Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Industry[1]

Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide you, sponsors, with recommendations for the conduct of developmental toxicity[2] studies for investigational preventive and therapeutic vaccines for infectious disease indications. The recommendations set forth in this document pertain to the assessment of the developmental toxicity potential of preventive and therapeutic vaccines for infectious diseases indicated for females of childbearing potential and pregnant individuals.[3] This guidance applies prospectively to investigational vaccines, i.e., vaccines under investigational new drug applications (IND) and vaccines the subject of a new biologics license application (BLA). These recommendations do not apply retrospectively to already licensed vaccines except those the subject of additional INDs. This guidance document finalizes the draft guidance entitled "Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications" dated August 2000 (65 FR 54534; September 8, 2000).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or

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[1] The Maternal Immunization Working Group in the Center for Biologics Evaluation and Research at the Food and Drug Administration prepared this guidance. The document was revised based on public comments submitted to the Division of Dockets Management on the draft guidance dated August 2000, and on recommendations made by an expert panel convened at a Workshop entitled "Non-clinical Safety Evaluation of Preventive Vaccines: Recent Advances and Regulatory Considerations" held December 2 & 3, 2002, Arlington, VA, discussing approaches for developmental toxicity assessments for vaccines.

[2] Developmental toxicity is any adverse effect induced prior to attainment of adult life. This includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally (Ref. 1).

[3] This document does not address concerns regarding male reproductive toxicity and male and female fertility studies.

recommended, but not required.

II. BACKGROUND

The Center for Biologics Evaluation and Research (CBER) reviews a broad spectrum of applications for investigational vaccines intended for the prevention and treatment of infectious diseases and indicated for immunization of adolescents and adults. Thus, the target population for vaccines often includes females of childbearing potential who may become pregnant during the vaccination period. A number of vaccines are in clinical development specifically for maternal immunization indications with the goal of preventing infectious disease in the pregnant mother and/or neonate through passive antibody transfer from mother to fetus. Unless the vaccine is specifically indicated for maternal immunization, no studies are conducted prior to product licensure to determine the vaccine's safety in pregnant women. During clinical development of most vaccines not specifically intended for use during pregnancy, pregnant women are ineligible to participate in clinical trials. If pregnancy occurs during a study, treatment is usually discontinued and the woman does not receive additional immunizations. Consequently, there are few clinical data to address developmental toxicity of the vaccine in pregnant women or females of childbearing potential at the time of product licensure.

As more women of childbearing potential participate in clinical trials and as more preventive and therapeutic vaccines are developed for adolescents and adults, there is increasing concern about the unintentional exposure of an embryo/fetus before information is available about the risk versus benefit of the vaccine. Also, following approval, vaccines not indicated for use during pregnancy may be recommended by health policy makers for use in pregnant women (Ref. 2). In addition, use of licensed vaccines in females of childbearing potential will likely result in inadvertent exposure of the pregnant woman and her fetus to the vaccine. Considering that more than half of pregnancies in the U.S. are unintended, it is unlikely that vaccine exposure would be avoided in these pregnancies prior to their clinical recognition (Ref. 3). In these situations, in the absence of clinical data, it is difficult for the practitioner to make an informed risk assessment, even in situations where immunization of pregnant women may be appropriate.

Until recently, few licensed vaccines have been tested for developmental toxicity in animals prior to their use in humans. However, for the reasons listed above, we, FDA, recommend that you address during the IND studies the risks versus the benefits of immunization programs for pregnant women and/or females of childbearing potential by performing developmental toxicity studies in animal models. Potential risks involved in prenatal immunization programs include developmental adverse effects caused by the inherent biological activity of the vaccine antigen and constituents of the vaccine product (e.g., adjuvants, preservatives, and stabilizers). In addition, potential adverse effects on the pregnancy status and or the developing embryo/fetus may be the result of maternal immune modulation (Refs. 4 and 5).

Because pregnant women are usually excluded from clinical trials, data from developmental toxicity studies in animal models offer one approach to screen for potential developmental hazards. Studies in animal models may frequently present the only information available to draw conclusions regarding developmental risk to be included in the product labeling required under

section 201.57(f)(6) in Title 21 Code of Federal Regulations (§ 201.57(f)(6)). As there is virtually no scientific literature on animal developmental toxicity testing for vaccine products, this guidance will outline general and specific recommendations that should be taken into account in the assessment of developmental toxicity for preventive and therapeutic vaccines for infectious disease indications.

