Current trends of nonclinical safety evaluation for new drugs

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Abstract: Nonclinical safety evaluation plays a critical role in the process of new drug development. International Conference on Harmonization (ICH) guideline M3 (R2) provides a key direction for the nonclinical safety evaluation process. Proper strategies and toxicological studies should be considered together to move the drug candidates forward efficiently and quickly to support clinical plans and market registration. Updates on ICH guidelines, such as ICH S6 and ICH S9, have great impact on the direction of development. With the increasing cost of development and competition in the industry, elements like predictivity, animal models, and regulatory compliance are also very important in the process. Therefore, an insight into all these factors is essential to toxicologists in the safety evaluation process. The ability to use the overall knowledge will result in a quicker and better new drug development program.

Key words: nonclinical safety; ICH guideline; toxicology; new drug development; small molecules; biologics

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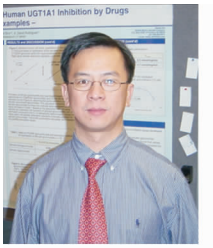

戴仁科，现任中山珐玛斯医药科技有限公司董事长，华南理工大学生物科学与工程学院教授，博士。回国后主要从事药物临床前 ADME-T/PK 和药物毒性研究，尤其在细胞水平和实验动物上的研究。围绕我国华南地区丰富的非人灵长类动物资源开发和应用，开展了大量卓有成效的工作，取得了食蟹猴药物代谢酶相关专利；并在动物模型、动物种属差异、药物代谢、药物相互作用风险评价、毒理、代谢组学等领域取得了可喜的成绩。先后主持承担和参与国家 863 高技术研究发展计划、科技部国际合作项目、国家自然科学基金科研项目、广州市重大科技专项等。

Nonclinical safety evaluation is a process to assess the safety of pharmaceutical products. The goal is to define dose limited toxicity of these products and mitigate the risk in first-in-man (FIM) study in clinical trials. In general, the task involves defining toxic effects in target organs, the dose-dependent manner, relationship to exposure, and potential reversibility of new drugs. ICH M3 (R2)[1] suggests a battery of nonclinical safety studies to elucidate all these aspects in order to help toxicologists to understand the intrinsic toxicity of new drugs. In addition, ICH has nine guidelines[2] in different subcategories of toxicology studies for nonclinical safety evaluation. A proper and adequate toxicology program ensures the sufficiency of toxicology studies for regulatory authorities such as US Food and Drug Administration (FDA), or Chinese State Food and Drug Administration (SFDA). This will lead to a faster and cost-saving nonclinical program to market registration.

1 KEY POINTS

ICH M3(R2) guideline forms the main framework for nonclinical safety evaluation to develop new drugs. The guideline outlines specific toxicology studies in different stages of development (for clinical trials, and market registration) to ensure that the rights, safety and well-being of clinical trial subjects are protected, and to ensure enough toxicology data to support clinical trials and new drug application (NDA) submission. To support the conduct of clinical trials, M3(R2) recommends the duration of repeated dose toxicity studies as shown in Tab. 1. For support of market registration, M3(R2) recommends the duration of repeated-dose toxicity studies as shown in Tab. 2.

Tab. 1 Recommended duration of repeated-dose toxicity studies to support the conduct of clinical trials[1]

Maximum duration of clinical trial	Recommended minimum duration of repeated-dose toxicity studies to support clinical trials	
	Rodent	Non-rodent
Up to 2 weeks	2 weeks	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
>6 months	6 months	9 months

Tab. 2 Recommended duration of repeated-dose toxicity studies to support the marketing[1]

Duration of indicated treatment	Rodent	Non-rodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	3 months	3 months
>3 months	6 months	9 months

It is clearly stated by the guideline that the long-term repeated-dose study for rodents is 6 months in duration for non-rodents and 9 months. This is different

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from the traditional concept that the long term toxicity study should be 1 year in duration[3].

Although M3(R2) recommends the duration for repeated dose toxicity studies as clearly defined in Tab. 2, it does not state whether or not the studies should have a recovery phase. In general, in the pharmaceutical industry, a recovery phase of one month or longer is usually incorporated into the top dose group of the studies. The increased time and cost of development are worthwhile, particularly in understanding the reversibility of the toxicity, which is extremely important to toxicity studies of new drugs.

ICH M3(R2) guideline has much implication for biologics-derived products, since most biologics are protein or protein-based, lots of toxicity studies on small molecules are not relevant to biologics. Traditional genotoxicity studies, such as Ames, mouse lymphoma, and chromosome aberration studies, are not needed for biologics. Furthermore, given the peculiarity of biologics, safety pharmacology studies are not needed as a separate subset of studies in the nonclinical safety evaluation program. All the safety pharmacology endpoints can be incorporated into the general repeated-dose toxicity studies[3].

