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Review

Use of controlled human infection models (CHIMs) to support vaccine development: US regulatory considerations

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ABSTRACT

In 2016, the United States (U.S.) Food and Drug Administration (FDA) licensed Vaxchora® for active immunization against disease caused by *Vibrio cholerae* serogroup 01 in adults. Vaxchora was the first US-licensed vaccine for which the primary evidence supporting effectiveness was derived from human challenge studies. Following this precedent, FDA has received numerous inquiries from manufacturers, academic researchers, funders and other stakeholders regarding how controlled human infection models (CHIMs) can be used to support the development of safe and effective vaccines to address public health needs. The aims of this article are to discuss: (1) Chemistry, Manufacturing and Controls (CMC) for challenge inocula, (2) conduct of controlled human infection studies under US IND and (3) use of CHIMs to support vaccine development. General concepts and regulatory considerations for the safe conduct of CHIMs and use of CHIMs to evaluate vaccine effectiveness are discussed.

Contents

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1. Introduction

Development of investigational vaccines frequently includes extensive pre-clinical and early phase clinical studies followed by implementation of large and complex Phase 3 studies to assess prevention of disease. This approach to vaccine development has limitations. For example, when the decision to advance a vaccine candidate to a Phase 3 clinical endpoint (field) study is based on immune markers (e.g., seroconversion rate or geometric mean antibody titers), the study may fail if the measurable immune markers do not correlate with, or reliably predict, protection from disease. In addition, field studies may not be feasible due to low incidence of disease (e.g., when outbreaks of disease wane before adequate and well-controlled clinical trials can be conducted) [1].

Recently, there has been increased interest in the role that controlled human infection models may have in advancing vaccine development [2]. Controlled human infection models (CHIMs) are studies in which human volunteers are deliberately infected with a well-characterized pathogen in a controlled manner while being closely monitored. To date, CHIMs have been developed for a broad variety of infectious diseases including influenza, respiratory syncytial virus, malaria, Cryptosporidium, cholera, norovirus and dengue [3]. Respiratory syncytial virus (RSV) CHIMs have been used to define the pathogenesis and clinical course of disease in healthy adults [4]. Dengue CHIMs have the potential to explore basic mechanisms responsible for enhanced disease [5]. Such studies provide a unique opportunity to directly understand disease pathogenesis, protective immune response in humans, and the efficacy of investigational candidates against challenge strains. When performed in an ethical and safe manner in accordance with Good Clinical Practice, such studies have the potential to provide data that can advance vaccine development and support licensure. CHIMs can facilitate identification of the most promising vaccine candidates to evaluate in Phase 3 field studies. Later in development, CHIMs have the potential to identify immune markers that can be used to support regulatory decisions, provide supportive data on efficacy against specific strains to be used in conjunction with a clinical endpoint study, or, in certain select circumstances, to provide primary evidence of effectiveness to support product licensure. As an example, in 2016, the United States (U.S.) Food and Drug Administration (FDA) licensed Vaxchora® for active immunization against disease caused by *Vibrio cholerae* serogroup 01, for use in adults 18 through 64 years of age traveling to cholera-affected areas [6,7]. Vaxchora was the first US-licensed vaccine for which the primary evidence supporting effectiveness was derived from human challenge studies.

The purpose of this article is to review U.S. regulatory considerations related to: (1) Chemistry, Manufacturing and Controls (CMC) for challenge inocula, (2) the conduct of controlled human infection studies under US IND, and (3) the use of CHIMs to support clinical development of investigational vaccines. This discussion does not establish data requirements or articulate agency policy or guidance regarding specific vaccine development programs or CHIMs.

2. Chemistry, manufacturing & controls (CMC) for challenge inocula

CMC considerations for challenge strains, although broadly similar to those for biologic products, are different in a few important ways. CMC for a vaccine product, for example, is expected to evolve through product development. While an investigational vaccine used in early phase studies might be produced at a small scale with characterization using non-validated assays, the manufacturing process and quality control testing are further optimized and validated to produce product for use in later phase studies and are expected to be finalized before licensure. In contrast, the method of preparation of a challenge inoculum is unlikely to change significantly throughout its use under IND. The inocula are often prepared on a smaller scale and on an as-needed basis. In some cases, the challenge organism is not culturable and must be prepared from infected material. For all of these reasons, preparation of challenge inocula according to the cGMP that is typical of late phase and commercial biologic product manufacture may not be appropriate, and in some cases may not even be feasible. Several aspects of CMC for challenge inocula are discussed below that, when properly implemented, will facilitate the development of inocula for use in challenge studies conducted under IND in a manner that is safe, as well as robust and consistent.

