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

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U.S. Department of Health and Human Services
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[1] [1] This guidance has been prepared by the Maternal Immunization Working Group in the Center for Biologics Evaluation and Research at the Food and Drug Administration. The availability of the draft guidance was announced in FR Vol. 65:54534, September 8, 2000. The document has been revised based on comments submitted to the Docket Management Branch and based 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. This guidance document represents the Agency's current thinking on the assessment of the developmental toxicity potential of preventive and therapeutic vaccines for infectious diseases. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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

Guidance for Industry[1]

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

Draft - Not for Implementation

I. INTRODUCTION

The document is intended to provide sponsors with guidance for the conduct of developmental toxicity studies for investigational preventive and therapeutic vaccines and to consider establishing clinical pregnancy registries for these products. 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[2]. This guidance will be applied prospectively to investigational vaccines. It does not apply retrospectively to already licensed vaccines except further conduct of additional IND studies. The Center for Biologics Evaluation and Research (CBER) reviews a broad spectrum of investigational vaccines for the prevention and treatment of infectious diseases indicated for immunization of adolescents and adults. Thus, the target population for vaccines often includes females in their reproductive years who may become pregnant during the time frame of vaccination. In addition, there are a number of vaccines in clinical development specifically intended for specific maternal immunization indications with the goal of preventing infectious disease in the vaccinee and/or young infant through passive antibody transfer from mother to fetus. Currently, unless the vaccine is specifically indicated for maternal immunization, no studies are conducted regarding the vaccine's safety in pregnant women prior to product licensure. During clinical development of most vaccines not intended for use during pregnancy, pregnant women are actively excluded from participation in clinical trials. In addition, if pregnancy

occurs during a study, treatment is usually discontinued and the woman does not receive additional immunizations. Consequently, there are seldom clinical data to address developmental risk of the vaccine in pregnant women or females of childbearing potential at the time of product licensure. However, as more women of child-bearing potential participate in clinical trials and as more preventive and therapeutic vaccines are being developed for adolescents and adults, there is increasing concern for the unintentional exposure of an embryo/fetus before information is available about the risk versus benefit of the vaccine. Moreover, following approval, vaccines not indicated for use during pregnancy may be recommended for use in pregnant women (1). 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 are unintended, it is unlikely that vaccine exposure would be avoided in these pregnancies prior to their clinical recognition (2). 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 or no licensed vaccines have been tested for developmental toxicity in animals prior to their use in humans. However, for reasons listed above, there is a need to assess the risks versus the benefits of immunization programs for pregnant women and/or females of childbearing potential that should be addressed during the pre-marketing phase of the product. 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, stabilizers). In addition, potential adverse effects on the pregnancy status and or the developing embryo/fetus may be the result of maternal immune modulation (3,4).

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 and may frequently present the only information available to draw conclusions regarding developmental risk to be included into the product label required under 21 CFR 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 considerations that should be taken into account in the assessment of developmental toxicity for preventive and therapeutic vaccines for infectious disease indications.

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II. DEFINITIONS

A. Vaccine

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 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 here (5).

B. Reproductive Toxicology

Reproductive Toxicology is "the study of the occurrence, causes, manifestations, and sequelae of adverse effects of exogenous agents on reproduction" (6).

C. Developmental Toxicity

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 (7).

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

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, developmental toxicity studies should be considered.

There are currently differences in the timing of these studies 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, data from nonclinical developmental toxicity studies should be available prior to the initiation of any clinical trial enrolling pregnant women.

Females of childbearing potential: For vaccines indicated for females of childbearing potential, subjects may be included in clinical trials without nonclinical developmental toxicity studies, provided appropriate precautions are taken, such as pregnancy testing and use of birth control. For these products, data from developmental toxicity studies should be included with the initial Biologics License Application submission, regardless of whether or not they have been submitted earlier to the Investigational New DrugApplication (IND).

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

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IV. DESIGN OF DEVELOPMENTAL TOXICITY STUDIES

A. General Considerations

Each vaccine will need to be evaluated on a case-by-case basis taking into consideration historical use, product features, intended target population and intended clinical use. The developmental toxicity study should be designed to detect potential developmental adverse effects induced by components present in the vaccine formulation. However, it should be recognized that 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, it should be kept in mind that 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 species-specific differences in the immune response, different developmental time lines, differences in placentation, etc. Nevertheless, developmental toxicity studies in animal models are the best currently available nonclinical tools to screen for adverse developmental effects of the product and information about developmental risk from animal data is frequently the only information available at the time of product licensure.

