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Review of embryo-fetal developmental toxicity studies performed for recent FDA-approved pharmaceuticals

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ABSTRACT

Details of embryo-fetal development (EFD) studies were compiled from published FDA approval documents for 43 small molecule drugs (2014–2015) and 37 monoclonal antibodies (mAbs, 2002–2015). Anti-cancer agents were analyzed separately. Rats and rabbits were the species used for EFD studies on 93% of small molecule drugs. Overall, the rat and rabbit were equally sensitive to maternal and fetal toxicity (including teratogenicity). Dosages equivalent to more than 50-times the human exposure (or 10-times for mAbs) were frequently used, but were unnecessary for 90% of drugs. EFD studies were not required for several recently approved mAbs owing to pre-existing scientific knowledge. The cynomolgus monkey was used for developmental toxicity testing of 75% of mAbs, frequently using an ePPND study design. Studies in pregnant rodents using homologous murine antibodies supplemented or replaced monkey studies under some circumstances. Most anti-cancer small molecules and mAbs were tested for developmental toxicity in at least one species.

1. Introduction

The purpose of this review is to compile information on the regulatory studies performed to detect possible hazards during pregnancy for both small molecule drugs and therapeutic monoclonal antibodies (mAbs) that recently obtained marketing approval in the USA. It is expected that this information will be useful to assess the impact of any proposed changes to the ICH S5(R2) guideline.

In this review, the term "fetal toxicity" is used to cover any manifestation of fetal harm whether induced during the fetal or embryonic periods, in accordance with the preferred term in the FDA drug label.

Before marketing authorization, new medicinal products must be assessed for developmental and reproductive toxicity (DART). In the majority of cases, this evaluation involves safety assessment studies in animals. Non-clinical studies are performed to identify potential hazards of the drug relating to male or female fertility, maternal or fetal health during pregnancy and neonatal health following maternal use during breastfeeding. The non-clinical data generated in the DART studies serve a crucial role in human safety assessment since reproductive and developmental toxicity cannot be assessed during clinical trials in humans. Human data may become available much later from case reports and registries.

Since 1993, the non-clinical DART studies are performed in accordance with the harmonized tripartite guideline on detection of toxicity to reproduction for medicinal products and toxicity to male fertility S5(R2) [1], issued by the International Conference on Harmonization (ICH, recently renamed International Council on Harmonization). This guideline is currently undergoing its first major revision [2]. The study designs described in the current ICH S5(R2) guideline were based on those initially devised by the FDA in 1966 [3] and subsequent variations in other regions.

Besides ICH S5(R2), other more recent ICH guidelines also give recommendations on the design and timing of DART studies; these include S6(R1) for biopharmaceuticals [4], S9 for anticancer drugs [5] and M3(R2) on nonclinical safety studies for the conduct of human clinical trials and marketing authorization [6]. The revised S5 guideline should address the integration of the various requirements and resolve inconsistencies. This review provides information mainly relevant to the choice of species for developmental toxicity testing, the value of EFD studies in two species for cancer and non-cancer drugs and the selection of dose levels for EFD studies. Other objectives of the S5 guideline revision, such as reducing animal use and the qualification of alternative tests, are discussed in an accompanying paper in this issue [7].

Because of the potential catastrophic consequences of an undetected teratogenic drug reaching the market, embryo-fetal development (EFD) studies are performed in two species whenever

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pertinent, a rodent and a non-rodent [8]. The preferred species are the rat [9] and rabbit [10], but the mouse [11] or minipig [12] may also be used. For biopharmaceuticals or other drugs that do not exert their pharmacological action in lower species, a non-human primate (NHP), usually the cynomolgus monkey, may be used as the only species [13]. NHPs are only used as a last resort, however, owing to the limited power of the studies arising from the low numbers of offspring available for examination. ICH S6(R2) states that developmental toxicity studies should only be conducted in NHPs when they are the only relevant species [14].

The design of the EFD study involves treating pregnant animals with the drug at least throughout the period of organogenesis, i.e. from the time of implantation on the uterus through to closure of the hard palate in the embryo. A cesarean section (laparotomy) is performed at the end of gestation so that litter parameters can be assessed and fetuses sampled for morphological examinations. The EFD studies are most often performed as stand-alone investigations, but ICH S5(R2) also presents various options for combining the EFD, fertility and/or pre- and post-natal development investigations into a single study [15]. ICH S6(R1) specifies an enhanced pre- and post-natal development (ePPND) study design in the NHP which may be used to evaluate all aspects of developmental toxicity for biopharmaceuticals. In the ePPND study, the pregnant monkeys are allowed to give birth and raise their infants for at least one month (usually 4–6 months); the neonates are given a morphological examination at birth [16]. Some of the mAbs included in this review were tested using an EFD study design before the advent of the ePPND study [17].