2.1. Strain selection and characterization

Prior to initiating a challenge study in humans, significant consideration should be given to selection of the challenge strain(s). If candidate challenge strains differ in virulence, the expectation is that the least virulent strain that will serve the goals of the challenge study would be used. An important factor in strain selection is the goal(s) of the challenge model (e.g., proof of concept versus definitive demonstration of effectiveness; demonstration of homologous versus heterologous protection; study of pathogenic mechanisms).

Characterization begins with the provenance of the candidate challenge material. The original source of a pathogen is likely to be a patient, and any information about the clinical presentation of that patient and other aspects of the clinical context is of value. Passage history of the challenge strain should be documented, including identification of the growth medium and other raw materials used in its isolation and passage, or in some cases, relevant information about animals used for propagation. Phenotypic characterization will vary depending on the nature of the pathogen. Generally, the presence of specific virulence factors and the range of antimicrobial susceptibility should be well-documented. Genotypic characterization (full genomic DNA sequencing) of the challenge strain should be provided. Such data complement phenotypic analyses, both for virulence factors and antimicrobial resistance. In addition, this information documents the integrity of genetic modifications to challenge strains and can be used to differentiate between the challenge strain and other strains that might be implicated in natural infection (e.g., by the presence of specific single nucleotide polymorphisms).

2.2. Microbial purity

Although a known pathogen is intended to be administered to human volunteers, it is important to establish that other contaminating pathogens are not being administered. For live bacterial preparations, which by their nature cannot be sterile, compendial assays such as USP < 61> (Microbial Examination of Nonsterile Products: Microbial Enumeration Tests) and USP < 62> (Microbial Examination of Nonsterile Products: Tests for Specified Microorganisms) have been used. Such culture-based approaches have limitations which depend, in part, on the growth requirements of the challenge strain. If modifications of these tests can be made that inhibit growth of the challenge strain, they will have greater discriminating ability. Other approaches, such as nucleic acid testing using DNA primers targeting specific potential contaminants of concern, may be appropriate (e.g., when other strains are manipulated in the facility where the challenge inocula are manufactured).

For use of virus-based challenge materials, methods described in the *FDA Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications* [8] could be useful in assuring the absence of adventitious agents, as might the use of next-generation sequencing (massively parallel sequencing).

2.3. Potency testing

Administration of hyper-potent doses of challenge inocula could lead to significant unanticipated morbidity. Conversely, the consequence of administering a sub-potent challenge may be that no useful information is derivable from the challenge study and that volunteers will have been placed at risk without justification. Therefore, potency is a critical parameter for challenge strain preparations. For bacterial challenges, potency will likely be measured in terms of colony forming units per dose, and for viral and/or parasitic challenges in terms of infectious particles or organisms per dose. In all cases the selected target dose should balance safety of the volunteers with an "attack" rate based on clinical response to the challenge inocula that will support the objectives of the proposed challenge study.

2.4. Stability

Stability is determined by assessment of potency and purity over time. Acceptable parameters for challenge inoculum stability are context dependent. In some cases, CHIMs may be performed using a standardized pre-manufactured inoculum that is stored under suitable conditions until use. In these cases, a stability program should include purity and potency testing at specified intervals. In cases where the challenge inoculum is prepared fresh after growth from an aliquot of a cell or virus bank, or harvested after growth in live animals, it is advisable to demonstrate that the challenge inoculum maintains its potency during the period between its preparation and its administration. In both pre-prepared and freshly prepared scenarios, a potency determination of the inoculum at the time of administration is desirable and will serve to verify the actual dose delivered. Also, for both scenarios CMC should include periodic testing of purity and potency of the cell or virus banks, if applicable. For challenge strains that have been genetically modified, demonstration of the integrity of the modifications should be integrated into the stability and pre-challenge testing program.

