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**Human Challenge Trials for Vaccine Development: regulatory
considerations**

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Adopted by the Sixty-seventh Meeting of the World Health Organization Expert Committee on Biological Standardization, 17- 21 October 2016. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

This guidance document published by WHO is intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, this document may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to this document be made only on condition that the modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the principles set out below.

1. Background

Human challenge trials are trials in which participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism. This challenge organism may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner.

In July 2014, WHO held a consultation on *Clinical evaluation of vaccines: regulatory expectations (I)*. One area that was considered as an important issue for facilitating vaccine development was related to human challenge trials. It was recognized that regulation of these trials need to be well defined by the NRAs and vaccine developers and manufacturers need to be aware of regulatory expectations.

The document on human challenge trials should be read in conjunction with the updated Guidelines on clinical evaluation of vaccines: regulatory expectations, adopted by the ECBS in October 2016.

2. Scope

The scope of this document is to provide guidance to national regulatory authorities (NRAs), manufacturers, vaccine developers, investigators, independent ethics committees, and potentially biosafety committees and national agencies that regulate genetically modified organisms (GMOs) if separate from the NRA. Only issues relevant specifically to the design and conduct of clinical trials enrolling healthy adult humans capable of truly informed consent and that involve the intentional exposure and potential infection with an infectious disease organism are discussed. All other issues common to the design, conduct and evaluation (assessment) of vaccine clinical trials may be found in the document *Clinical evaluation of vaccines: regulatory aspects*, which is to be considered by the WHO Expert Committee on Biological Standardization in October 2016.

3. Introduction

Infectious human challenge studies involve deliberate exposure of human volunteers to infectious agents. Human challenge studies have been conducted over hundreds of years and have contributed vital scientific knowledge that has led to advances in the development of drugs and vaccines. Nevertheless, such research can appear to be in conflict with the guiding principle in medicine to do no harm. Well documented historical examples of human exposure studies would be considered unethical by current standards. It is essential that challenge studies be conducted within an ethical framework in which truly informed consent is given. When conducted, human challenge studies should be undertaken with abundant forethought, caution,

and oversight. The value of the information to be gained should clearly justify the risks to human subjects. Information to be gained should clearly justify the risks to human subjects.

Although human challenge trials are not a required element of every vaccine development programme, there are many reasons why a developer may request to conduct with humans a “challenge-protection” study that might normally be conducted in animals. Animal models are often quite imprecise in reflecting human disease, and many infectious organisms against which a developer might wish to develop a vaccine are species-specific for humans. Human challenge trials may be safely and ethically performed in some cases, if properly designed and conducted. Tremendous insight into the mode of action and the potential for benefit in the relevant species – humans – may be gained from challenge trials. However, there are also limitations to what challenge trials may be able to ascertain because, like animal model challenge-protection studies, a human challenge trial represents a model system. Because there are often such significant limitations to animal models, the model system of the human challenge trial may significantly advance, streamline and/or accelerate vaccine development (2).

It is important to note that not all diseases for which vaccines might be developed are suitable for conducting human challenge trials. In many cases, human challenge with a virulent or even an attenuated organism would not be considered ethical or safe. For example, if an organism causes a disease with a high case fatality rate (or there is a long and uncertain latency period) and there are no existing therapies to prevent or ameliorate disease and preclude death, then it would not be appropriate to consider human challenge trials with such an organism. However, a human challenge trial might be considered when the disease an organism causes has an acute onset, can be readily and objectively detected, and existing efficacious treatments (whether curative or palliative) can be administered at an appropriate juncture in disease development to prevent significant morbidity (and eliminate mortality).

It will also be important to consider the regulatory framework in which the human challenge trial may be conducted because, in some countries, challenge stocks are expected to be regulated in the same manner as vaccines and are expected to be studied with authorization in accordance with clinical trial regulations, whether or not an investigational vaccine is to be used in the same clinical investigation protocol. For instance, a challenge trial might be conducted to titrate the challenge organism in humans before using the challenge in a vaccine study, in order to know the proper dose of the challenge organism to give and to characterize the symptoms, kinetics, shedding, and transmissibility to be expected from the challenge. The dose of challenge organism is usually titrated to induce a relatively high attack rate while limiting disease severity. In cases when challenge should be studied in compliance with clinical trial regulations, there is greater clarity about regulatory expectations, including the quality of the challenge stock to be used, because the clinical trial regulations or requirements would apply. However, in many countries, because the challenge stock is not itself considered to be a medicinal product, such characterization/model development studies would not come under the NRA’s review and authorization. Thus, much less clarity exists on regulatory expectations and quality matters in such cases.