III. VACCINE TARGET POPULATION AND TIMING OF PRE-CLINICAL DEVELOPMENTAL TOXICITY STUDIES

For the purpose of this document, vaccines are a heterogeneous class of preventive, in some cases therapeutic, medicinal products, the administration of which is intended to elicit an immune response(s) that can prevent and/or lessen the severity of one or more infectious diseases. A vaccine may be a live attenuated preparation of bacteria, viruses, or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombinant deoxyribonucleic acid (DNA) in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above. Antigens may be presented plain or delivered in combination with other antigens, adjuvants, additives and other excipients. Therapeutic vaccines for non-infectious diseases and monoclonal antibodies used as immunogens are not considered in this guidance (Ref. 6).

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, for vaccines indicated for adolescents and adults and for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women, we recommend that you consider developmental toxicity studies.

There are currently differences in the timing of these developmental toxicity studies, as follows, to support inclusion of either pregnant individuals or females of childbearing potential in clinical trials.

Maternal immunization: For products indicated specifically for immunization of pregnant women, we recommend that you have the data from non-clinical developmental toxicity studies available prior to the initiation of any clinical trial enrolling pregnant women.

Females of childbearing potential: For vaccines indicated for females of childbearing potential, you may include subjects in clinical trials without non-clinical developmental toxicity studies, provided that appropriate precautions are taken by subjects enrolled in these trials to avoid vaccination during pregnancy, such as pregnancy testing and use of birth control. For these products, we recommend that you include data from developmental toxicity studies with the initial BLA submission (§ 601.2), regardless of whether such studies have been submitted earlier to the IND.

Males: Currently, males may be included in Phase I, II, and III clinical trials in the absence of nonclinical male fertility studies, although such studies may be recommended for certain

products in the future.

IV. DESIGN OF DEVELOPMENTAL TOXICITY STUDIES

A. General Considerations and Recommendations

The decision whether a developmental toxicity study needs to be performed should be made on a case-by-case basis taking into consideration historical use, product features, intended target population and intended clinical use. We recommend the developmental toxicity study be designed to detect potential developmental adverse effects induced by components present in the vaccine formulation. However, despite efforts to maximize the predictive value of developmental toxicity studies, there may always be limitations in evaluating or screening for potential risks and thus, limitations in reducing the uncertainties of risk. Also, lack of adverse effects on embryo/fetal development in an animal study does not necessarily imply absence of risk for humans. Factors that may limit risk prediction include, but are not limited to, species-specific differences in the immune response, different developmental time lines, and differences in placentation. Nevertheless, developmental toxicity studies in animal models are the best currently available non-clinical tools to screen for adverse developmental effects of the product in humans. Information about developmental risk from animal data is frequently the only information available at the time of product licensure. The good laboratory practice regulations in 21 CFR Part 58 apply to nonclinical laboratory studies that support or are intended to support applications.

1. Previous clinical experience

All available clinical experience in pregnant women should be considered in any potential application with respect to the design of developmental toxicity studies in animals. Clinical experience derived from immunization of pregnant women may be helpful in the evaluation of the potential for any adverse outcome on the viability and development of offspring. Such information may also aid in the design/monitoring of appropriate non-clinical studies, and for product labeling. However, clinical data that may have been obtained from small numbers of pregnant women enrolled in non-IND studies, e.g., immunized with the vaccine or a related product, will generally not replace the need for animal developmental toxicity studies.

2. Previous non-clinical experience

We recommend that you review all data generated from prior acute or repeat dose non-clinical toxicity studies for their possible contribution to the interpretation of any adverse developmental effects that appear in the developmental toxicology studies. In addition, data from prior non-clinical studies do frequently form the basis for the choice of the animal model and vaccine dose used in the developmental toxicity study.

