Adjuvants can be used in relation with different antigens and are often not very species-specific. They should be tested in two species unless otherwise justified (rodent and non-rodent)

Adjuvants belonging to different biological classes might exert a high level of species specificity (e.g. some cytokines), that makes this discussion only theoretical as testing in more than one animal species does not make sense. However, other adjuvants (e.g. oil emulsions) exert less species specificity and based on toxicological principles testing in at least two appropriate species is the default option. The evidence found in the second species does support the evidence in the first one.

The choice of species depends primarily on the choice of antigen the adjuvant is intended to be combined with. Ideally the selected species should be the same as in which the proof-of-concept has been studied.

4.3.1. Local tolerance

The local irritation induced by an adjuvant should be studied depending on the route of administration. For example:

- For oral and intranasal administration local and regional tolerance need to assessed.

- For injectable vaccines, special consideration should be given to the possibility of induction of later granulomatous reactions as seen for example when using particles and also some mineral oils.

4.3.2. Induction of hypersensitivity and anaphylaxis

Adjuvants themselves might be immunogenic and testing should be considered with respect to the induction of hypersensitivity in appropriate models (e.g. passive cutaneous anaphylaxis assay [PCA], and the active systemic anaphylaxis assay [ASA]). An adjuvant-induced increase of IgE against the antigen should be considered as a possible concern for induction of hypersensitivity and anaphylaxis.

4.3.3. Pyrogenicity

Adjuvants should be tested with respect to their possible pyrogenic effects. Alternative *in vitro* tests for fever-inducing substances are under development and should be used if validated.

4.3.4. Systemic toxicity

Adjuvants of various classes may be distributed systemically and may induce toxicity in various organs. Protocols should be designed to establish dose-relationships and include repeated administration at intervals reflecting the proposed clinical use. Full necropsy and tissue collection should be conducted. Histopathology should always include

- pivotal organs: heart, lung, brain, liver, kidney, reproductive organs etc.

- skin (if the site of administration),

- primary and secondary immune organs: spleen, thymus, bone marrow, lymph nodes (local and distant to the application site)

Full tissue examination is recommended in case of novel adjuvants with no prior nonclinical and clinical experience.

Toxicity would mainly result from the immunostimulating effect of the adjuvant, but direct toxicity on non-targeted organs cannot be excluded. The range of doses may remain relatively low reflecting its clinical use rather than reaching necessarily a maximum tolerated dose. With respect to the endpoints, refer to the Note for Guidance on Repeated Dose Toxicity.

4.3.5. Reproduction toxicity

As vaccination programs may include women of childbearing potential, it is of importance to consider the need for reproduction toxicity studies. Furthermore, vaccines might be intended to be given during pregnancy in order to prevent infectious disease in the young infant through passive immunization. Reproduction toxicity studies with adjuvant intended to be used in this type of vaccines should be performed. The protocol should reflect the intended schedule of administration. As the immunological response to the booster might be different from the first response, it should also be considered to give the first dose before mating, while giving the booster during the pregnancy.

4.3.6. Genotoxicity

Adjuvants might be derived from biological as well as from synthetic origin. In line with requirements published for biotechnological products (ICH S6) genotoxicity studies for biologically derived adjuvants might not be regarded as relevant. For synthetic adjuvants the standard battery (ICH S2B) can be seen as the default position and any deviations should be scientifically justified.

4.3.7. Carcinogenicity

As adjuvants are intended to be used only a few times with low dosages the risk of induction of tumours by these compounds in a direct way is negligable. Furthermore, the action of the adjuvant is to stimulate the immune system, and not to act as a general immunosuppressant, reducing the risk on the spontaneous formation of lymphoid tumours. Therefore, carcinogenicity studies are not needed.

4.3.8. Combination of adjuvants

Administration of substances with immunomodulatory properties, along with adjuvants improving the presentation of the antigen may further increase adjuvant activity. An appropriate set of toxicity studies should be provided to support its safety of the combination in addition of data on each individual component. Toxicity studies with the separate constituents might be seen as pilot studies. A study with the final combination should be done under GLP.

4.4. TOXICITY OF ADJUVANT IN COMBINATION WITH THE PROPOSED ANTIGEN

The pre-clinical safety aspects of the combination of adjuvant with the proposed antigen should be considered in line with the existing Note for Guidance Preclinical Pharmacological and Toxicological testing of vaccines CPMP/SWP/465/95. Specific attention should be given to:

4.4.1. Local tolerance

Injection of antigens in combination with adjuvants might induce more severe local reactions than after administration of the adjuvant alone. The optimal dose-ratio of adjuvant and antigen with respect to benefit and risk should be explored.

4.4.2. Repeated dose toxicity studies

A dosing schedule should be used in accordance with the proposed clinical schedule. In order to ascertain the safety of the repeated schedule (where an increase in the severity of the immune response might occur) the number of administrations should be higher than the number planned for human administration.

4.4.3. Characterization of the immune response

As a minimal requirement the following non-clinical immunogenicity data are expected:

- Dose-response studies investigating the effect of different doses of adjuvant combined with different doses of vaccine antigen.