1. Previous clinical experience

All available clinical experience in pregnant females should be considered in any potential application with respect to the design of reproductive 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 pre-clinical studies, and for product labeling.

However, clinical data that may have been obtained from a small number of pregnant women enrolled in non-IND studies, e.g., immunized with the investigational vaccine or a related product, will generally not replace the need for animal developmental toxicity studies.

2. Previous non-clinical experience

All data generated from prior acute or repeat dose nonclinical toxicity studies should be reviewed for their possible contribution to the interpretation of any adverse developmental effects that appear in the developmental toxicology studies, i.e., fetal toxicity secondary to maternal toxicity. In addition, data from prior nonclinical 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

Candidate vaccine formulations for clinical trials should be prepared under conditions of Good Manufacturing Practice for clinical trial material (8). Also, the nonclinical lot should be adequately representative of the formulation intended for the clinical investigation. Ideally, nonclinical testing should be done on the same lot as proposed for the clinical trial. If this is not feasible, nonclinical lots should be comparable to clinical lots with respect to physico-chemical data, stability, formulation etc. 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, the applicability of nonclinical studies conducted with earlier clinical formulations of the vaccine to the commercial formulation of the vaccine will be made on a case-by-case basis. For a product specifically intended for maternal immunization nonclinical developmental toxicity studies should be performed in advance of clinical studies that enroll pregnant women. In these cases, to avoid performing multiple developmental toxicology studies during development, sponsors may find it advantageous to conduct Phase 1 and Phase 2 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, the need for additional development toxicity studies for the product under investigation will be examined on a case-by case basis. Combination vaccines in clinical development, for which the individual components are licensed and on which developmental toxicity assessments have been performed, may not be subject to requirements for 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 concern exist that combining the individual licensed products may increase their toxic potential, additional developmental toxicity studies are likely needed. Similarly, if no developmental toxicity studies have been conducted for the individual already licensed or unlicensed components developmental toxicity studies need to be conducted. 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 and considered in determining the need for developmental toxicity studies in animal models. In these cases, the sponsor is advised to contact the 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 studies primarily for detection of toxicity on reproduction dividing the reproductive cycle into different segments, defined as stages A – F (7). 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 from implantation through 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, additional studies may be required to address additional segments of the reproduction cycle on a case-by-case basis. CBER is recommending use of the ICH S5A guideline as a general point of reference to assist in the general design of developmental toxicity studies and evaluation of endpoints. However, the most important feature distinguishing vaccines from drugs or other biological products is the intended vaccine-induced immune response. Furthermore, vaccines are usually administered in limited, episodic dosages with months or even years between doses. They include a broad range of product categories such as live attenuated, inactivated, recombinant, polynucleotide, polysaccharide, and 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 nonclinical testing strategies outlined in the ICHS5A document may not be directly applicable to vaccines and study designs outlined in the ICHS5A document will need to be tailored to the vaccine product under consideration. Specific considerations that should be taken into account when designing developmental toxicity studies for vaccines are outlined below. It is recommended that the sponsor establishes an early dialogue with CBER to reach agreement on a specific protocol including study endpoints **prior** to the conduct of the study.

B. Specific Considerations

1. Animal model

It is recognized that responses induced in an animal model may not always be predictive of the human response. The sponsor should provide a justification for the choice of the

animal model. 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, these animals may only be considered if no alternative models are available.

In addition to demonstrating an immune response in the pregnant female exposure of the fetus to the antibody should be verified. Since there are differences between primates, non-rodents and rodent animal species in terms of timing of maternal antibody transfer to the offspring, it is suggested that the pre- and postnatal exposure of the offspring to maternal antibody be evaluated as a criterion for selecting the most appropriate experimental model. 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 studies using rats or rabbits it is recommended to assign 40 animals to each group whereby animals can be further allocated to the Caesarean and littering subgroup using 20 animals each.

2. Pharmacodynamics

It is recommended that information about onset and duration of the antibody response be obtained in pilot studies since this 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. It is recognized that antibody induction presents only one aspect of the overall immune response induced by the vaccine and that other immunological parameters, such as cytokines, induction of cytotoxic T cells, etc., may be evenly important. However, given the relative lack of validated assays to assess the induction of these 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 and development and growth of the embryo/fetus and the offspring, the female is exposed during the interval from implantation through closure of the hard palate to the end of pregnancy. The offspring should be followed to weaning and observed for normal growth and development. It is recommended to submit one subgroup of pregnant females to Caesarean examination at the end of pregnancy for routine uterine and fetal examinations. Another subgroup is allowed to litter and rear their offspring to weaning in order to monitor the post-natal development of the offspring up to weaning.