3. Vaccine formulation

We recommend that you perform the non-clinical developmental toxicity study on the same lot as proposed for the clinical trial. If this is not feasible, we recommend that non-clinical lots be comparable to clinical lots with respect to physico-chemical data, stability, and formulation and be manufactured in accordance with applicable cGMPstandards.
In addition, even though pivotal clinical studies are frequently conducted with an intended final formulation, optimizations of formulations are frequently made prior to product marketing. In these cases, we will assess, on a case-by-case basis, the applicability of non-clinical studies conducted with earlier clinical formulations of the vaccine to the commercial formulation of the vaccine. For a product specifically intended for maternal immunization, we recommend that you perform non-clinical developmental toxicity studies in advance of clinical studies that enroll pregnant women. In these cases, to avoid performing multiple developmental toxicology studies during development, you may find it advantageous to conduct Phase I and Phase II studies in non-pregnant subjects. Results from these studies can be used as the basis for advancing the most promising product formulation(s) to studies that enroll pregnant women.

4. Vaccine product class

There are a number of vaccines in clinical development that may be similar to or of the same product class as either investigational or already licensed products, for which developmental toxicity studies may have been performed. In these cases, we will examine the need for additional development toxicity studies for the product under investigation on a case-by case basis. Regarding combination vaccines in clinical development, for which the individual components are licensed and on which developmental toxicity assessments have been performed, we may not recommend further developmental toxicity assessments. However, if the combination vaccine is formulated with new adjuvant, new preservative or if significant changes to the individual products or their manufacture were made and/or concerns exist that combining the individual licensed products may increase their toxic potential, we recommend additional developmental toxicity studies. Similarly, if no developmental toxicity studies have been conducted for the individual licensed or unlicensed components, we recommend that you conduct developmental toxicity studies. In some instances, documentation on clinical and epidemiological data, e.g., exposure to the infectious agent or use of related, licensed vaccines during pregnancy, may be sufficient to evaluate the risk of the investigational product and may be provided by you and considered by FDA in determining the need for developmental toxicity studies in animal models. In these cases, we recommend that you contact FDA to reach agreement regarding the need for additional developmental toxicity studies for that particular product.

5. Application of ICH guidance document S5A

The ICH S5A guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products," addresses the design of animal studies primarily for detection of toxicity on reproduction, dividing the reproductive cycle into different segments, defined as stages A – F (see Ref. 1). The ICH S5A guidance suggests that different studies can be conducted to address the various segments of the reproduction cycle. For preventive and therapeutic vaccines for infectious diseases, the primary concern is potential untoward effects of the test article on development and growth of the embryo and fetus. Thus, the primary focus is on developmental toxicity studies to detect adverse effects on the pregnant/lactating female and development of the embryo/fetus and the offspring following exposure of the female to the vaccine from implantation through the end of pregnancy, with follow-up of the offspring through weaning. These stages are defined as stages C, D, and E in the ICH S5A document. Depending on the product and on a case-by-case basis, we might require additional studies to address additional segments of the reproductive cycle.

We recommend use of the ICH S5A guidance as a general point of reference to assist you in the general design of developmental toxicity studies and evaluation of endpoints. However, we want to emphasize distinguishable factors relevant to vaccines. The most important feature distinguishing vaccines from other pharmaceutical products is the intended vaccine-induced immune response. Also, vaccines are usually administered in limited, episodic dosages with months or even years between doses. Vaccines include a broad range of product categories such as live attenuated, inactivated, recombinant, polynucleotide, polysaccharide, protein antigens, vectored vaccines, and conjugate vaccines. These may be adjuvanted or consist of a combination of different vaccine antigens. Thus, given the complexity of these issues, the non-clinical testing strategies outlined in the ICH S5A document may not be directly applicable to vaccines, and study designs outlined in the ICH S5A document may need to be tailored to the vaccine product under consideration. Outlined below are specific considerations that we recommend you take into account when designing developmental toxicity studies for vaccines. We also recommend that prior to the conduct of the study, you establish an early dialogue with CBER to reach agreement on a specific protocol including study endpoints.

B. Specific Considerations

1. Animal model

We recommend that you provide in your IND submission a justification for the choice of the animal model to be used in the developmental toxicity study. This should include a demonstration that the species is able to develop an immune response to the vaccine antigen, even though there may be quantitative and qualitative differences in immune responses between species. The laboratory

species most often used for developmental toxicity studies, on the basis of availability of background data and historical experience, are rats, rabbits and mice. Most human vaccines are immunogenic in rodents or rabbits. In some cases, only non-human primates may show an adequate immune response. However, because of the technical and logistic difficulties involved in using non-human primates for developmental toxicity studies, we recommend you only consider these animals if no alternative models are available.