- Comparative studies to assess the effect of a new adjuvant with reference to a vaccine antigen alone or adjuvanted with a well-established adjuvant

The nature and extent of an immune response (humoral and cellular) determines the efficacy of a vaccine. The type of an immune response against the same vaccine antigen might be different in animals and in man. Thus, these data should be extrapolated only very carefully. On the other hand a proof-of-concept needs to be provided from non-clinical investigations before clinical trials can be started.

If feasible, further studies in relevant animal models should focus on the more detailed investigation of the immunological mode of action of the new adjuvant (see Proof of Concept, § 4.1).

If a combination of adjuvants is proposed, the rationale for this choice should be provided based on experimental data.

5. CLINICAL

5.1. INTRODUCTION

The inclusion of an adjuvant in a vaccine must always be justified. There must be evidence to demonstrate that the benefit in terms of improvement of the immune response has been achieved without an undue increase in local and systemic adverse reactions.

It is critical that the clinical data demonstrate that the amount of adjuvant used in the vaccine is appropriate to enhance the immune response to the antigen(s), to further direct the immune response towards the intended effect, or to improve the safety profile. In a combination vaccine, the adjuvant should improve the response to at least one of the relevant antigen(s) without exerting a clinically significant detrimental effect on immune responses to any other antigen in the vaccine. Any increase in the rates and/or severity of adverse reactions as a consequence of the presence of an adjuvant in a vaccine is of concern. Therefore, the risk associated with the adjuvant must be outweighed by the potential benefit conferred by enhancement of the immune response.

This section addresses:

- The clinical assessment of a novel adjuvant when it is to be incorporated either into a novel (*i.e.* as yet unlicensed) or licensed prophylactic vaccine and

- The clinical data that would be required to support any change (removal, addition and/or replacement) in the adjuvant content of a licensed vaccine.

The general principles covered in this section are applicable to both single antigen and combination vaccines and to any of the possible routes of vaccine administration. There are special considerations for the characterisation of the immune response as part of the assessment of safety and efficacy. The various scenarios to be considered include the following (note that the term *established adjuvant* refers to any such compound that is already included in at least one licensed vaccine to enhance the immunogenicity of one or more antigens):

1. Novel vaccine

- Inclusion of one or more novel or established adjuvant(s) in a novel vaccine in order to enhance the immune response to one or more antigens or further direct the immune response towards the intended effect.

2. Changes to an already licensed vaccine

Changes to already licensed vaccines may be made to enhance or modulate the immune response and/or to improve the safety profile. In special circumstances (e.g. pandemic influenza vaccine) inclusion of an adjuvant may be used in order to reduce the amount of antigen needed. Changes may include:

- Addition of one or more novel or established adjuvant(s).

- Increase in the amount of an adjuvant.

- Decrease or removal of one or more adjuvant(s) (without replacement).

- Replacement of one or more adjuvant(s) with one or more novel or established adjuvant(s).

5.2. PRELIMINARY STUDIES

Whether the adjuvant is a novel or an established compound, the preliminary studies should establish the effect of the adjuvant on the nature of the immunological responses to the antigen(s) with which it is to be combined. If more than one adjuvant is to be used in a vaccine, then the studies should evaluate the effect(s) of the combination of adjuvants on responses to the antigens. In addition, for a vaccine intended to contain more than one adjuvant/antigen combination, the action of each adjuvant on its intended antigen should be documented.

5.2.1. Effect of the adjuvant on the immunological response

In general, the characterisation of the immune response should involve the administration of each antigen that is anticipated in the final product alone and with the adjuvant(s). In the development of combination vaccines, it may be sufficient to compare the combination without adjuvant with the combination plus each adjuvant. These early studies should also provide important, although limited, data on safety.

It is likely that these studies will be performed mainly in healthy adults and in relatively small numbers of individuals. If the vaccine is wholly or predominantly intended for use in infants or young children or is very likely to be administered to the elderly, subsequent to studies in healthy adults some data should be obtained from these age groups if possible.

The studies should involve a comprehensive assessment of the potential effects of the adjuvant on the immune response to all antigens that are to be included in the final product. In addition, the potential that the adjuvant itself might be immunogenic should be explored. The range of tests that will be appropriate will depend on the nature of the antigen and of the adjuvant and cannot be pre-specified in detail in this Note for Guidance. In addition, it is recognised that advances in the assessment of immunological responses may mean that experimental methodologies are used in describing the effects of the adjuvant.

Whenever possible, the assessment of the humoral immune response should include the detection and titration of functional antibodies (neutralising, opsonophagocytic or bactericidal, antibodies) against an international standard (WHO or equivalent). Immunoglobulin subclass responses should be investigated. Circulatory and/or secretory IgA may be measured if relevant. It may also be appropriate to estimate other properties of the antibody response such as avidity.

Assessment of the cell-mediated component of the immune response is considered important. It is recommended that studies should monitor antigen specific T-cell responses (including Th1, Th2 and T regulator cells, and/or relevant cytokines). The range of tests performed, with an explanation of the rational for each investigation, should be justified in the application dossier.

It would not be envisaged that the adjuvant would have to be administered alone in these studies. If the adjuvant is novel, there should usually be sufficient safety data from the pre-clinical studies to allow for it to be given with antigen(s) from the outset. The same situation should apply to an established adjuvant when it is to be given at a higher dose than usual or by a new route of administration. However, if there is suspicion that an adjuvant might accumulate, consideration could be given to a pharmacokinetic evaluation in humans. If it is considered that the administration of adjuvant alone in clinical studies might be necessary, it may be appropriate to obtain further scientific /regulatory advice from EU Regulators.