4. Dosage

It is recommended that a single dose level which is capable of inducing a immune response in the animal model be assessed. Where possible, animals should be administered 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, etc), a dose that exceeds the human dose on a mg/kg bases while still capable of inducing an immune response in the animal should be administered.

5. Frequency and Route of Administration

The vaccination regimen should optimize maternal antibody titers throughout the embryonic, fetal and early post-natal periods whereby timing and number of doses will depend on the onset and duration of the immune response of the particular product. Because of concerns that daily dosing regimen may lead to overexposure to the vaccine antigen that could potentially result in immune tolerance, episodic dosing of pregnant animals rather than daily dosing is recommended. 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. It is recommended to 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 high level of antibody throughout

342 the reminder of gestation. In certain cases, subgroups of animals that are dosed at
343 certain time points may be included to evaluate if the vaccine acts as a selective toxicant
344 bearing in mind that it may be difficult to adjust vaccine administration with gestational
345 timelines.
346 The route of administration should mimic the clinical intended route of administration.
347
348 **6. Control groups**
349 It is recommended that control animals be dosed with the vehicle at the same time and
350 frequency as test group animals. The potential toxicity of each of the components
351 presented in the vaccine formulation should be evaluated. Thus, additional groups
352 should be considered if the vehicle or components other than the vaccine antigen causes
353 effects or affect the action of the test substance. In addition, if the vaccine is formulated
354 with adjuvant, inclusion of an adjuvant only arm should be considered, in particular if the
355 adjuvant is novel.
356
357 **7. Endpoints**
358 In general, the study endpoints should include those recommended for studies for effects
359 on prenatal and postnatal development including maternal functions as stated in the ICH
360 S5a document (Ref. 7). When deciding on the endpoints to be evaluated one should
361 take into consideration the nature of the vaccine and particular concerns associated with
362 that product. The following parameters listed are intended to provide a basic panel of
363 endpoints to be evaluated that are not meant to be all inclusive.
364
365 7.1 Premating/preinsemination period
366 Clinical observations including data on general appearance and body weights
367 should be obtained weekly and on days of test article administration.
368
369 7.2 Gestational period

Maternal animals should be observed during the study for signs of morbidity and mortalities. Clinical observations regarding general appearance and behavior should be recorded. The evaluations should include body weight and body weight change, potential signs of local toxicity, food consumption, duration of pregnancy, abortions and premature deliveries and parturition (for maternal animals not subjected to Caesarian sectioning).

7.3 Caesarean sectioning group

7.3.1 Maternal Observations

For groups subjected to Caesarean sectioning at terminal examination, a necropsy (macroscopic examination) should be conducted and maternal tissue with macroscopic findings should be preserved for histological evaluations as deemed necessary by the gross findings. For example, histological evaluations may be indicated if effects on organ to body weight ratios have been observed. The number and distribution of corpora lutea, implantation sites, viable and nonviable fetuses and early and late resorptions should be recorded. A gross evaluation of the placenta should be performed.

7.3.2 Fetal examinations

Individual body weights of live fetuses should be obtained. Each viable fetus should be examined 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.

7.4 Natural delivery group

7.4.1 Maternal observations

In addition to the parameters outlined in 7.2, duration of gestation and parameters such as the fertility index, gestation index, and live birth index should

be determined. Animals that deliver a litter are sacrificed at the end of the pre-weaning period. A gross necropsy of the thoracic, abdominal and pelvic viscera should be performed. The number and distribution of implantation sites should be recorded 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. Aborted fetuses and/or delivered pups should be examined to the extent possible.

7.4.2 F1 generation

Postnatal follow-up from birth to weaning is recommended to assess normal growth, body weight gain, and nursing activity as indicators for normal development. It is also recommended to 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, a necropsy should be performed, any abnormalities recorded and gross lesions retained for possible histological examinations. Pups that die before examination should be evaluated for vital status at birth. Pups found dead should be examined 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, an assessment of the vaccine induced antibody response should be included 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 weaning period. In addition, cord blood samples should be obtained to

assess placental transfer of maternal antibodies from animals in the Caesarean subgroup. It is recommended to 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. Additional immune parameters may be evaluated 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, respective assessments may be included.

9. Additional assessments

In cases where preclinical developmental toxicity studies reveal vaccine-induced adverse effects on either the pregnant/lactating animal, embryo/fetal development or development of the offspring further studies are required 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, etc.