It should be understood that a pathogenic challenge strain will not have the “safety” of an intended safe candidate vaccine. However, its quality should be comparable to a candidate vaccine at the same clinical trial phase. Ideally, a human challenge study to establish the challenge model (i.e. without use of an investigational medicinal product) should also match the same expectations for conduct of a vaccine study – i.e. compliance with good clinical practice (GCP) and should be subject of approval or concurrence under a Clinical Trial Authorization by national regulatory authorities and ethics committees on the basis of relevant requirements appropriate for this type of studies. If such framework does not exist, countries are invited to establish an appropriate regulatory and ethical framework for challenge studies. However, there may be no regulatory framework to promulgate such expectations in the country where the challenge study is to be conducted. Trial sponsors, vaccine developers, researchers and others should determine from the relevant NRA what regulatory expectations they may have when clarity does not exist and when the human challenge study is intended to support the development of a vaccine candidate they would like to ultimately license (i.e. gain marketing authorization or registration).

4. Purposes of human challenge trials in vaccine development

HCT are considered as a model by which “challenge-protection” can be evaluated and they represent one possible approach for vaccine development.

Therefore, all principles for clinical evaluation of vaccines should apply, including approval by the NRAs and ethical committees, as well as compliance to GCP.

A vaccine developer may conduct human challenge trials to accomplish one or more of a number of aims. The aims of the study determine which clinical phase the study is in. Human challenge trials are often a type of efficacy-indicating study, but most would not be considered to be pivotal efficacy studies. Almost all would be pilot in nature, performed to gain useful information to aid in the development of a vaccine. Several challenge trials might often be performed during the course of vaccine development.

Potential purposes of human challenge trials could include one or more of the following:

- characterization of the challenge stock and model system: titration, symptoms, kinetics, shedding, transmissibility;
- clearer understanding of the pathogenesis of and immunity to the organism in order to guide decisions on what (type and/or quantity) immune responses a vaccine might need to elicit in order to protect against that disease – i.e. insight for vaccine design (studies for this purpose may be referred to as experimental medicine studies);
- identification of potential immune correlates of protection (ICPs, which would then require validation in a traditional efficacy study);

- identification of the optimal trial design for traditional pivotal efficacy trial(s) (e.g. case definitions, endpoints, study design aspects);
- generation of appropriate hypotheses to be formally tested in traditional efficacy trials;
- proof-of-concept as to whether a particular vaccine candidate might provide protection or not;
- down- or up-selection among various potential lead vaccine candidates to advance only the best to large pilot or pivotal efficacy trials and to eliminate those not worth advancement;
- de-risk or “left-shift”¹ risk of failure in a vaccine development programme;
- comparison of vaccine performance in endemic settings versus an efficacy trial population,² including evaluating the impact of prior immunity in the context of prevalent endemic diseases and conditions;
- support for emergency use of an investigational vaccine (e.g. in an influenza pandemic);
- a basis for licensure (this purpose would be a rare exception rather than the routine);
- exploration post-licensure of whether immunity to vaccination wanes, and if or when booster doses might be required for durable protection;³
- others.

No single study could accomplish all of the above aims. For instance, if the human challenge model system does not adequately mimic the wild-type disease and the situation in which a vaccine would need to protect, then a human challenge trial would not be usable as a primary basis for licensure.

5. Study design of human challenge trials

As in all studies, the aim(s) of the human challenge trial guides the study design. Consequently, even for the same disease, the challenge model may vary according to the purposes and design of the study to be conducted. In some cases (e.g. to identify appropriate efficacy trial design and case definitions), the challenge model may need to mimic wild-type disease as closely as feasible. In other cases, consideration might be given to the use of an attenuated challenge organism (e.g. a previous vaccine candidate) or a model system in which objective early signs (e.g. parasitaemia, viraemia) signal the onset of disease. These signals could trigger initiation of treatment to prevent actual disease onset or morbidity. Initiation of treatment should be based on pre-specified criteria in the study protocol.

¹ When a timeline of vaccine development is viewed as a graph from early to the left to late to the right, shifting the risk of failure earlier, or left, in the timeline could minimize risk to human subjects by not conducting large efficacy studies of vaccines that would not prove efficacious, could result in significant cost- and resource-savings and could minimize lost opportunity costs by abandoning an unpromising candidate before committing greater expenditures to higher-phase clinical trials.