5.2.2. Dose-finding studies

It is essential that there should be sufficient data to demonstrate that the amounts of adjuvant and antigen that are chosen for further study represent an acceptable balance between immune responses and the risk of adverse effects. In most adjuvant-antigen combinations, the aim will be to use as little as possible of one or both of these so as to achieve the required immune response with the minimum of adverse reactions. A preliminary estimate of the relative amounts of each adjuvant and antigen to be combined should emerge from the investigations, described in 5.2.1,which may overlap with dose-finding studies.

The extent of the dose-finding studies that would be considered necessary will be at least partly influenced by the aim of the final product. For example, if it is proposed to incorporate an established adjuvant at a dose that is already in use in at least one licensed product, then it may be more important to focus on different amounts of antigen. Alternatively, if it is proposed to add the adjuvant to the same dose of an antigen or combination of antigens that is already approved in one or more products, then it may be more important to focus on the amount of adjuvant. However, in the case of a novel adjuvant and/or a novel antigen, alone or in combination, more extensive dose-finding studies would likely be necessary.

Whenever possible, these studies should be performed in the target population for the vaccine. However, this may, on occasion, prove difficult so that a dose may have to be chosen on the basis of studies in a population that may differ from the target population. Also, when the dose-finding studies fail to point to a single antigen-adjuvant dose, more than one product may have to be evaluated in confirmatory trials. In these cases, it is desirable to characterise the immune response to the chosen antigen-adjuvant combinations in at least a subset of subjects who are enrolled into the confirmatory trials.

5.3. CONFIRMATORY TRIALS

5.3.1. General considerations

In general, clinical trials should be randomised, double blind, controlled trials. The design of the trials should depend on the characteristics of the antigen /adjuvant formulation. It is anticipated that the majority of trials, especially if a modification is being made to the antigen content of a licensed vaccine, will likely involve only an assessment of immune responses against validated immunological correlates for protection. If there is no validated immunological correlate for protection, but a formal assessment of efficacy is feasible, the provision of immunogenicity data alone should be justified.

These trials should be performed in the final target population. If this spans a wide range of age groups, studies may need to pre-stratify by age group or more than one study may need to be performed. For example, in some instances, the demonstration of enhancement of the immune response to at least one antigen may be reasonably expected to apply in only one or some of the possible age groups.

5.3.2. Possible scenarios

5.3.2.1. New vaccines with a new or established adjuvant

The *Note for Guidance on Clinical Evaluation of New Vaccines* (EWP 463/97) applies whenever the product in question meets the definition for a new vaccine[4] as described in the guidance. Therefore, further details will not be discussed herein.

5.3.2.2. Changes to the adjuvant content of a licensed vaccine

At least one confirmatory study is needed to support a change(s). The study design will be determined by the primary objective, as follows:

Changes for efficacy reasons

If the primary objective is to enhance the immune response to one or more antigens, or further direct the immune response towards the intended effect, in general the trial should be designed to demonstrate the superiority of the modified over the existing product. For combination products, superiority should be shown with respect to the immune response to at least one of the antigens and the study should have the secondary aim of demonstrating non-inferiority with respect to responses to any other antigen(s) that may be present. The demonstration of non-inferiority with respect to other antigens is relevant only if superiority is demonstrated with respect to the designated primary efficacy variable(s). The definition of what constitutes superiority and non-inferiority of immune responses must be justified according to the antigen(s) in question.

If an adjuvant is to be given at a higher dose than used previously and/or via a different route of administration a specific safety study may need to be considered Whether or not such a study should be wholly performed before first licensure of the modified product should be discussed with EU Regulators before submitting an application for a marketing authorisation.

Changes for safety reasons

If the primary objective is driven by (a) safety reason(s), the clinical program should aim to show non-inferiority of the amended vaccine with respect to the existing vaccine in terms of immune responses to each antigen. The definition of what constitutes non-inferiority must be

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[4] New vaccines are those containing antigens not yet described in the Ph.Eur. monographs or WHO requirements, or using a new conjugate for a known antigen, or any new combination of known and/or new vaccines.

justified according to the antigen(s) in question. The safety data from this study would be expected to show an improvement in the safety profile.

The safety data should allow for estimation of, with a reasonable degree of precision, the likely rates of reactions that may be expected based on the known properties of the adjuvant(s) and antigen(s). In some cases, it may be appropriate that the data focus on immune mediated reactions. In all instances, the risk-benefit relationship for the modified product should be at least as favourable as for the existing product.

A post-marketing surveillance program should be considered whenever there has been a change in the adjuvant content of an already licensed vaccine.

5.3.3. Statistical considerations

The hypotheses to be tested and the statistical methods to analyse them have to be clearly stated in the trial protocol. The sample size should ensure that the trial has sufficient power to answer its scientific question. For any test on non-inferiority, the non-inferiority margin has to be defined and justified in advance. In planning the analysis and sample size of the clinical trial possible multiplicity issues have to be accounted for appropriately. For further details please refer to the relevant methodological guidelines[5].