ICH S6[4] has only an update as addendum 〔ICH S6(R1)〕 for species selection of animals as well as dose selection of studies. For species selection, ICH recommends that "when no relevant species can be identified, because the biopharmaceutical does not interact with the orthologous target in any species, use of homologous molecules, transgenic models and/or animal models of disease can be considered." This means if biologics have no activity in animals, a homologous should be developed and used in an animal species, which has a similar target as in humans. Usually, rodents (rat) are the first choice.

Furthermore, the guideline S6(R1) states that *The text in ICH S6, Section 3.3 paragraph 2 is no longer appropriate. Immunohistochemical examination of potential binding of monoclonal antibodies and related products to the target epitope (tissue cross reactivity) should not be used for selection of relevant species for safety evaluation.* This means that only binding of human tissues provides valuable information on tissue cross reactivity, and that binding in animal tissues is of limited value. S6(R1) recommends that when biological activity of the biologics is well understood or the clinical candidate is pharmacologically active in only one species, then a single species of animal is enough for conduct of all the nonclinical toxicity studies. And rodents are usually recommended in this case.

For dose selection, S6(R1) recommends using pharmacokinetics and pharmacodynamics (PK-PD) approach. It states that 10-fold multiples over the maximum clinical exposure is usually enough for safety margin in animal studies. The guideline also recommends that 6-month duration is enough as the long term toxicity study.

ICH has new guideline S9[5] for pharmaceuticals under development for serious and life-threatening malignancies, such as advanced cancer. The guideline applies to both small molecules and biologics. However, ICH S9 should be used with caution. It clearly states that it is for serious and life-threatening malignancies or advanced cancer. Although the guideline does not explicitly specify what is considered serious and life-threatening malignancies, we would associate such malignanices with end stage cancer, probably with life expectancy less than 1 year or less. It is believed that different regulatory agencies have a different definition of serious and life-threatening malignancies.

ICH S9 recommends that genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with advanced cancer and that carcinogenicity studies are not required for market registration. The guideline also recommends that safety pharmacology studies are not required as stand-alone studies, but they can be included in general toxicology studies.

ICH S2(R1)[6] Guideline for genotoxicity testing was just signed on November 9, 2011. Many of the important changes in this update were designed to: ① reduce the number of irrelevant positive results for *in vitro* mammalian assays; and ② follow the 3Rs for genotoxicity testing (Replacement, Refinement and Reduction).

Some highlights are as follows:

In vitro mammalian cell assay battery

· Reduction in top concentration from 10 – 1 $mmol \cdot L^{-1}$

· Testing of precipitating concentrations no longer required

· *In vitro* micronucleus study acceptable as a third alternative study *in vitro* assays

· *In vivo* cytogenetic assay battery

· Rat blood acceptable for *in vivo* micronucleus analysis

· Reduction of over 50% in cell growth in chromosome aberration study unnecessary

· Reduction of about 80% in RTG (relative total growth) in mouse lymphoma study

In addition to the above updates from the ICH guidelines as well as some general industrial approaches, one should always consider that toxicology studies should identify target organs in animals, potential AEs, and the relevance of the animal data to humans. Good toxicology data should possess fine predictability for humans. This requires use of appropriate animal species, scientifically sound-designed studies, as well as appropriate duration of the studies. Also, animal numbers and good statistically methods are important to the predictability of animal data[7-8].

Regulatory compliance is also another important issue for nonclinical safety evaluation. One should make sure the battery of toxicology studies are conducted in a qualified contract research organization (CRO), the study data are properly generated, and the studies are scientifically designed. Moreover, the conclusion of the studies should be properly drawn, and the data are not over or under interpreted.

2 CONCLUSION

Nonclinical safety evaluation is a complicate process. With an insight into the nature of drug development and general principles of toxicology as well as updated ICH guidelines, one can successfully elucidate the toxicity of the potential pharmaceuticals, resulting in a speedier and better new drug development program.

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当前新药非临床安全性评价的趋势

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摘要: 非临床药物安全性评价为新药的研发发挥了重要作用。人用药品注册技术要求国际协调会(ICH)新药研发指南M3(R2)是非临床药物安全性评价的方向性指导文献。正确的评价策略和相关毒理学研究应该一起综合考虑,以促进新药候选物高效、及时地向前发展,从而支持临床试验计划和市场登记进展。然而,随着发展成本增加和行业的竞争,毒性预测、动物模型和法规遵从性也是新药深入研发过程中非常重要的因素。此外,ICH 其他指导文献,例如 ICH S6 和 ICH S9,也是给新药深入研发带来冲击力很大的指导文献。因此,深入理解所有这些文献的本质意义对从事新药安全评价人员来说是很重要的,增强综合使用各方面总体知识的能力将促进新药深入研发更快、更好地实施。

关键词: 非临床药物安全性; ICH 指南; 毒理学; 新药研发; 小分子药物; 生物药物

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