Regarding dose selection, ICH S5(R2) states that some minimal toxicity is expected to be induced in the high dose dams. In the absence of maternal toxicity or marked fetal lethality in preliminary studies, 1000 mg/kg/day is suggested as a limit dose. Current practice for other types of non-clinical safety study, however, is to avoid doses that result in unrepresentative high exposures with respect to the maximum recommended human dose (MRHD). In accordance with ICH M3(R1), the high dose level in general toxicology studies is generally limited to the dose that results in 50-times the human exposure at the MHRD (see below for discussions on the appropriate metric of exposure). This argument is not always accepted by regulators for DART studies, sometimes leading to much higher doses in the EFD studies than in the general toxicity studies. The opinion of most reproductive toxicologists is that the low dose level in EFD studies should result in a clinically relevant exposure and that high margins (e.g. more than five) between the dose levels should be avoided. Dose levels resulting in large multiples over the human exposure are not useful for risk assessment. Following this reasoning, a high dose level in excess of 25-times the human exposure are not particularly helpful for risk assessment in human pregnancy. Alternatively, a limit dose of 50-times the human exposure could be considered in accordance with ICH M3(R2).

There have been many case reports on the use of therapeutic mAbs in pregnant women e.g. [18,19], including for the treatment of cancer [20], even though most therapeutic mAbs carry label warnings against their use during pregnancy. For example, therapeutic mAbs for the treatment of arthritis are discouraged during pregnancy, even though the most effective small molecule therapies for the treatment of early stage or active arthritis, i.e. methotrexate and leflunomide, are labelled as teratogenic [21]. Under some circumstances, biologic anti-cancer agents may be a safer option during early pregnancy than small molecule drugs, owing to low placental transfer of immunoglobulins during the first trimester. The relative risk of mAbs to the fetus may then increase as pregnancy progresses and active transport of IgGs across the placenta becomes more effective up to the time of birth [19]. Antibodies which lack a Fc moiety, such as certolizumab for the treatment of arthritis, however, are not actively transported across the placenta and are thus less likely to have adverse effects on the fetus.

Some of the first approved therapeutic mAbs, such as certolizumab, that do not exert their intended pharmacological action in rodents or rabbits due to a lack of interaction with the orthologous target, avoided the use of NHPs by testing a homologous (or surrogate) antibody in a rodent. This approach as an alternative to studies in the NHP was discouraged, however, in the subsequent revision of ICH S6, the following is stated: “Studies with homologous proteins can be used for hazard detection and understanding the potential for adverse effects due to exaggerated pharmacology, but are generally not useful for quantitative risk assessment”.

2. Methods

The submission dossier of each drug on the FDA website (www.accessdata.fda.gov) was reviewed for details of the DART studies. The lists of drugs by year of approval were compiled from the Biopharma website (www.biopharma.com). Further details of study designs were found on the websites of the Japanese Pharmaceuticals and Medical Devices Agency (www.pmda.go.jp) and the European Medicines Agency (www.ema.europa.eu). Details of regulatory exchanges were found on the Pharmapendium website (www.pharmapendium.com).

Only limited details could be obtained on the DART study designs and experimental results for some drugs. Thus, not all drugs are included in each of the presented categories. When the margin of exposure with respect to the human is not published for all dose groups, the missing values have been calculated from the dose levels assuming linear kinetics.

2.1. Scope

All therapeutic categories of small molecule drugs were reviewed. The review of biopharmaceuticals was limited to monoclonal antibodies (mAbs), which comprise the vast majority of biopharmaceuticals licensed to date. The ICH S5(R2) guideline does not include recommendations for vaccines, which are thus not included in this review. DART studies are now required for preventative vaccines, following issue of a FDA guidance on considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications in 2006 [22]. The revised ICH S5 guideline is expected to incorporate requirements for vaccines.

All new chemical entities approved by the FDA in 2014 and 2015 were reviewed. New drug approvals for combination drugs were excluded from the analysis. For mAbs, the review period was extended to all approvals since 2002 (i.e. since the issue of the ICH M3(R2) guideline) in order to have a representative sample size.

Because malignant tumors are life-threatening, the non-clinical DART requirements are less stringent for anti-cancer agents than for other pharmaceutical classes. The ICH S9 guideline states that EFD studies are useful to evaluate the potential risk for patients who are or might become pregnant. EFD studies are theoretically not required for pharmaceuticals that are genotoxic and target rapidly dividing cells or belong to a class that has been well-characterized as causing developmental toxicity. While EFD studies are part of the marketing application, they are not considered essential to support clinical trials intended for the treatment of patients with advanced cancer. In cases where an EFD study is positive for fetal lethality or teratogenicity, a confirmatory study in a second species is usually not warranted. In view of these differing regulatory requirements, small molecule drugs and mAbs intended for the treatment of cancer are considered separately in this review from drugs for other indications.