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V. ESTABLISHMENT OF PREGNANCY REGISTRIES

If the vaccine is administered to females of childbearing potential or is specifically indicated for immunization during pregnancy, the safety of that vaccine in human pregnancy may need to be further evaluated in a systematic manner under a Phase IV commitment. Alternatively, data on potential risks with the use of the vaccine in pregnant individuals may be obtained for already marketed products in order for the sponsor to update the product label. It is, therefore, recommended that pregnancy registries are established for the purpose of monitoring the post-licensure experiences from vaccinated pregnant women and their offspring to determine risks associated with use of the vaccine during pregnancy. The establishment of a pregnancy registry may encourage health care providers to prospectively report exposures in pregnancies. This will

result in better postmarketing data and provides a less biased sample than the retrospectively reported cases commonly seen with adverse experience reporting. In contrast to drug exposures during pregnancy that are typically defined as any exposure to a product from the first day of the last menstrual period (LMP), vaccination occurring prior to conception or even the LMP may need to be included in the definition of "vaccine exposure during pregnancy". The time period prior to the LMP will depend on the particular product under consideration. The decision to conduct a pregnancy registry should be made on a case-by-case basis and may depend on several parameters such as the availability and extent of data derived from nonclinical and clinical studies, type of vaccine and known adverse effect(s) of the wild-type disease on the pregnant woman and the fetus. The agency has also published guidance with regard to the design of pregnancy registries and suggested outcomes entitled "Draft Guidance for Industry: Establishing Pregnancy Registries" (Ref.9).

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欧米におけるワクチン非臨床試験に関するガイダンスの比較 - 既に発行済みの EMEA のガイダンスを基準とし、WHO ドラフトの関連項目を記載。なお、WHO は毒性試験のみならず、多くのことが記載されているため、EMEA の記載から外れる部分は、表最後にリストアップした（WHO 緒言：P.9 はガイドライン作成に参考になる）。

EMEA (CPMP): CPMP/SWP/465/95	WHO ドラフト関連項目	CBER（Non-Clinical Safety Assessment of Vaccine）
毒性試験の記載の EMEA と WHO の対応は概ね、以下のようになっている。 A1：単回, A2：反復, H：局所 ⇔ 基本的な毒性試験（4.1 全般） B/C：生殖, D/E：変異原性及びがん原性 ⇔ 追加毒性試験（4.2 全般） F2：薬理試験（免疫原性、安全性薬理） ⇔ 免疫原性試験（3） G：薬物動態 ⇔ 薬物動態（4.2.5）		
【緒言】 感染物質または毒素あるいはそれにより生成された抗原に対し特異的で能動的な免疫を誘導できる抗原物質を含有する製剤	**WHO-1.1** 感染症に対し特異的、能動的かつ防御的な宿主免疫を誘導できる免疫原物質を含有する異種の医薬品	
- 化学的あるいは物理的手段により不活化され、適切な免疫原性を保持した微生物 - 抗原性を保持したまま無毒化あるいは弱毒化された生微生物 - 有機体から抽出/分泌された抗原、あるいは組換え DNA 技術による産生された抗原	- 化学的および／または物理的手段により不活化され、適切な免疫原特性を保持している微生物 - 免疫原特性を保持しつつ、弱毒性のために選択された生微生物 - 微生物から抽出されたか、微生物により分泌されるか、組み換え DNA 技術により製造された抗原 - キメラ微生物 - 生きたベクターあるいは核酸投与後に宿主で *in vivo* で生成した抗原 - *in vitro* で化学合成により製造された抗原	
抗原は、①そのまま、②化学的あるいは物理的手段により無毒化、あるいは③免疫原性を増加するために、凝集化、重合化、または担体と結合させることがある	抗原は①そのまま、②突然変異導入で不完全または改変、③化学または物理的手段で無毒化、④免疫原性を増加するために凝集、重合または担体に結合	
【適応範囲】 複合ワクチンを含む新ワクチン製品の前臨床評価を対象	**WHO-緒言・1.1** 新ワクチンの開発及び既承認ワクチンに対する改良（新アジュバントの導入）	**(3)** Definition of Vaccine
適応されるワクチン - 欧州薬局方モノグラフや WHO 要求事項に未掲載の抗原を含む新ワクチン - 既知抗原の新規 conjugate 体 - 既知あるいは新抗原の新しい組み合わせ - 新規投与方法（route/delivery）は特別な安全性を考慮した試験が必要 - 主要なワクチン製造過程の変更は前臨床試験の必要性を再検討 - 生微生物を含有する新ワクチン製品	適応されるワクチン 感染症に対する予防および治療ワクチン適応症	Preventive vaccines Pre- and post-exposure prophylaxis Therapeutic vaccines against infectious disease
適応外のワクチン - 毎年更新されるインフルエンザワクチン - immunogens として使用されるモノクロ抗体: see ICH S6 - 組換え DNA 蛋白ワクチン: see ICH S6 注釈 - DNA ワクチン - 遺伝子治療、遺伝子組み換え体細胞療法	適応外として明記されているのは - 非感染症のための治療ワクチン（がんワクチン） - 免疫原性に使用されるモノクロ抗体(抗イディオタイプ抗体)	