[5] e.g. ICH Note for Guidance on Statistical Principles for Clinical Trials (ICH topic E9)
Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)

Session 9

Regulatory Issues for Cancer Vaccines

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CVADD 2005, Pestana Palace Hotel, Lisbon, Portugal
7th September 2005

Public Perception

Popular induction depends upon the emotional interest of the instances, not on their number.
Bertrand Russell, 1927.

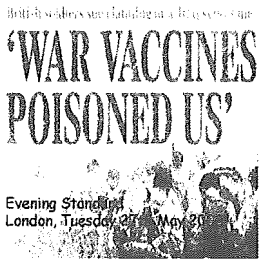
Vaccines are politically and socially very sensitive products where rates of real associated adverse events must be far lower than for most therapeutic medicines.


Autism fear over NHS whooping cough jab

Daily Mail
London, 16th March 2004

Some suspected but unsubstantiated or disproved associations between vaccines and health conditions

DTwP/ : neurological damage, atopy
sudden infant death
D T aP IPV Hib HepB : unexplained death in second year of life
Lyme : autoimmune arthritis
Hep B : multiple sclerosis
MMR : autism and Crohn's
Bovine serum : vCJD
Thimerosal : autism
Aluminium hydroxide: macrophagic myofascitis


'WAR VACCINES POISONED US'

Evening Standard
London, Tuesday, 27th May 20

Some proven/probable casual relationship between vaccines and health conditions

- **Inactivated/subunit vaccines**

Swine flue and Guillam Barre syndrome
Killed measles vaccine and atypical measles
Tick borne encephalitis - reactogenicity
Resp. Syncytial virus vaccine and enhanced disease

- **Live vaccines**

Measles vaccine and convulsions
Mumphs and aseptic meningitis
Oral poliovirus and acute flaccid paralysis due to reversion
Smallpox vaccine and myocarditis
Excessive viable counts in BCG - local reactions

Casual relationship between vaccines and health conditions

It is important to stress that none of these events could have been predicted by laboratory or animal tests or even limited clinical trials before licensure and widespread use. All identified by post-market surveillance.

Specific concerns arising from vaccines as medical products

- Generally given to large number of healthy people, often children.
- Current attitude regarding risk-benefit favours safety over efficacy.
- However, for therapeutic cancer vaccines an increased level of toxicity may be acceptable if the benefit is substantial.

Regulatory challenges arising from vaccines as medical products

- One package "fits all approach" NOT possible
- Diverse products & manufacturing process
- How and with what it is given
- Who is it given to and why
- Case by case assessment

- New vaccines and adjuvant technologies together with use of novel production and delivery systems pose unique regulatory challenges.

Regulatory considerations relevant for therapeutic cancer vaccines common to all biologicals

- Active substance complex and less well defined than chemical entities (not peptide)
- Complexity of production and mode of action warrants special consideration
- Production in living systems rather than by chemical means introduces unknown factors: contamination, sterility, endotoxins
- Use of complex adjuvats, excipients and stabilisers (combinations/interactions)

Therapeutic Cancer Vaccines

General Categories:

Synthetic peptides (conjugate vaccines)
Purified or recombinant proteins (acellular vaccines)
Multi antigen preparation including shed/secreted antigen or cell lysates / multiple adjuvants

Cellular : autologous or allogenic tumour cells, modified tumour cells, secretary cells, lymphocytes, antigen presenting cells (DC), shed or secreted tumour antigen,

Viral and plasmid vectors containing therapeutic gene

EU Regulatory Developments for Therapeutic Cancer Vaccines

- No specific guidelines at present
- EMEA VEG - guidelines in work plan 2005
- European Pharmacopoeia: General monograph on Vaccines for Human Use 2002:153- in work plan by Grp Exps 15 (Vaccines and Sera) to include section on therapeutic vaccines
- Direct application of new CHMP guidelines on Adjuvats in Vaccines for Human Use- effective from July 2005

EU general guidelines relevant for all vaccine safety testing

- CPMP 1997. Note for Guidance on the Pre-clinical, Pharmaceutical and Toxicological Testing of Vaccines. CPMP/SWP/565.95
- CPMP 1999. Note for Guidance on the Clinical Evaluation of New Vaccines. CPMP/SWP/463.9
- CHMP 2005. Note for Guidance on Adjuvants in Vaccines for Human Use. CPMP/EWP/VEG 286.71

CPMP - Committee for Proprietary Medicinal Products
CHMP - Committee for Medicinal Products for Human Use
http¥¥www.emea.eu.int

EU specific guidelines relevant for vaccine (biologicals) safety testing

- CPMP Points to consider on Human Somatic Cell Therapy CPMP/BWP/41450/98 : Useful for whole cell cancer vaccines
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. CPMP/ICH/302.95 CPMP 1999. Useful for recombinant protein and peptide
- Note for Guidance on the Quality, Preclinical Aspects and Gene Transfer Medicinal Products CPMP/BWP/3088.99 Viral vector/DNA
- Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines. CPMP/BWP/477.98

FDA/WHO guidelines

- Points to consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology CBER/FDA, 1985 - Recombinant protein/peptide vaccines
- Guidance for Human Somatic Cell Therapy CBER/FDA 1998 - Viral vector and cell based vaccines
- Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Inf Dis Cons CBER, FDA 2000. Vaccines for pregnant women/child-bearing age
- WHO guidelines on Non clinical Evaluation of Vaccines WHO/BS/03.1969.