In addition to demonstrating an immune response in the pregnant female, we recommend that you verify the exposure of the fetus to maternal antibodies. Thus, since there are differences between primates, non-rodents, and rodent animal species in terms of timing of maternal antibody transfer to the offspring, we recommend that you evaluate the pre- and postnatal exposure of the offspring to maternal antibody as a criterion for selecting the most appropriate experimental model. In addition, the species selected should be amenable to fetal and postnatal examinations.

In cases where lack of an appropriate animal model hinders the assessment of an immune response, developmental toxicity studies may still provide important information regarding potential embryo/fetal toxic effects of the vaccine components/formulation and safety of the product in the pregnant animal. In most cases, it is sufficient to conduct developmental toxicity studies using only one species; thus, there is no requirement for the routine use of two species, i.e., one rodent and one non-rodent.

The number of animals per group should be sufficient to allow meaningful interpretation of the data. For example, for a developmental toxicity study using rats or rabbits, we recommend that you assign an adequate number of animals to each group to allow an evaluation of at least 40 animals per group. These animals can be further allocated to the Caesarean and littering subgroup using 20 animals each.

2. Pharmacodynamics

We recommend that you obtain information about the onset and duration of the antibody response in pilot studies because these data may help in selecting the proper species, study design, and dosing schedules. Initial information can be derived from non-pregnant animals. However, it may also be necessary to perform these pilot studies in a small group of pregnant animals to evaluate antibody formation in relation to test article exposure and placental antibody transfer to the fetus if there is evidence that antibody formation may differ in pregnant versus non-pregnant animals.

We recognize that antibody induction presents only one aspect of the overall immune response induced by the vaccine and that other immunological parameters, such as cytokines and induction of cytotoxic T cells, may be as

important. However, given the relative lack of validated assays to assess the induction of these other parameters, antibody assessments are currently used as a marker for vaccine induced effects in these studies. This does not exclude the evaluation of additional immunologic parameters on a case-by-case basis. For example, if data are available which indicate that a vaccine antigen induces a particular cytokine response, respective cytokine measurements may be included, especially if the cytokine is one that may affect pregnancy.

3. Experimental procedure

In order to detect adverse effects on the pregnant/lactating female animal and development and growth of the embryo/fetus and the offspring, we recommend that the female be exposed to the vaccine during the interval from implantation through closure of the hard palate and also at later stages of pregnancy. The offspring should be followed to weaning and observed for normal growth and development. We recommend that you submit one subgroup of pregnant females to Caesarean examination at the end of pregnancy for routine uterine and fetal examinations, and allow another subgroup to litter and rear their offspring to weaning in order to monitor the post-natal development of the offspring up to weaning.

4. Dosage

We recommend that you assess a single dose level that is capable of inducing an immune response in the animal model. Where possible, we recommend that you administer animals the maximum human dose (e.g., 1 human dose = 1 rabbit dose) regardless of body weight. If it is not feasible to administer the maximum human dose (e.g., limitation in total volume that can be administered; dosing induced local toxicity affecting pregnancy), we recommend that you administer a dose that exceeds the human dose on a mg/kg bases while still capable of inducing an immune response in the animal.

5. Frequency and route of administration

We recommend that the vaccination regimen optimize maternal antibody titers throughout the embryonic, fetal, and early post-natal periods. Timing and number of doses will depend on the onset and duration of the immune response of the particular product. Because of concerns that a daily dosing regimen may lead to overexposure to the vaccine antigen that could potentially result in immune tolerance, we recommend episodic dosing of pregnant animals rather than daily dosing. In addition, episodic dosing appears to be more relevant, as it better mimics the clinically proposed immunization schedule for most preventive and therapeutic vaccines for infectious disease indications. Considering the short gestational period of animal species most frequently used, it may be necessary to administer priming doses to the animals several days or weeks prior to mating in

order to elicit a peak antibody production during the critical phases of pregnancy, i.e., the period of organogenesis.

When dosing prior to implantation, stress reactions may be observed in the animal that may affect the pregnancy status. Therefore, with treatment of animals prior to mating/insemination, it may be necessary to add more animals to the study to ensure that sufficient animals become pregnant for evaluation.

