (on file), IND, Marketing approval
Briefing Packages	The briefing packages are the official way to request health authority feedback. They can be prepared by all departments – clinical, manufacturing, or nonclinical. Nonclinical background information and questions are commonly included in briefing packages for each department.	Agency-specific guidelines	–	Usually before next development step (e.g., before CTA, IND or filing)
Special Protocol Assessment	A special request for the FDA's feedback on the carcinogenicity study protocol. It contains the draft protocol, an integrated summary of nonclinical and clinical data, and justification for the selected doses and other critical design features.	FDA Guideline[33]	–	Usually when pivotal clinical trials commence
Paediatric Investigation Plan/Pediatric Study Plan	The plan contains a summary of nonclinical findings alongside with a summary of the nonclinical strategy to support paediatric use.	EMA Guideline[34] and template, FDA Guideline[37]	–	Before Phase II or pre-IND
Risk Management Plan	The plan contains a summary of safety-related findings.	EMA Guideline[39]	Module 1	Marketing approval (Europe and some other regions)
Regular reports	Safety findings are also reported as part of regular reports, such as DSURs, PSURs/PBRERs, orphan drug annual reports, and IND annual reports (these can be replaced by a DSUR).	ICH E2F,[40] ICH E2C,[41] and specific EMA and FDA guidelines and regulations	–	Usually annual submissions

between many different internal departments and contract research organisations. Companies establish their own procedures for preparing reports, starting with the fundamental question of whether to prepare complete regulatory reports routinely for all studies or only write the complete reports when necessary for submissions. The first approach may waste resources because many compounds do not proceed into clinical development. However, with the second approach, submissions can become extremely challenging because of tight timelines, which can be exacerbated by having to prepare many reports, sometimes for studies completed years ago.

To complicate matters further, nonclinical guidelines focus primarily on scientific methods and development strategy. In particular, the GLP and other guidelines provide only high-level requirements for study reports rather than detailed guidance on report structure. Unlike clinical reporting, which is guided by ICH E3, there is no single detailed reporting guideline for nonclinical reporting – not surprising given the variety of nonclinical studies. Overall, the quality and validation requirements for the studies and reports vary greatly, from strict GLP rules for pivotal safety evaluations to a more academic approach for pharmacology reports (some health authorities do not even require signatures for these). Hence, the internal reporting criteria must be set appropriately, but even when requirements for report content and formatting are set, many reports, especially for pharmacology, do not contain any standard text and must be written from scratch.

In addition to writing and editing documents, keeping track of all the reports in the nonclinical package is an important activity for a nonclinical submission writer. This requires considerable attention because these reports build on each other to form the full picture of a compound's pharmacological, pharmacokinetic, and toxicological properties. The key difference between clinical and nonclinical regulatory writing is, however, the wider variety and greater quantity of nonclinical reports required during drug development.

In-between activities and supporting documents

Applications for clinical trials and marketing approval are the largest health authority submissions. Over the course of a compound's development, however, nonclinical writers will prepare many other regulatory documents.

Briefing packages, which most regulatory writers are familiar with, are the official way to request health authority feedback. They consist of up-to-date summary data on a compound, followed by specific questions, the sponsor's position on these questions, and supportive arguments. Briefing packages can be prepared by all departments – clinical, manufacturing, or nonclinical. Nonclinical background information and questions are commonly included in briefing packages for each department because clinical or manufacturing concerns may hinge on a nonclinical finding or study.

The Special Protocol Assessment (SPA) for carcinogenicity studies is a special request for the FDA's feedback on the study protocol. Classic rodent carcinogenicity studies take up two years of in vivo treatment (meaning up to 3 years from start to final report) and cost up to $4 million.[32] Given the uncertainty of a compound reaching the market, carcinogenicity studies are usually conducted during a late stage of clinical development, typically starting when pivotal clinical trials are initiated. The late start, cost, and length of these studies make them a risky undertaking. Recognising this, the FDA has included carcinogenicity protocols, along with stability protocols and pivotal clinical protocols, in its current SPA programme.[33] In addition to the draft protocol, the SPA request contains an integrated summary of nonclinical and clinical data and justification for the selected doses and other critical design features.

