zing agents, and alcohols), environmental chemicals (*eg*, lead, methylmercury, and pesticides), pharmaceuticals (*eg*, steroids and anticholinergics), and even herbal medicines (*eg*, canthaxanthine and ginkgo biloba), and is therefore a very important area for toxicologists. As a result of diligent screening, most chemicals that can cause severe acute ocular effects have either been eliminated from industrial and commercial usage or are tightly controlled for proper use. However, subtler ocular effects that are not easily detectable in acute ocular screening assays can lead to eventual significant vision deficits. Fortunately, the eye is a uniquely transparent organ that allows for easy access and modern technological advances now enable us to evaluate ocular structure and function in both the anterior and posterior chambers of the eye through non-invasive means. For the anterior chamber, common assessments now include slit-lamp biomicroscopy, pachymetry, tonometry, and specular microscopy. For the posterior chamber, available techniques include indirect ophthalmoscopy, electroretinograhy, and spectral domain optical coherence tomography. These endpoints of interest and agents which can alter the endpoint will be discussed along with the strengths and limitations of these tools as illustrated by specific examples.

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T3.8 临床前药物安全性评价试验的设计及数据分析

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摘要: 在临床前药物安全性评价试验中实施药品非临床研究质量管理规范(GLP)保证了试验数据的真实性、完整性和可靠性。试验结论的科学性则取决于试验设计和对数据分析评价的质量。药物临床前安全性评价试验的设计主要体现在动物种属选择,剂量水平设置,给药周期(包括恢复期)拟定,观察指标选取(包括征状观察、体重、摄食量、临床病理、心电图、体温等),毒代研究,终末解剖等方面。在试验设计时需要尽可能多的掌握受试物已有的试验或文献资料,明确其药学、药效、药代,尤其是受试物的血浆稳定性,体外代谢特征,即 eADME 信息,及安全性特点;获取相同或相似品种的临床前安全性试验资料,分析这些药物的试验设计,获取它们的安全性信息。另外,需要根据受试物的特点确定是否需要一些特殊的指标,比如免疫调节药物需要增加较多的免疫功能评价指标。对于创新药或者缺少相同或相似品种临床前安全性试验资料的受试物可以开展相应的预试验帮助试验设计。伴随着试验数据的不断生成,我们需要对这些数据进行阅读和评价,在所有试验数据出来之后,还需要对这些数据进行整合和综合评价。在分析试验数据时,我们应该尝试在委托方、试验单位及药物监管机构三个角度审视我们的数据和结果。我们需要结合受试物的药效学信息,明确毒性反应和药理作用的关系,是否是药理作用的放大。另外,我们需要结合受试物的类别,评价已经出现的毒性反应是否合理,比如喹诺酮类抗生素常常出现神经系统、胃肠道、心脏、关节软骨及光毒性。最后,我们需要整合所有试验数据判定所出现的异常是否与受试物相关。

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T3.9 非临床安全性评价在新药早期研发中的作用

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摘要: 近年来,为了降低药物开发的失败率,尽早终结毒性化合物,非临床药物安评部门在药物开发的一开始,即靶点选择阶段,就已介入新药的研发。非临床药物安评部门的专家们通过文献阅读,根据已有的转基因动物或阳性对照物的研究结果找出靶点调节后可能产生的安全隐患并为研究部门就靶点的选择提出建议。靶点选择之后,非临床药物安评部门将继续在今后的安评实验中继续关注哪些可能存在的安全隐患。在化合物优化阶段,非临床药物安评部门将开展一些列的体外药理活性分析实验(其中包括受体结合,离子

通道,酶活性和药物载体等实验),早期心血管安评实验,基因毒理和普通毒理(耐受性)实验以便进一步研究候选化合物的安全性并为下一步的长期毒理实验设计和剂量选择提供依据。据悉,75%的药物副作用是剂量依赖性的,可以通过药理活性分析来预测。化合物的药理活性可以分为主要活性和次级活性。主要活性是化合物作用其意向靶标产生的,次级活性是由化合物与其意向靶标以外的靶标相互作用(即靶标外相互作用)而产生的。靶标外相互作用通常与药物的副作用有关。因此,及早鉴别并减少甚至消除候选药物的次级活性是减少药物副作用发生概率的关键。早期心血管安评实验,基因毒理和普通毒理(耐受性)实验是按照国际协调会议(ICH)指导原则,如 ICH S7A4, ICH S7B5 和 ICH M3(R2)6,进行的。ICH 指导原则唯一要求的体外药理活性分析实验是化合物对 hERG 通道的作用,hERG 通道的抑制将引发 QT 间隙延长并进一步导致致死性心律失常(尖端扭转型室性心动过速)。

T3.10 Nonclinical safety assessment in oncology drug development

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Abstact: Cancer is the third leading cause of death worldwide, with tremendous unmet medical needs. The important/unique factors that influence cancer drug development strategy include: life-threatening nature for malignant tumors, high death rate from cancer, limited effectiveness for existing therapies, and desire to provide new effective anticancer pharmaceuticals to patients more expeditiously. For these reasons, flexibility is needed in designing a program of nonclinical (preclinical) studies for anticancer pharmaceuticals. The development and adoption by the three ICH regulatory bodies of ICH S9 provided a harmonized global agreement on the design of an appropriate program of nonclinical studies for the development of anticancer pharmaceuticals. This guidance provided recommendations for nonclinical evaluations to support the development of anticancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options. This guideline aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals. The nonclinical safety assessment program for cancer therapy as recommended by ICH S9 is different from that nonclinical safety program for general medicine [as by ICH M3(R2)]. The key differences included the following: no need for non-rodent studies for initiation of clinical trials with cytotoxic drugs; limited duration of toxicity study covers continued treatment in Phase Ⅰ & Ⅱ; allowing clinical trial get to active dose as quickly as possible; no need for chronic studies (6/9 month), and 13-week toxicology studies to be conducted in late stage development to conserve resources and reduce animal use; abbreviated reproductive toxicity package (no need for fertility and peri- and postnatal studies); safety pharmacology assessments could be conducted within the general toxicology studies. The implementing of ICH S9 will enable fast first-in-patients study; protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals and other resources.

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T3.11 Bhas 42 细胞转化实验高通量检测方法的建立及对植物性雌激素的研究

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摘要: 目的研究建立以 H_2O_2 判定结果的 96 孔板细胞转化实验方法,并对植物性雌激素染料木黄酮和