3. Conducting controlled human infection studies under US IND

In the US, studies in which a live organism is administered to human subjects are required to be conducted under an Investigational New Drug Application (IND) [9]. The basis for this determination is that the organism is intended to affect the structure or function of the body and therefore meets the definitions of a biological product (21 CFR600.3(h)) and a drug (201(g)(1) of the FD&C Act). As is the case for all studies conducted under U.S. IND, CHIM studies should be conducted under the provisions of Good Clinical Practice [10]. In some cases, it may be advantageous for a sponsor of a challenge study to submit an IND Master File [11], under which relevant information (e.g., CMC information on the challenge strain; data from previous clinical studies) can be organized and used to support studies by multiple sponsors under different INDs via cross-referencing, with permission of the Master File sponsor. However, submission of an IND Master File is not a requirement; CHIM studies using a specific challenge strain can be conducted under one IND.

3.1. Safety evaluation of the controlled human infection model

Careful assessment of the expected risks associated with exposure to the challenge organism is a critical component of preclinical evaluation of a CHIM. Sponsors should provide with the IND submission adequate information to assess risks to subjects in the proposed studies (21CFR312.42). For controlled human infection studies, sponsors should include: (1) a description of possible risks to be anticipated based on clinical manifestations associated with natural infection and (2) data from prior clinical studies conducted with the challenge strain, if available. When a challenge strain has been attenuated, data from preclinical studies in relevant animal models may provide additional information regarding risks and the potential for severe or serious outcomes. Such data could support initiation of a Phase 1 clinical study with the challenge strain.

Sponsors are encouraged to seek pre-IND meetings with FDA to obtain early feedback on the design of the proposed study from a safety perspective [12]. Although the specific approach will depend on factors such as the challenge pathogen being administered and the study population and location, certain general considerations apply. For example, sponsors should provide data to justify the selection of the starting dose of the challenge inoculum. Staggered escalation of the challenge dose, with safety review between dosing cohorts, can enhance the safe conduct of the study. Eligibility criteria for human challenge studies should exclude persons at increased risk for complications following challenge (e.g., immunocompromised individuals). In certain cases, development of appropriate eligibility criteria may require recognition and management of pathogen-specific risks (e.g., gallbladder disease and increased risk of chronic carriage with *Salmonella typhi*) [13].

Pre-specifying clinical symptoms that prompt specific interventions (e.g., early antimicrobial drug treatment) can reduce the likelihood that volunteers are exposed to serious risks. In cases where effective interventions are not available (e.g., for some virus challenge models), investigators should provide evidence (based on a detailed assessment of wild-type disease in healthy adults and any other relevant data) that the challenge model can be conducted with minimal risk of long-term sequelae. In cases where effective interventions are available, investigators should design the model such that intervention occurs at the earliest stage of infection at which useful clinical data can be obtained and significant and unreasonable risks are avoided. For example, in a malaria CHIM, most clinical/scientific questions can be addressed by monitoring subjects only until they become parasitemic and not waiting until they become symptomatic; thus, it is reasonable to anticipate that for most studies using a malaria CHIM, antimalarial treatment should be initiated when parasitemia is detectable. In contrast, for many bacterial enteric disease models, an assessment of shedding of the challenge strain in stools may have little scientific/clinical value because it may not correlate well with clinically important outcomes; thus, it may be reasonable to observe subjects through a period of manifestation of clinical disease. In all cases, a strong rationale should be provided for the timing and composition of interventions, the length of follow up after treatment and/or resolution of symptoms, and the plan for verifying that subjects do not relapse or develop late infectious sequelae as a result of the challenge. An additional strategy to reduce risk to study volunteers involves pre-specifying criteria in the clinical protocol (i.e., number and type of adverse events related to the challenge) that would prompt halting the study for safety review.

Systematic monitoring, recording, and reporting of safety data during human challenge studies is subject to the same requirements as for other IND studies. Sponsors have a responsibility to conduct ongoing safety evaluations, including periodic review and analysis of safety data, as well as to update consent forms, protocols and the Investigator's Brochure. The sponsor must notify FDA and all participating investigators of potential *serious* risks as soon as possible but no later than 15 days after receiving the safety information and determining that it qualifies for expedited reporting [14].

3.1.1. Controlled human infection studies in females of reproductive potential

In the absence of a compelling rationale and justification, pregnant women, lactating women and women actively trying to become pregnant should be excluded from controlled human infection studies. Females of reproductive potential should be counselled on the potential risks of participating in challenge studies and take precautions to prevent pregnancy. At least two forms of contraception, including a long-acting contraceptive, may be sufficient for CHIM studies using most challenge organisms. However, additional measures may be required for studies involving challenge with pathogens known to be associated with congenital infection (e.g., Zika virus). As with all clinical research, females of reproductive potential should be screened for pregnancy prior to enrollment and monitored throughout the study using sensitive markers (e.g., serum human chorionic gonadotropin (hCG)) with a plan to avoid infectious challenge in the event of pregnancy. All pregnancies exposed to challenge organisms should be followed to assess the pregnancy outcomes.

