20. Preclinical and/or Nonclinical Studies

François Noël, May 2021
(reviewed by Dr. Iolanda M. Fierro, INPI & DeXpert Assessoria e Consultoria Tecnocientífica)

Worldwide, academia has increasingly been called upon to participate in drug discovery and development projects together with industry. To facilitate entry into this growing job market in Brazil, it is important to become familiar with the different stages of this long process and with the specific terminology used in this multidisciplinary field. Unfortunately, there is no consensus on several terms (see entries 12 and 13 of this glossary), which is why we decided to comment here on a term that generates some confusion, namely preclinical and/or nonclinical studies.

Two levels of confusion can be identified with respect to these terms: one temporal and the other related to content.

- Temporal aspect: At first glance, and without controversy, "preclinical studies" can be understood as studies conducted BEFORE a drug candidate enters the clinical development phase. On the other hand, the term "nonclinical studies" is broader in temporal scope, including animal studies conducted both BEFORE and DURING the clinical phase. Clarifying this issue, Delouche (Camargo Research Group) points out that many pharmaceutical companies identify themselves as operating in the preclinical phase of development when their substances have not yet been tested in humans. Meanwhile, many service providers use the term "nonclinical studies" to describe their laboratory facilities and activities, with the purpose of including in their portfolios the assays performed during clinical studies. It should be recalled that clinical studies begin after approval of an application submitted to the regulatory agency, known as an IND (acronym for Investigational New Drug application) at the United States Food and Drug Administration (FDA). Because the terms "preclinical" and "nonclinical" are similar and largely overlapping, they are often used interchangeably, which led Delouche to conclude that it would not be incorrect to use either of these terms to describe the studies that support an IND submission to the FDA. On the other hand, it is clear that it would make no sense to refer to animal toxicity studies conducted during clinical trials as preclinical.

- Content aspect: In Brazil, the National Health Surveillance Agency (Anvisa) does not propose formal definitions for preclinical and nonclinical studies and therefore does not clearly define their content. In a note on the use of animals in preclinical studies (Anvisa-1, 2017), Anvisa indicates that it uses this term to refer to animal studies aimed at ensuring the efficacy and safety of drugs before conducting clinical studies. Thus, the term "preclinical studies" does not encompass ALL studies conducted before the clinical phase, such as *in vitro* studies of efficacy and pharmacokinetics (despite the etymology of the term preclinical, derived from the Latin *pre*, meaning before, and the Greek *kline*,

meaning bed). Conversely, similar to the FDA, Anvisa uses the term "nonclinical studies" in its specific guideline on toxicology and pharmacological safety studies required for drug development (Anvisa-2, 2013). In this case, the proposed nonclinical safety studies include single-dose (acute) toxicity, repeated-dose toxicity, reproductive toxicity, genotoxicity, local tolerance, and carcinogenicity, in addition to studies relevant to the assessment of pharmacological safety and toxicokinetics.

Within this context, what is the position (or lack of position) of regulatory agencies regarding the use of these two terms?

The European Medicines Agency (EMA) uses either term in the titles of its guidelines and employs them interchangeably in the text. Meanwhile, the FDA has chosen to use the term "nonclinical" in its guidance on nonclinical safety studies required for the conduct of human clinical trials and subsequent marketing authorization for pharmaceutical products (FDA-1, 2010), with the caveat that such studies are "*often referred to as preclinical studies when conducted before the first clinical studies in humans*". According to the **FDA definition, "*a nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety*"** (FDA-2). In Brazil, Anvisa does not address this terminological issue and, depending on the document, uses one term or the other, apparently indiscriminately, with preferences possibly reflecting the choices of authors and/or consultants (Andrade et al., 2016).

Conclusion

There is no consensus regarding the use and meaning of the terms "preclinical studies" and "nonclinical studies," and they may even be considered interchangeable by some, at least in certain cases.

An alternative and "provocative" proposal

Although not grounded in the literature, when considering a possible map of the drug discovery and development process, an interesting alternative would be to use the term "preclinical studies" for animal studies conducted with the selected prototype intended for validation as a drug candidate and for submission of an IND, that is, BEFORE clinical studies. There would be no clearly delimited list of what would constitute such preclinical studies, but they would certainly include subchronic toxicity studies, toxicokinetics, definition of metabolites and tissue distribution, genotoxicity and reproductive toxicity, as well as safety evaluations of the cardiovascular system, pulmonary function, and general behavior (safety pharmacology). *In silico* and *in vitro* studies for the identification of active substances and for prototype selection and optimization would belong to the discovery process in the strictest sense of the term (see entry 14 of this glossary). From this perspective, the term "nonclinical studies" could then be used preferentially for animal toxicology studies conducted DURING clinical trials, such as chronic toxicity studies, reproductive toxicology (male fertility and pre- and postnatal development of offspring), and carcinogenicity.

References

Andrade EL, Bento AF, Cavalli J, Oliveira SK, Schwanke RC, Siqueira JM et al. Non-clinical studies in the process of new drug development – Part II: Good laboratory practice, metabolism, pharmacokinetics, safety and dose translation to clinical studies. *Brazilian J. Med. Biol. Res*. 49(12):e5646, 2016.

Anvisa-1. Nota da Anvisa sobre o uso de animais em estudos pré-clínicos (atualizada em 20/03/2017), https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/anos-anteriores/nota-da-anvisa-sobre-o-uso-de-animais-em-estudos-pre-clinicos

Anvisa-2. Guia para a condução de estudos não clínicos de toxicologia e segurança farmacológica necessários ao desenvolvimento de medicamentos. GESEF/ANVISA, Brasília, 31 de janeiro de 2013 – Versão 2

Delouche C. https://premier-research.com/perspectives/preclinical-and-nonclinical-studies-what-is-the-difference-and-where-in-your-program-should-they-fall/

FDA-1. Guidance for Industry. M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. 2010.

FDA-2. Code of Federal Regulations, Title 21, volume 1, Chapter 1-A, Part 58: Good laboratory practice for nonclinical laboratory studies.