² The target population in a particular country may have a higher rate of individuals with, for instance, sickle cell trait, poorer nutritional status or greater parasitic load in “normal” flora, any of which might affect immune responsiveness in the endemic setting and thus efficacy (benefit), compared to the efficacy trial population (ideal setting), or safety (greater risks). Either would have an impact on the risk/benefit decision-making.

³ This might entail a challenge study in adults to extrapolate when children might need booster doses.

Another important consideration for a human challenge model system would be its usefulness for positive or negative prediction. If used for down-selection, de-risking or to identify vaccine candidates that would not warrant advancement to large human efficacy studies, the usefulness for negative prediction should be high. If intended to be used for evidence of vaccine efficacy, the usefulness for positive prediction of the model system might need to be nearly as compelling and credible as a traditional pivotal efficacy trial might be. Whether the purpose of the study or studies is to provide supportive evidence for licensure or to help inform and design traditional efficacy studies or vaccine design, human challenge trials may contribute to the preponderance of evidence upon which regulators could take a clinical trial or licensure decision. Thus, the purpose of the study would influence the design, which would in turn influence conclusions and decisions that might be made from the study results by regulators.

6. Operational aspects

In addition to general principles for all clinical trials in human subjects, there are some unique and important operational aspects to the conduct of a human challenge trial. Human challenge trials should be undertaken in accordance with a protocol and in special facilities that are designed and operated in a manner that can prevent the spread of the challenge organism to people outside the study or to the environment. These clinical facilities should be capable of providing continuous monitoring and medical attention at the appropriate point(s) in time after the challenge is given. In addition to providing immediate access to appropriate medical care and treatment, the facilities should be designed to prevent the spread of disease, particularly when the challenge organism is a genetically modified organism or an organism that is not endemic to the locality. These facilities may need to be operated in a manner that permits all waste (including excrement) to be collected and decontaminated before release. All staff, including janitorial and administrative staff, might be required to work in personal protective gear appropriate for the pathogenicity of the challenge organism and its potential hazard to the environment. It should be noted that not all human challenge trials require such a high level of control. When the challenge organism is attenuated and the wild-type organism is likely to be present in the locality anyway, it may be adequate to conduct human challenge trials in an outpatient setting or with appropriate procedures to prevent spread (e.g. use of BCG vaccine as a challenge organism, use of bandaging that could cover and prevent spread from an intramuscular injection – so long as the organism is not shed by other means, use of malaria challenge during winter months in temperate region). There may be other circumstances for undertaking HCT. For example, when the target organism of the vaccine to be developed is not present in the location where the target group for its indication lives (eg, in case of a traveler vaccine), and when the risk of spread of the organism is low, HCT with appropriate procedure could be undertaken.

It may be necessary to ensure housing of controls and vaccinees together if an objective of the human challenge trial is to identify potential for transmissibility. In such a situation, only the vaccinees or unvaccinated participants might be challenged, and the controls, who were not

challenged, would be monitored for evidence of acquiring the challenge organism through contact with the challenged vaccinees. In this way, transmissibility of the challenge organism may be determined. In order to achieve the study objective of identifying transmissibility, it would be necessary to conduct the study in-house even if the challenge organism was attenuated and the wild-type organism was present in the locality.

It should be noted that human challenge trials have been, and can be, successfully conducted in low- and middle-income settings. The same standards would apply as in more developed countries. The investigators need to be qualified, independent ethics committee review is required, and assurance of compliance with the local NRA's requirements and regulations is needed. If relevant, assurance of compliance with the national agency that regulates GMOs, and/or local biosafety committees, may also be needed. If a controlled inpatient setting is required for the given study, this would also need to be in place.

7. Some key ethical considerations

Ethics in clinical trials include the precept of “minimizing risks to subjects and maximizing benefits”. Review of the proposed human challenge study by an independent ethics committee is essential. By their nature (i.e. intentional infection of humans with disease-causing organisms), human challenge trials would seem to contradict this basic precept. Further, clinical trials should be designed and conducted in a manner that minimizes risks to human subjects while maximizing the potential for benefit. Consideration must be given to both potential individual risks and benefits, as well as to potential societal benefits and risks, such as release into the environment of a pathogen that might not otherwise be present. Provisions in clinical trial ethics are made for situations in which there may be greater-than-minimal risk but no (or little) potential for individual benefit, when knowledge may be gained to the benefit of the larger societal population with whom the potential trial participant shares significant characteristics.