We recommend that you administer one or several additional doses during organogenesis (i.e., implantation to closure of the hard palate) to evaluate potential direct embryotoxic effects of the components of the vaccine formulation and to maintain a high level of antibody throughout the remainder of gestation. In certain cases, subgroups of animals that are dosed at certain time points may be included to evaluate if the vaccine acts as a selective toxicant, bearing in mind that it may be difficult to adjust vaccine administration with gestational timelines. We recommend that the route of administration mimic the clinical intended route of administration.

6. Control groups

We recommend that you dose control animals with placebo at the same time and frequency as test group animals. Since the potential toxicity of each of the components presented in the vaccine formulation will need to be evaluated, we recommend that you consider additional groups if components other than the vaccine antigen contained in the vaccine formulation (e.g. excipients, preservatives) cause effects or affect the activity of the test substance. In addition, if the vaccine is formulated with adjuvant, we recommend that you consider the inclusion of an adjuvant-only control arm, particularly if the adjuvant is novel.

7. Endpoints

In general, the study endpoints should include those recommended for studies for effects on prenatal and postnatal development including maternal functions as stated in the ICH S5A document (see Ref. 1). When deciding on the endpoints to be evaluated, we recommend that you take into consideration the nature of the vaccine and particular concerns associated with that product. The following parameters listed are intended to provide a basic panel of endpoints to be evaluated that are not meant to be all-inclusive.

a. Premating/preinsemination period

Clinical observations including data on general appearance and body weights should be obtained weekly and on days of test article administration.

b. Gestational period

We recommend that you observe maternal animals during the study for signs of morbidity and mortality, and record clinical observations regarding general appearance and behavior. We recommend that the evaluations include body weight and body weight change, potential signs of local toxicity, food consumption, duration of pregnancy, abortions, premature deliveries, and parturition (for maternal animals not subjected to Caesarian sectioning).

c. Caesarean sectioning group

i. Maternal Observations

At terminal examination of groups subjected to Caesarean sectioning, we recommend that you conduct a necropsy (macroscopic examination) and preserve maternal tissue with macroscopic findings for histological evaluations as deemed necessary by the gross findings. For example, histological evaluations may be indicated if you observe effects on organ to body weight ratios. We recommend that you record the number and distribution of corpora lutea, implantation sites, viable and nonviable fetuses, and early and late resorptions and that you perform a gross evaluation of the placenta.

ii. Fetal examinations

We recommend that you obtain individual body weights of live fetuses and examine each viable fetus for gross external, visceral, and skeletal alterations. Late resorptions and dead fetuses should also be examined for gross external alterations to the extent possible. All fetuses should be examined internally to determine sex.

d. Natural delivery group

i. Maternal observations

In addition to the parameters outlined in section IV.B.7.b (Gestational period), we recommend that you determine the duration of gestation and parameters such as the fertility index, gestation index, and live birth index. Animals that deliver a litter should be sacrificed at the end of the pre-weaning period. We recommend that you perform a gross necropsy of the thoracic, abdominal and pelvic viscera, and record the number and distribution of implantation sites as well as any observed abnormalities. Animals that die or are sacrificed because of moribund condition, abortion or premature delivery should be examined for the cause of death and pregnancy status recorded. We recommend that you also examine aborted fetuses and/or delivered pups to the extent possible.

ii. F1 generation

We recommend postnatal follow-up from birth to weaning to assess normal growth, body weight gain, and nursing activity as indicators for normal development. We also recommend that you include into the study design tests to screen for normal neuro-development, for example, auditory and visual function tests. Viability and lactation indices should be determined and individual sexes should be recorded. At terminal sacrifice, we recommend that you perform a necropsy, record any abnormalities and retain gross lesions for possible histological examinations. We recommend that you evaluate pups that die before examination for vital status at birth and examine pups found dead for gross lesions and cause of death.

8. Immunological endpoints

In addition to evaluating potential developmental adverse effects and adverse effects on the pregnant animal, we recommend that you include an assessment of the vaccine induced antibody response to verify exposure of the embryo/fetus to maternal antibody. Serum specimen from maternal animals prior to and at additional time points following dosing should be collected to assess the development of antibodies. Sampling is usually conducted prior to test article administration and at day of Caesarean sectioning (where applicable) and at the end of the weaning period.