Key components for the safety assessment of vaccines

- Developmental studies
- Pre-clinical evaluation
  Pharmacological and toxicological testing
- Clinical studies
  Safety and Efficacy
- Quality control testing
  Batch to batch consistency
- Post-marketing surveillance
  Performance in target population
- Inspection of manufacturing sites

General strategy to demonstrate safety common to all vaccines

- Scientific understanding of product and its manufacturing process
- Control of manufacturing process - quality of raw materials, documented procedures
- Reproducibility and consistency of product lot (setting in-process and lot release specifications)
- Test methods suitable, reliable and reproducible to characterize the product
- Rational design of non-clinical and clinical studies to reflect intended use

Scope of New Regulatory Guidance on Adjuvant in Vaccines for Human Use

- Regulatory guidance to manufacturers and authorities concerning data to submit in a vaccine MAA on
- QUALITY
- Non-Clinical SAFETY
- EFFICACY (Clinical)

- The principles should also be applicable to quality and non-clinical aspects (but not clinical aspects) of therapeutic vaccines (inc. cancer vaccines).

Not covered in New Regulatory Guidance on Adjuvant in Vaccines for Human Use

- Carriers for haptens, antigen and peptides (e.g. CRM_{197}, meningococcal OMP, tetanus and diphtheria toxoids that are used for conjugate polysaccharide vaccines.
- Stabilisers and excipients

CHMP Guideline on Adjuvants
QUALITY: Info on adjuvant

- Description - Nature, chemical composition, function of each component as known
- Manufacture to be described in detail- source and purity of starting materials, process parameters, biochemical, biological / adsorptive properties
- Characterisation- structure, qualitative and quantitative, physical and biochemical characteristics purity, bioburden, endotoxin, manufacturing residuals
- Routine testing and stability - to be selected from characterisation tests: purity, concentration

CHMP Guideline on Adjuvants
QUALITY: Info on antigen/adjuvant combination

- Development & Manufacture to be described in detail- mechanisms of association & its efficacy, adsorbtion/binding characteristics, compatibility with antigen(s)/other adjuvants
- Characterisation- level & consistency of adsorbtion/binding, integrity of antig., physical properties, impact on (routine) testing
- Routine testing and stability - to be selected from characterisation tests: identity, potency

CHMP Guideline on Adjuvants
NON-CLINICAL
Rationale & Proof of Concept

- Physical presentation
- Antigen uptake, persistence and distribution
- Targeting to specific cells/receptors
  - Innate immune system
  - Dendritic cells, macrophages, APC, skin LC
  - Toll-like receptors
- Immunepotentiation/modulation
  - Intracellular transport & processing of antigens
  - Association with MHC I or II, cytokine profiles, CTL responses, T-cell response, functional Abs
- Demonstrate protection by challenge

CHMP Guideline on Adjuvants

NON-CLINICAL TOX

General principles

- Follow patters of vaccine use
- Two species (rodent & non-rodent) but consider species-specificity (e.g. cytokines) and proof of concept studies
- Study combination of adjuvants if relevant
- Pharmacokinetics.- serum conc. of antigen not required. Distribution studies in some cases (modified toxins)

CHMP Guideline on Adjuvants

NON-CLINICAL TOX

Info on adjuvant alone

- Local tolerance (inflammation, consider route)
- Induction of hypersensitivity & anaphylaxis (app. models for PCA/ASA, antigen spec. IgE)
- Pyrogenicity (IV rabbit/validated in vitro)
- Systemic toxicity to tissues/organs (+histo) full tissue examination for novel adjuvants with no prior experience
- Reproductive toxicity (reflect intended schedule of administration)
- Genotoxicity carcinogenicity (not needed)

CHMP Guideline on Adjuvants

NON-CLINICAL

Info on antigen/adjuvant combination

- Local tolerance (dose ratio)
- Repeat dose toxicity (>human dose)
- Characterisation of immune response
  - Extrapolate to humans with caution
  - Dose-response studies, suitably controlled
  - Immune response to vector (carrier mediated suppression on repeat dosing)
  - Immunological mode of action (as for proof of concept studies), functional Abs.

CHMP Guideline on Adjuvants

CLINICAL : General Principles

" A final evaluation of the newly developed vaccine formulation can only be conducted in clinical trials"

- Risk-benefit relations to be considered case by case but cancer vaccines not in scope.

Specific considerations for cancer therapeutic vaccines

- Microbiological safety. Sterility studies for freshly prepared cellular products that cannot be cryopreserved not feasible. Alternative strategies.
- Surrogate for in vivo potency test may be based on genomics/proteomics approach and should be encouraged.

Adopted from Development of Therapeutic Cancer Veccines
K Kawakami and RK Puri , CBER, FDA, UDA, Dev Biol Stan 2004

Specific issues for characterisation of cancer therapeutic vaccines

- Purified protein antigens: relatively simple, can be assessed by a number of analytical tools.
- Tumor cell lysates/polyvalent vaccines: manufacturing process for generating cell lysates must be carefully controlled. Select two or more antigens to define identity of the product by a number of techniques (e.g. 2D-gels patterns).