Ethical considerations about challenges in clinical trials should be thoroughly evaluated. A recent model for considering how ethical principles should be applied in human challenge trials is that from a discussion of such principles during a recent WHO Consultation. The use of placebo in vaccine trials was the main topic of a WHO Expert Consultation in January 2013 and a set of considerations for NRAs and ethics committees is provided in the WHO meeting report (3, 4). These considerations are intended to facilitate review of proposed use of placebo in vaccine trials on a case-by-case basis. Such considerations may also be useful in human challenge trials.

Acknowledgement is due to the reality that some persons are greater risk-takers than others, while some persons are quite risk-averse and would not accept the risk of receiving a challenge. The key to asking individuals to accept the risk from a challenge study, in which they have little potential to receive individual benefit, is the element of informed consent. Healthy adults may

consent when they are well-informed and understand what risks they are accepting to take, even if those risks may be considerably greater than minimal (e.g. accepting that they will develop an acute, but manageable, disease that will resolve but in the meantime may cause considerable morbidity, such as severe diarrhoea managed with fluid and electrolyte replacement). There could be some potential for direct benefit if the trial participant becomes immune to the disease caused by the challenge (or wild-type) organism but, conversely, pre-existing immunity upon exposure to wild-type virus in the future may be harmful. Thus, in appropriate situations, it may be considered ethical to ask healthy and informed adults to consent to volunteer and participate in a human challenge trial whether they will receive an investigational vaccine that may or may not protect them from the challenge organism, a placebo that will not protect them, or only the challenge organism itself. However, accepting such risks requires absolutely that the elements of voluntary consent are based on truly being informed. It is for this reason (i.e. the need for truly informed consent) that consideration of conducting human challenge studies in children, or in any other vulnerable population which would have diminished capacity to give informed consent, would not be deemed acceptable at this time. A possible exception to this principle that might be considered would be a challenge model using as the challenge organism a licensed live, attenuated vaccine.

The need to minimize risks to subjects in clinical trials calls for the investigators to give due consideration to whether or not the challenge organism need be pathogenic or not, or to what degree. As noted above, the aim or purpose of the study may drive this decision about pathogenicity or attenuation, but the ethics of minimizing – to the extent that is feasible within the frame of sound science – any risks to human subjects should also bear due consideration in this regard. Key to the considerations is the credibility of the data to support regulatory decision-making, which also needs to be taken into account when deciding how pathogenic or attenuated the challenge organism need be.

Authors and acknowledgements

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Switzerland, attended by the following participants: Dr P. Annunziato, Merck & Co., Kenilworth, United States of America; Dr N. Bhat, Program for Appropriate Technology in Health, Seattle, United States of America; Dr A. Chatterjee, Biological E Ltd., Hyderabad, India; Dr K. Chirgwin, Bill & Melinda Gates Foundation, Seattle, United States of America; Dr G. Coleman, Health Canada, Ottawa, Canada; Dr D. Tuan Dat, The Company for Vaccines and Biological Production No. 1 (Vabiotech), Hanoi, Viet Nam; Dr P.E. Fast, International AIDS Vaccine Initiative, New York, United States of America; Dr G. Foglia, Sanofi Pasteur, Swiftwater, United States of America; Dr U. Fruth, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland; Dr M. Gruber, Center for Biologics Evaluation and Research, United States Food and Drug Administration, Rockville, United States of America; Dr P.M. Heaton, Bill & Melinda Gates Foundation, Seattle, United States of America; Dr D. Kaslow, Program for Appropriate Technology in Health, Washington DC, United States of America; Dr I. Knezevic, Technologies Standards and Norms, World Health Organization, Geneva, Switzerland; Dr O. Lapujade, Prequalification Team, World Health Organization, Geneva, Switzerland; Dr Y.H. Lee, Biopharmaceuticals & Herbal Medicine Evaluation, Ministry of Food & Drug Safety, Chungcheongbuk-do, Republic of Korea; Dr D.J.M. Lewis, Institute of Biosciences and Medicine, University of Surrey, Guildford, United Kingdom; Dr A. Lommel, Paul-Ehrlich Institut, Langen, Germany; Dr J. McEwen, Therapeutic Goods Administration, Canberra, Australia; Dr V. Moorthy, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland; Dr P. Neels, Vaccine-Advice BVBA, Zoersel, Belgium; Dr M. Nijs, GlaxoSmithKline Biologicals, Wavre, Belgium; Dr S.A. Nishioka, Department of Science and Technology, Ministry of Health, Brasilia, Brazil; Dr A. Podda, Novartis Vaccines Institute for Global Health, Siena, Italy; Dr M. Powell, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Dr A. Ramkishan, Central Drugs Standard Control Organization, New Delhi, India; Dr R. Sheets, Consultant, Silver Spring, United States of America; Dr J. Shin, Expanded Programme on Immunization, World Health Organization Regional Office for the Western Pacific, Manila, Philippines; Dr P. Smith, MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, United Kingdom; Dr J. Southern, Medicines Control Council, Cape Town, South Africa; Dr Y. Sun, Paul-Ehrlich Institut, Langen, Germany; Dr K. Vannice, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland; Dr D. Wood, Technologies Standards and Norms, World Health Organization, Geneva, Switzerland; Dr Z. Yang, Office of Evaluation III, Center for Drug Evaluation, Beijing, People's Republic of China.