3.1.2. Managing the risk of environmental transmission

Infectious pathogens may have the potential to be transmitted horizontally to third parties such as household members, study staff, the community, and to the environment. The FDA routinely considers the environmental impact of CHIMs conducted under IND (21 CFR Part 25). Ordinarily, a request for FDA action on an IND is categorically excluded from the requirement to submit an EA (21 CFR 25.31(e)), unless extraordinary circumstances indicate that the specific proposed agency action may significantly affect the quality of the environment (see 21 CFR 25.21). Thus, in some cases (for example the CHMI clinical trial is closely monitored and is limited to a designated study group), FDA action on an IND for a CHMI study will not significantly affect the quality of the environment and an EA is not required to be submitted. However, if there are "extraordinary circumstances" that indicate that FDA action on an IND may significantly affect the quality of the environment, then the categorical exclusion will not apply and the Agency will require preparation and submission of an EA (21 CFR 25.21).

The potential for environmental transmission may influence the study setting as well as the need to institute specific precautions to mitigate this risk. For example, it may be important to conduct the study in a clinical research unit and ensure that study staff use protective gear for the period during which volunteers are infectious. In these cases, it may be necessary to screen participants for shedding/infectivity prior to discharge. For challenge studies considered appropriate to conduct in outpatient settings, it may be necessary to exclude volunteers with household members who may be at risk for infectious complications (e.g., immunocompromised, older adults, young children, pregnant women) or who work in professions that place them at increased risk for subsequent transmission (e.g., health care workers, food handlers).

3.1.3. Ethical considerations

Since CHIM studies performed in the US are required to be conducted under IND, federal regulations regarding the safety and protection of subjects (21 CFR parts 50, 56, and 312) apply to these studies. A cornerstone of subject protection under these regulations is the requirement that studies are subject to approval by an Institutional Review Board (IRB), or for study sites outside the U.S. approval by a comparable independent ethics review committee (IEC). Among other considerations, IRB/IECs are charged with ensuring that risks to subjects are minimized and that the risks are reasonable when weighed against the anticipated benefit to the subject (if any) and against the importance of the knowledge that may be expected to result from the study.

FDA's function is complementary to the IRBs' in that one of FDA's primary objectives in reviewing a clinical protocol submitted to an IND is to assure the safety and rights of subjects (21CFR312.22). When human subjects would be exposed to an "unreasonable and significant risk of illness or injury," the FDA has the authority to issue a clinical hold. A clinical hold is an order to delay a clinical investigation or to suspend an ongoing investigation (21CFR312.42).

The conduct of CHIMs in certain populations (e.g., older adults, immunocompromised, pregnant women, children) raises ethical questions when there is a risk for serious harm and/or the study volunteer(s) cannot appreciate the risks well enough to make a fully informed decision. For children, additional safeguards dictate that administration of an investigational agent must offer a prospect for direct benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit balance must be at least as favorable as that presented by accepted alternative treatments (21CFR50, Subpart D). For example, the risks associated with a CHIM study of wild-type influenza infection in children do not appear to be reasonable, minimized, or justified by social value. By contrast, a live attenuated influenza virus vaccine (LAIV) has been administered to pediatric populations as a "challenge" to study the immunology of influenza infection and to identify immune correlates of protection in children [15]. In this manner, pediatric CHIM studies using the licensed live attenuated influenza virus (LAIV) vaccine could meet the 21 CFR Subpart D criteria if conducted in an ethical and safe manner and in accordance with Good Clinical Practice.

Ethical considerations for CHIM studies can be context-dependent. Differences in incidence and transmission of an infectious disease could lead to regional differences in benefit-risk assessment [16]. For example, in a region with a high burden of morbidity due to an infectious disease, a local IRB, IEC or national regulatory authority might find that the potential benefit derived from a CHIM study of that disease outweighs the potential risks to local subject volunteers if they determine that infection with the challenge organism does not pose an unacceptable risk to study participants and might confer direct benefit (e.g., protective immunity to wild-type infection) or yield knowledge that can accelerate development of a vaccine. In contrast, in a region with no transmission or disease burden, an IRB, IEC or national regulatory authority might conclude that benefit-risk assessment is unfavorable for a CHIM study of the same infectious disease.