In addition, we recommend that you obtain cord blood samples to assess placental transfer of maternal antibodies from animals in the Caesarean subgroup. We recommend that you also assess antibody levels from a representative number of pups/litters at the end of the weaning period to verify exposure of the neonates to maternal antibody induced. Antibody evaluations in developmental toxicity studies serve the purpose of verifying an effect of the vaccine in the test species as opposed to evaluating potential immunotoxic effects. You may evaluate additional immune parameters on a case-by-case basis. For example, if evidence exists that the vaccine antigen or other vaccine components can trigger the release of a particular cytokine potentially affecting pregnancy, you may include respective assessments.

9. Additional assessments

In cases where non-clinical developmental toxicity studies reveal vaccine-induced adverse effects on either the pregnant/lactating animal, embryo/fetal development, or development of the offspring, we recommend you conduct further animal studies to evaluate the cause of the effect. Such studies may include broader immunological evaluations, e.g., histochemical analysis for antibody depositions, as well as neurological assessments.

V. REFERENCES

1. International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Industry (ICH-S5A) Detection of Toxicity to Reproduction for Medicinal Products, (59 FR 48746, September 22, 1994), http://www.fda.gov/cder/guidance/s5a.pdf.

2. Recommended adult immunization schedule-United States, 2002-2003, MMWR October 11, 2002, Vol. 51 (40); 904-908.

3. Colley, Gilbert B., Brantley, M.D., Larson, M.K., *Family Planning Practices and Pregnancy Intention, 1997.* Atlanta, GA: Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2000, http://www.cdc.gov/reproductivehealth/prams/pdf/97/PRAMS_sr_97.pdf.

4. Barrow, P.C., *Reproductive toxicology studies and immunotherapeutics*. Toxicology 185 (2003), 205-212.

5. Thellin, O., Heinen, E., *Pregnancy and the immune system: between tolerance and rejection*. Toxicology 185 (2003), 179-184.

6. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (January 1999), http://www.fda.gov/cber/gdlns/cmcvacc.pdf.

厚生労働省「ワクチンや抗がん剤など特殊な成分の医薬品における
非臨床安全性試験の実施手法等に関する研究」班
平成１８年度　第１回合同班会議

ワクチンの非臨床安全性試験の実施手法等に関する研究班
抗がん剤の非臨床安全性試験の実施手法に関する研究班

合同班会議議事次第

○日時　平成１８年６月１３日　１４：００～１７：００

○ 場所　医薬品医療機器総合機構　会議室１

○ 議事

１．開会の挨拶（主任研究者：井上）
２．ワクチン研究班討議趣旨説明（分担研究者：佐藤）
３．抗がん剤研究班討議趣旨説明（分担研究者：小野寺）
４．各班毎の討議
　４－１．ガイドライン案について
　４－２．今後の検討課題について
　４－３．その他
５．各班討議結果の説明と今後の予定
６．事務連絡　（事務担当：菊池）
７．閉会の挨拶（主任研究者：井上）

○ 配布資料

１．平成 17 年度総括研究報告書
２．ワクチンの非臨床安全性試験に関するガイドライン案（資料１）
３．「ワクチンの非臨床安全性試験に関するガイドライン案」
　に対するQ&A　（資料２）
４．抗悪性腫瘍剤の非臨床安全性試験に関するガイドライン案
　（資料抗悪１）

第１回ワクチンの非臨床安全性試験の実施手法等に関する研究班会議

議事次第

○日時　平成１８年６月１３日　１４：１５～１６：４０

○場所　医薬品医療機器総合機構　会議室１

○議事

１．ガイドライン案について
２．ガイドライン案に対するQ&A について
３．今後の検討課題について
４．その他

○配付資料

１．ワクチンの非臨床安全性試験に関するガイドライン案（資料１）
２．「ワクチンの非臨床安全性試験に関するガイドライン案」に対するQ&A（資料２）

平成18年度第1回ワクチンの非臨床安全性試験の実施手法等に関する研究班会議議事録

日時：2006年6月13日、午後2時～5時
場所：医薬品医療機器総合機構　会議室1
出席者：主任研究者；井上　達
　　ワクチン　分担研究者；三瀬勝利、皆葉清美、佐藤洋一
　　研究協力者；佐神文郎、松井元、山崎秀樹、藤巻由紀夫、真鍋貞夫
　　事務局；菊池