Adopted from Development of Therapeutic Cancer Veccines
K Kawakami and RK Puri , CBER, FDA, UDA, Dev Biol Stan 2004

Specific issues for characterisation of cancer therapeutic vaccines

- Autologous and allogeneic vaccines:
  - Process of generating single cell suspension from tumour tissue must be carefully documented/controlled.
  - Donor screening and cell line characterisation critical.
  - Radiation dose must be controlled.
  - Select several cell markers to define purity & identity.

Adopted from Development of Therapeutic Cancer Vaccines
K Kawakami and RK Puri , CBER, FDA, UDA, Dev Biol Stan 2004

Regulatory acceptance

Gaps in pre-clinical testing

- Interactions between vaccine components
- Animal models for safety, particularly immunotoxicity.
- Lack of standardised approach (difficult to comparison between pharmaceutical and immunological data and inter laboratory).
- Animal models and surrogate markers of protection for proof of principle studies.
- Role for in vitro biological systems and in silico studies.

厚生労働科学研究費補助金「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」による出張報告書

財団法人 佐々木研究所 病理部・部長
中江　大

１．出張の目的

本出張の目的は，抗がん剤の非臨床安全性試験の実施手法のガイドライン等を確立するための情報収集の一環として，米国における現状と将来予測に係わる情報を取得することである．

２．日程

平成 17 年 6 月 19 日	出国・渡米 米国コロンビア特別区ワシントン市着 米国毒性病理学会年次学術集会参加 ワシントン市泊
平成 17 年 6 月 20 日	（北米）毒性病理学会年次学術集会参加 ワシントン市泊
平成 17 年 6 月 21/22 日	米国食品医薬品局・Center for Drug Evaluation and Research 訪問，担当者面談 ワシントン市泊
平成 17 年 6 月 23 日	離米 機中泊
平成 17 年 6 月 24 日	帰国

３．内容報告

３．１．FDA/CDER 訪問，担当者面談

今回の面談は，本研究班の構成員である小野寺 博志 博士(PMDA)および佐神 文郎 博士（日本製薬工業協会，JPMA）が FDA/CDER の Dr. Kenneth L. Hastings を通して行ってくださった折衝を受け，本出張者の依頼に対する FDA/CDER の渉外担当者である Dr. Justina A. Molzon の認証に基いて設定された．面談の FDA 側出席者は，いずれも CDER/Division of Oncology Drug Products (DODP)の Supervisory Pharmacologist である Dr. John L. Leighton と Dr. David E. Morse であった．また，本出張者は，面談の後に前出の小村 博士とお会いし，個人的立場での補足情報をいただくことができた．なお，本面談については，事前の準備作業の中で FDA/CDER 側が一時「international regulatory meeting」であるという認識を示したが，本出張者より，今回の行動があくまでも厚生労働省科学研究費補助金に基く学問的な情報収集活動であって，公式・非公式を問わず日米規制当局間の交渉という性格を持たないことを説明し，その上で本出張者が日本の規制当局をいかなる形においても代表する立場にない旨を認識させるという経緯があったので，念のために申し添える．

今回の面談においては，Dr. Leighton・Dr. Morse 共に非常に協力的であり，きわめて多岐にわたる御説明をいただいた．本出張者は，さらに，本研究の今後の進展過

程において本出張者または本研究班関係者からの要請による追加的な情報提供に御協力いただけるよう両博士に依頼し，幸いなことに御快諾をいただいた．このことは，本出張の有益な成果のひとつであるものと考える．以下は，今回の面談で得られた主要な成果（情報）の概略である．

３．１．１．ガイドラインまたはその代替物について：既知のように，FDA は抗がん剤の非臨床安全性試験の実施手法のガイドラインを有しておらず，本研究班としては CDER/DODP の Dr. Joseph DeGeorge らによる学術論文（DeGeorge JJ, Ahn C-H, Andrews PA, Brower ME, Giorgio DW, Goheer MA, Lee-Ham DY, McGuinn WD, Schmidt W, Sun CJ, Tripathi SC. Regulatory considerations for preclinical development of anticancer drugs. Cancer Chemother Pharmacol 41, 173-185, 1998）が事実上の代替物として機能しているものと理解していた．しかしながら，FDA としては，DeGeorge 論文があくまでも学術論文であることから，少なくとも公式見解として参照していないとのことである．特に近年は，同論文発表後の時間経過により内容に実情に合わない部分が多くなってきたこともあって，そうした立場が強まっている．ただ，公式に参照すべき文書が存在していないことも事実なので，実際的には，DeGeorge 論文の一部や，たとえば「Handbook of Anticancer Drug Development（Budman DR, Calvert AH, Rowinsky EK 編，Lippincott Williams and Wilkins 社，米国ペンシルバニア州フィラデルフィア市，2003 年刊行）」などの成書をはじめとする内外の種々の文献を，ケースバイケースで非公式に参照しているようである．