Additional documents that include nonclinical contributions are Paediatric Investigation Plans/Pediatric Study Plans[34-37] and Risk Managements Plans,[38,39] which require summaries of either overall nonclinical findings or safety-related findings. Safety findings are also reported to the various health authorities as part of regular reports, such as safety update reports (e.g., Drug Safety Update Reports, Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports for Medicinal Products),[40,41] orphan drug annual reports,[42,43] and IND annual reports.[44] The reporting requirements for these vary, but a compilation of either all nonclinical studies or all safety findings (including a literature search) during the reporting period is always expected.

Nonclinical regulatory writers

As described above, nonclinical regulatory documentation comprises a wide range of activities involving many different stakeholders. Thus, nonclinical and clinical regulatory writers require somewhat different skill sets.

Because of the many areas in which a compound must be tested nonclinically and the number of reports, nonclinical writers in pharmaceutical companies, unlike many clinical writers, do not specialise in a specific therapeutic or document category area. Nonclinical writers work closely with scientific experts across domains to prepare regulatory documents. Nonclinical development includes many specialised fields, so in some companies, the role of a nonclinical writer may consist of more editing than writing. In any case, a strong background in biological sciences, usually with some practical research experience, is necessary to understand the many in vitro and in vivo assays conducted.

As mentioned earlier, nonclinical development is a highly innovative field, with new technologies constantly being introduced, so a nonclinical writer needs to keep abreast of new scientific and technical advancements (see Box 2).

Box 2. New FDA requirement for electronic submission of data for certain toxicology studies

The managerial aspect of nonclinical submissions has recently become even more challenging due to a new FDA requirement for electronic data submission[49] coming into effect for certain toxicology studies (Standard for the Exchange of Nonclinical Data [SEND],[50] a nonclinical variant of the Study Data Tabulation Model [SDTM]). Until now, raw study data have been archived and only submitted on request. This shift has led to an industry-wide scramble to prepare standardised study outputs and to reform processes to include these data files in FDA submissions.[51] Because the SEND data files are included in CTD Module 4, nonclinical writers involved in the assembly of nonclinical packages may find themselves coordinating both the preparation of study reports and the delivery of SEND files.

However, former scientists in a specific nonclinical domain, most often in toxicology, may switch to regulatory writing and thus provide specialised service in writing reports and summaries. In addition, some guidelines mandate that a scientific expert contribute to specific documents. For instance, GLP guidelines require an expert pathologist (often with veterinary qualifications) to write and sign the pathology study report, a critical component of in vivo toxicology study reports.[45]

Some scientists prepare reports and regulatory documents frequently, but others do so only rarely, so scientists often must be trained in report writing and the specific requirements of regulatory submissions documents, and especially in the differences with academic writing. However, scientists rely on nonclinical writers for more than preparing articulate and sound documentation; they also expect advice on regulatory matters, either by liaising with the regulatory lead or by providing information about best practices. Therefore, writers must keep up to date with official guidelines and continuously learn about best practices. For example, interpretation of the GLP guidelines can differ between countries,[46] and studies conducted in a country that is not included in the OECD Mutual Acceptance Data system may be not accepted by some health authorities, such as in South Korea[47] and the UK,[48] which do not accept GLP studies conducted in China. Staying alert for such issues is another key part of a nonclinical writer's work.

Like other regulatory writers, nonclinical writers need to be skilled at managing projects and dossiers, communicating with and mediating between a variety of collaborators, understanding and following regulatory guidelines, and learning on the job. However, different from clinical writers, nonclinical writers must have a strong background in the biological sciences and must take a generalist approach to be able to cover the wide range of assays and topics included in nonclinical development.

Conclusion

Nonclinical evaluation is an essential and complex scientific programme that extends throughout a compound's full lifecycle and requires extensive regulatory documentation. Nonclinical regulatory writing has not been viewed as an integral part of nonclinical research until recently due to its high reliance on direct scientific input and wide range of assays. Scientists have been expected to both conduct studies and produce regulatory-compliant reports, so dedicated nonclinical writing has remained a niche profession. However, the increasing complexity of drug development, and, correspondingly, of regulatory requirements is leading to a growing need for expert nonclinical writing support and indeed the pharmaceutical industry is adapting to this. This increasing demand should continue in the years to come.

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