議論に入る前に、ワクチンガイドラインは、ICHのトピックとするには時期尚早であるとの理由から今回は見送られたとのICH横浜の報告があった。

前年度に引き続き、ガイドライン案の検討を行った。また、今回は、製薬協が実施したガイドライン案に対するQ&Aについても検討を行った。

ガイドライン案については、ほぼ完成しており、今回大きな修正はなかったことから、議論はQ&Aを中心に行ったが、特段大きな論点はなかった。製薬協としては、今回の議論を持ち帰り、ガイドライン案及びQ&Aを修正し、次回の班会議までに関係者に送付し、次回の班会議でガイドライン案及びQ&Aを確定することとなった。

厚生労働省「ワクチンや抗がん剤など特殊な成分の医薬品における
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合同班会議議事次第

○日時　平成１８年１１月７日　１４：００～１７：００

○ 場所　医薬品医療機器総合機構　会議室４

○ 議事

１．開会の挨拶（主任研究者：井上）
２．ワクチン研究班討議趣旨説明（分担研究者：佐藤）
３．抗がん剤研究班討議趣旨説明（分担研究者：小野寺）
４．各班毎の討議
　４－１．ガイドライン案について
　４－２．今後の検討課題について
　４－３．その他
５．各班討議結果の説明と今後の予定
６．事務連絡　（事務担当：菊池）
７．閉会の挨拶（主任研究者：井上）

○ 配布資料

１．班員名簿
２．ワクチンの非臨床安全性試験に関するガイドライン案　（資料１）
３．「ワクチンの非臨床安全性試験に関するガイドライン案」
　に対するQ&A　（資料２）
４．抗悪性腫瘍薬の非臨床における安全性評価に関するガイドライン(最終)
　（資料抗悪１）
５．抗悪性腫瘍薬の非臨床における安全性評価に関するガイドライン(翻訳)
　（資料抗悪２）
６．「抗悪性腫瘍薬の非臨床における安全性評価に関するガイドライン案」
　に対するQ&A　（資料抗悪３）

第２回ワクチンの非臨床安全性試験の実施手法等に関する研究班会議

議事次第

○日時　平成１８年１１月７日　１４：１５～１６：４０

○場所　医薬品医療機器総合機構　会議室４

○議事

１．ガイドライン案について
２．ガイドライン案に対するQ&A について
３．今後の検討課題について
４．その他

○配付資料

１．ワクチンの非臨床安全性試験に関するガイドライン案（資料１）
２．「ワクチンの非臨床安全性試験に関するガイドライン案」に対するQ&A（資料２）

平成18年度第2回ワクチン・抗がん剤の非臨床安全性試験の実施手法等に関する研究班会議議事録

日時：2006年11月7日、午後2時～5時

場所：医薬品医療機器総合機構　会議室4

出席者：主任研究者；井上　達

ワクチン　分担研究者；三瀬勝利、皆葉清美、佐藤洋一

研究協力者；佐神文郎、松井元、山崎秀樹、藤巻由紀夫、真鍋貞夫

抗がん剤　分担研究者；中江　大、小野寺　博志、笛木　修

研究協力者；浦野　勉、込山　則行、甲斐　修一、西村　千尋

事務局；菊池

議事内容

ガイドライン案及びQ&Aの最終確認を行った。特に大きな修正点はなかった。

次に報告書の作成について検討した。報告書は、本ガイドライン及びその英訳版、Q&A、最終化されたWHOガイドライン及びFDAガイドラインの原著及び翻訳版、EUガイドラインの原著及び翻訳版を取り纏めることとなった。報告書は1月中旬（15日目途）までに完成させ、報告書が作成された後、医薬品研究に投稿することとなった。

2）抗がん剤の非臨床安全性試験の実施手法等に関する研究　関係資料

【資料 11】抗悪性腫瘍薬の非臨床における安全性評価に関するガイドライン（最終）

【資料 12】Guideline on the Non-Clinical Safety Evaluation of Anticancer Drugs (Draft, 6th Edition)

【資料 13】抗悪性腫瘍薬の非臨床における安全性評価に関するガイドライン（案）に対するQ&A

【資料 14】班会議資料

1）第１回班会議

2）第２回班会議