一方，今回の面談で得られたおそらくもっとも重要な成果（情報）は，FDA がまさに抗がん剤の非臨床安全性試験の実施手法に関するガイドラインを作製中であるというものであろう．同ガイドラインは，2-3 年以内の策定を目標に，現在内部ドラフトを準備している段階であり，その第１版が年内にもイントラネット上にアップロードされるかもしれないとのことである．このガイドラインドラフトに FDA 外部の者が閲覧することができる時期は明確でないが，本研究班としては厳重なフォローアップを行い，時機を失することなく情報を入手することが必要である．

３．１．２．抗がん剤候補に関する規制主体について：FDA における抗がん剤候補に関する規制は，従来，一般的医薬品（医療機器）候補と同様，主として化学物質を扱う CDER，主として生物学的産物を扱う CBER，主として装置を扱う CDRH により分担して行われてきた．なお，それらの組み合わせ物質については，少なくとも 2002 年末以後，前述の OCP の調整の下で規制が行われるようになっている．しかしながら，FDA においては，数年前よりはじまった機構改編が現在も断続的に行われており，抗がん剤候補を含む種々の医薬品（医療機器）候補の規制についてもその影響が及んでいる．

FDA は，2003 年の７月以後，CBER が管轄していた種々のカテゴリーに属する医薬品（医療機器）候補の規制を CDER の管轄下に移すと共に，並行して CDER の機構改編を行いつつある．CBER から CDER に管轄が移動されたものは，モノクローナル抗体，ワクチンと血液製剤を除く蛋白製剤（インターフェロンを含むサイトカイン類・血栓溶解剤等の酵素製剤・その他の新規蛋白製剤等で，植物由来・動物由来・微生物由来・リコンビナント蛋白の全てを含む），免疫修飾物質（非ワクチン・非アレルゲン性で，既存の免疫反応を抑制ないし修飾するもの），造血細胞とその機能に影響する成長因子・サイトカイン類・モノクローナル抗体などである．一方，CBER の管轄下に残されたものは，細胞またはその構成成分より成るもの，遺伝子治療用製品，ワクチン，アレルゲン性抽出物，抗毒物，血液・血清製剤およびその関連物質などである．以上の管轄移動の影響を受けて，抗がん剤候補の規制に関しては，CDER において行われる部分が増大している．しかしながら，実際の抗がん剤候補の規制は，一部がなお CBER・

CDRH の管轄下で行われており，OCP のイニシアチブによる組み合わせ物質に関する試みもあって，割り振りや共同作業について，ケースバイケースでの試行錯誤がなお続いているようである．

CDER における抗がん剤候補の規制に関連する部門としては，現在，Office of Center Director (OCD)に直属する Office of New Drugs (OND)の下に設置されている Offices of Drug Evaluations (ODEs)において，主として化学物質を管掌している DODP が ODE I に，主として生物学的産物を管掌している Division of (Therapeutic) Biological Oncology Products (DBOP) (CBER に由来) が ODE VI に，画像診断に係わる部門である Division of Medical Imaging (and Radiopharmaceutical) Drug Products (DMIDP) (小村博士による追加情報では CDER に移管されたばかりとのこと) が ODE III に，それぞれ属している．しかしながら，FDA としては，本年の５月に開始して９月に完了（同時に場所も移動）する予定で３段階に分けて進行させている CDER 改編の第２段階として，DODP・DBOP・DMIDP をそれぞれの ODEs から OND の直下に新設する Office of Oncology Drug Products (OODP)の下に移行して，OODP のイニシアチブによって抗がん剤候補の規制を一括することを企図し，まさに現在実行している最中である．したがって，FDA における抗がん剤候補の規制は，前項に述べたガイドラインの策定と併せ，機構面においても，近い将来，より整理された形で行われるものと考えられる，ただし，実際には，CDER/OODP と OCP (Center より格下の Office であるが，機構的には CDER と同格で併存) の間での調整が必要であり，CDER・CBER・CDRH 間でも CDER における OODP 体制の確立を前提とした再調整が求められ，それらの結果により将来的に一層の組織改編が考慮される可能性もあるなど，なお課題を残しているようである．

３．１．３．抗がん剤候補の非臨床試験のあり方について：抗がん剤はその作用を発現させる機序別に分類されることが多く，この作用機序別分類は抗がん剤候補の規制においても応用される．我が国における抗がん剤（候補）の作用機序別分類においては，一般に，まず「細胞毒性型」と「非細胞毒性型」に大分類した上で，それぞれについてさらなる細分類が行われている．一方，FDA/CDER/DODP としては，同様に抗がん剤候補を作用機序別に分類して取り扱うことを重要視しているものの，「細胞毒性型」と「非細胞毒性型」への大分類に意義を感じておらず，むしろそうした行為を避けるべきものと認識しているようである．彼等は，抗がん剤候補を構造的特性（低分子・抗体・アンチセンス分子・生物学的産物など）と作用機序（DNA 影響性・細胞膜影響性など）により分類し，個々の候補の規制をそれらの特性に応じて適切に組み合わせた試験結果の評価によって行うべきであると考えている．この評価にあたっては，当然ながら Good Laboratory Practice (GLP)および Good Experimental Practice (GEP)に基いた標準的試験法によるデータの質を重要視する一方，毒性のあり方にも注意を払う．たとえば，抗体やある種の生物学的産物などは，既存の非臨床安全性試験が無効であることもあるので，ヒト由来 tissue array や当該物質の類似体・類縁体など利用できる種々の手法・物質を使った試験を行うことも考慮する．また，組み合わせ物質については，繰り返して既述した OCP のイニシアチブによる調整が既に開始されていて，なお試行錯誤が続いている段階であるが，構成成分個々について検討（構成成分の一部に既知のものが含まれているかどうかが重要）した上で，全体について *in vitro* でのデータなども参考に検討しているようである．