【一般的な考え方】 ヒトの反応予測可能な適切な動物モデルがないため、動物種選択を個別に実施 安全性の評価は、「一般的な全身毒性」、「予期される毒性の増強」、「局所毒性」、「発熱性」、「自己免疫または感作などの有害な免疫反応」、及び（場合によっては）「催奇形性／生殖作用」によって行われる 新規ワクチンでは、既存医薬品で要求される全ての検査が必要ない可能性が認識されてはいるが、前臨床安全性試験は常に試験プログラムの一部分とすべきである。しかしながら、既知の抗原を含む複合ワクチンの場合は、必ずしも必要ではないことがある。それでも免疫原性試験は推奨される（§F1）。 投与方法は臨床経路と一致させる。不可能な場合は正当な理由により他の経路も容認されるが正当な理由が必要。神経病原性や毒素の完全無毒化試験など、特定の安全性評価を行う試験では、他の投与経路を用いることが多い。局方に記載の方法が適応できるかを考慮する。 アジュバント、保存剤、賦形剤などの添加剤にも注意が必要（§R）	**WHO-4.1** 利用可能な最良の科学に基づく判断が、非臨床安全性試験の必要性、試験の種類、試験デザイン及びデータの解釈（リスク/ベネフィット、動物モデル、投与）に必要（4.1） 試験デザインの際、考慮する点 - 適切な動物種/系統 - 投与スケジュールおよびワクチン投与方法 - エンドポイントの評価タイミング - 投与経路は臨床試験で使用する経路に一致 評価のポイント：標的臓器・用量・曝露経路・曝露期間と頻度・観察された毒性作用の回復性 専用の単独の毒性試験、または試験デザインに毒性エンドポイントを組み込んだ安全性/免疫原性試験が実施できる。また、局所刺激性の評価も含める。	**(7)** Key Components in Non-clinical Assessment - Immunogenicity - Pyrogenicity testing - General safety testing - Neurovirulence testing - Reversion to virulence - Biodistribution studies - Integration studies - Safety studies - Efficacy studies **(19)** Lot **(20)** Study design
歴史的にワクチン使用による神経毒性が知られていることから、新規ワクチン開発では、神経毒性を評価できるモデルが必要（Neurovirulence Tests）	**WHO-6.1** 野性型微生物に神経親和性がある、あるいは、ウイルスワクチンの弱毒化に神経組織による継代が使用された場合は、少なくともワクチンシードのレベルで神経病原性に対する試験を実施。 ただし、神経病原性試験は必ずしも全ての生弱毒化ワクチンに必要なわけではない 小動物モデルでの神経病原性試験は許可される	
【A.1 単回投与試験】 ヒト用量に対して適切な安全マージンを与える用量 少なくとも 1 種類の動物種 毒性変化がみられた場合は、さらに用量反応関係を検討 これら試験結果は、主要器官の病理組織検査を行うことにより、動物の免疫原性試験（§F1）や安全性薬理試験（§F2）の一部になるかもしれない 異常毒性試験や発熱性試験の通常製造試験については、§Q 参照	**WHO-4.1** 単回/反復の分類は明記されない 4.1.3 に以下が予想される場合の単回投与試験実施について記載 ・ ワクチンで誘導される抗体が、生ウイルスベクターを中和して、対象遺伝子の発現を制限する場合（抗アデノウイルス免疫反応） ・ 動物に誘導された免疫反応が、ワクチン製剤中に存在する種特異的蛋白と反応する場合（アジュバントとして使用されるヒト組み換えサイトカイン）	
単回投与試験結果は、主要器官の病理組織検査を行うことにより、動物の免疫原性試験（§F1）や安全性薬理試験（§F2）の一部になるかもしれない（A.1）	専用の単独の毒性試験、または試験デザインに毒性エンドポイントを組み込んだ安全性/免疫原性試験が実施できる。（4.1）	