The draft document was posted on the WHO website for the first round of public consultation as appendix of the Guidelines on clinical evaluation of vaccines, from 30 October to 30 November 2015.

The second draft was prepared by a WHO drafting group and the document was posted on the WHO website as appendix to Guidelines on clinical evaluation of vaccines, for a second round of public consultation, from 1 February to 15 March 2016. Comments were received from: IFPMA (Dr Bonnie Brock, Sanofi Pasteur, Swiftwater, United States of America *provided consolidated comments of the International Federation of Pharmaceutical Manufacturers and Associations*); Dr Aline Rinfret, Health Canada, Ottawa, Canada and Dr. Karen Farizo, Center for Biologics

Evaluation and Research, United States Food and Drug Administration, Rockville, United States of America.

The WHO meeting of the Working Group on clinical evaluation of vaccines, held on 3 May 2016, led to the conclusion that the Guidelines on Human Challenge Trials should be provided as a separate document instead of an appendix to the Guidelines on clinical evaluation of vaccines. The meeting was attended by the following participants: Dr Gina Coleman, Health Canada, Ottawa, Canada; Dr Mimi Darko, Food and Drugs Authority, Accra, Ghana; Dr Daniel Etuko, National Drug Authority, Kampala, Uganda; Dr Elwyn Griffiths, Consultant, Kingston Upon Thames, United Kingdom; Dr Stephen Kennedy, University of Liberia, Monrovia, Liberia; Dr Ivana Knezevic, Technologies Standards and Norms, World Health Organization, Geneva, Switzerland; Dr John McEwen, Therapeutic Goods Administration, Canberra, Australia; Dr Mair Powell, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Dr Rebecca Sheets, Consultant, Silver Spring, United States of America; Dr Yuansheng Sun, Paul-Ehrlich Institut, Langen, Germany; Dr Kathryn Zoon, National Institutes of Health, Bethesda, United States of America; Dr James Southern, Medicines Control Council, Cape Town, South Africa.

Based on the comments received during the public consultation and the discussion of the Working Group on clinical evaluation of vaccines, on 3 May 2016 at the World Health Organization, Geneva, the document WHO/BS/2016.2287 entitled “Human Challenge Trials for Vaccine Development: Regulatory Considerations” was prepared by Dr Rebecca Sheets and Dr Ivana Knezevic.

A third public consultation was conducted from 27 July to 16 September 2016. During that period, document was posted on the WHO biologicals web site and comments were received from: Dr Douglas Pratt, Center for Biologics Evaluation and Research, United States Food and Drug Administration, Rockville, United States of America; Dr Marion Gruber, Center for Biologics Evaluation and Research, United States Food and Drug Administration, Rockville, United States of America; Dr Joachim Auerbach, GSK Vaccines Institute for Global Health, S.R.L., Siena, Italy; Dr Audino Podda, GSK Vaccines Institute for Global Health, S.R.L., Siena, Italy; Dr Patricia Njuguna, KEMRI Wellcome Trust Research Programme, Kilifi, Kenya; Dr Peter Smith, London School of Hygiene and Tropical Medicine, London, United Kingdom.

Taking into account comments from the Expert Committee on Biological Standardization and the participants of the ECBS meeting held in October 2016, document was finalized.

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