抗がん剤の安全性審査において第１相臨床試験に入る前に必須な非臨床試験としては，FDA/CDER/DODP としても統一的な見解がないが，現時点での基本的な態度として，２種の動物を用いた 28 日間反復投与毒性試験の結果を重要視しているとのことである．この際は，第１種で全身，第２種で事前情報と第１種での結果により選択された臓器

について評価し，選択された臓器での結果が異なる場合に第２種での全身評価を行って，第１相臨床試験に入れるかどうか総合的に判断しているようである．もちろん，28 日間試験の結果によっては，第１相臨床試験開始の前に必要な別の試験の追加を要求する場合もある．

なお，抗がん剤の非臨床安全性試験としては，ある意味で当然ながら遺伝毒性と生殖毒性を重視しており，動物を用いた慢性毒性・生殖毒性併合試験を有用と考えているが，必要があれば動物発がん性試験を行うことも選択肢として排除しないとのことである．

４．結論

本出張においては，抗がん剤の非臨床安全性試験の実施手法のガイドライン等の確立に有用となる米国における現状と将来予測に係わる情報を取得することができた．本出張者としては，Dr. Leighton と Dr. Morse による御説明がきわめて多様かつ多量であったため，それらのすべてを消化しきれなかったのでないかとの危惧と反省を感じているが，これに関して，両博士から今後も追加的に御協力いただける旨を伺っているのが幸である．最後に，本出張においては，本報告書に記載した諸博士のみならず，それ以外の本研究班関係各位も含めた多くの方々の御尽力および御協力により，以上の成果を得ることができたものであり，この場に謝辞を記すものである．

付録．（北米）毒性病理学会(Society of Toxicologic Pathology, STP)年次学術集会

本年の STP 年次学術集会は，第 24 回を迎え，「Cardiovascular Toxicologic Pathology: Risk Assessment and Risk Management」を主題として，Colin Rousseaux 理事長の下に，米国コロンビア特別区ワシントン市の JW Marriott Hotel で開催された．なお，同集会のプログラムについては写を添付したが，本出張者として演題を発表していないのでその抄録等は存在しない．

同集会においては，主題が化学物質等の心血管毒性とその規制に係わることであったので，発表された諸演題の中に，今回の出張目的に直接的に関係するものがなかった．しかしながら，間接的ながら参考になるものもいくつかあり，たとえば，６月 20 日の午後のシンポジウム（「Local Delivery of a Cardiovascular Effect: Drug Eluting Stents and Other Devices」）において発表された米国食品医薬品局（U.S. Food and Drug Administration, US FDA，以下単に FDA と表記）の Office of Combination Products (OCP)に所属する Dr. Patricia Love による演題「The Regulatory Challenges of Combination Products」は，注目された．同演題は，近年増加しつつある化学物質・生物学的産物・装置などの組み合わせ物質の規制に関する FDA の取り組みについて述べたものであった．FDA は，「Medical Device User Fee and Modernization Act of 2002」法に基いて，これらの組み合わせ物質の規制を管掌させるべく，2002 年 12 月に OCP を設置した．OCP は，個々の組み合わせ物質の一義的な評価業務を従来からの規制主体である Center for Drug Evaluation and Research (CDER)・Center for Biologics Evaluation and Research (CBER)・Center for Devices and Radiological Health (CDRH)のいずれかに割り振るほか，複数の主体による評価が行われる場合の作業迅速化のための調整，各主体による評価基準の標準化と適正化，組み合わせ物質規制に関するガイドライン等の作成などを任務とする組織

である．FDA としては，組み合わせ物質に関して，OCP の管轄下に，より統合された環境でスムーズな規制を行うべく作業を進めているが，現時点において，なお試行錯誤の段階にあるとのことである．今回の発表は心血管系疾患に焦点を合わせたもので薬剤溶出性ステントを例として行われたが，近年の抗がん剤（候補）にこうした組み合わせ物質が現れてきていることより，本研究において抗がん剤の非臨床安全性試験の実施手法のガイドライン等を確立するためには今後 OCP の構想と行動について注目する必要があるものと考える．また，６月 22 日午後には，「Cardiovascular Safety Pharmacology and Modern Risk Assessment」と題するシンポジウムが行われた．本出張者は後述する FDA/CDER 訪問のため一部しか参加できなかったが，同シンポジウムにおいては主として安全性薬理学の立場からの発表が行われ，特に QT 時間延長に関する話題が中心的であった．独立行政法人 医薬品医療機器総合機構(PMDA)から FDA に出向中である小村 純子 博士（後出）によれば，最近の FDA による抗がん剤の安全性審査においては，QT 時間延長に関する問題がしばしば指摘されるという．そのことの是非について議論があるものの，本研究において抗がん剤の非臨床安全性試験の実施手法のガイドライン等を確立するにあたっては，日米（欧）の整合性を確保する意味で，考慮するべき情報かもしれない．