Because the potential benefits and risks of controlled human infection studies can be variable and dependent on specific details, it is rarely useful or appropriate to conclude *a priori* that broad categories of CHIM studies are ethical (or unethical). FDA's approach to the evaluation of CHIM study proposals is case-specific. When proposals to conduct controlled human infection studies under US IND raise ethical issues, FDA may consult with medical ethicists as appropriate. While safety is the primary consideration, and

action (e.g., clinical hold) may be necessary if risks to subjects are unreasonable and significant, FDA is committed to working with investigators to identify and establish safety surveillance and risk mitigation strategies that enable controlled human infection studies to proceed when scientifically and ethically justified, and with appropriate subject protections.

3.2. Use of CHIMs to support clinical development of investigational products

Vaccine efficacy studies conducted in the field are subject to multiple limitations and challenges. Disease incidence may be low, and/or transmission dynamics may be unpredictable. The clinically asymptomatic period between inoculation and disease expression usually precludes identification of exposed individuals and characterization of immune status both pre- and post-infection. CHIMs can be powerful tools to overcome these and other challenges.

Since CHIMs take considerable time and effort to develop, it is important to consider at the outset how the CHIM will be used to evaluate the investigational vaccine. When submitting a protocol for a controlled human infection study to be conducted under IND, sponsors should state their objectives and explain how data obtained from the CHIM study will support clinical development. When CHIMs are developed by entities other than vaccine manufacturers, communication between these entities, vaccine manufacturers, and regulators may improve the likelihood that the CHIM will enhance the efficiency of vaccine development. In early stages of development, CHIMs can lead to an improved understanding of disease pathogenesis and/or protective immune responses in humans to inform rational vaccine design. CHIMs can also facilitate identification of the most promising vaccine candidates to evaluate in Phase 3 field studies. CHIMs can be utilized to identify immune markers that can be used to support regulatory decisions. For example, influenza challenge studies in adults corroborated the association between serum hemagglutination inhibition antibody (HI) titers $\geq$ 1:40 and protection from influenza disease [17]. This enabled the licensure of numerous seasonal inactivated influenza vaccines via FDA's accelerated approval pathway through use of HI titers as a surrogate marker reasonably likely to predict clinical benefit [18]. Controlled human infection studies can also provide supportive data on vaccine efficacy against specific strains that can complement data from clinical disease endpoint studies. In certain select circumstances, controlled human infection studies can provide primary evidence of effectiveness to support product licensure (see Section 4.1).

Once the purpose of the CHIM has been determined, a critical next step is to establish the clinical parameters of the model, such as a reproducible attack rate and severity of disease in response to a precisely measured and delivered inoculum. Typically, a placebo-controlled dose (inoculum) escalation study is necessary to accomplish this goal. A placebo group is important because the clinical outcomes in a CHIM study are usually not binary but are instead defined by a spectrum of severity of disease manifestations. For example, one of the endpoints for a CHIM of an enteric pathogen is the difference between study groups in the volume of stools. Thus, a placebo group provides a baseline for characterizing the attack rate and the severity of disease.

The initial validation study(ies) for a CHIM model should be designed to characterize the duration of disease, response to rescue therapy (if relevant/necessary), and the kinetics and compartments of pathogen replication. Additional considerations may be important, depending on the intended use of the model. For example, if the goal is to demonstrate efficacy of a vaccine intended for travelers to a region endemic for the targeted disease, the challenge model should be validated in subjects with no history of exposure to the disease.

4. Evaluation of vaccine effectiveness to support a biologics licensing application

4.1. Use of CHIM(s) to provide primary evidence of vaccine effectiveness

For approved drugs and biological products, all indications must be supported by substantial evidence of effectiveness (21CFR201.57(2)(v)) 21CFR312.126(b). The gold standard for demonstrating effectiveness of an investigational vaccine is a prospective, randomized, double-blind, controlled field study, wherein the control arm receives a placebo (or active control) and the primary endpoint is prevention of clinical disease following natural exposure to an infectious pathogen. Therefore, the rationale for relying on a CHIM to provide primary evidence of vaccine effectiveness will depend, in part, on the feasibility of conducting a field study. When the sponsor considers a field study to be infeasible, and evidence submitted to the IND are adequate to support this assertion, CHIM studies are among the alternative approaches for demonstrating effectiveness that can be considered. As an example, when the cholera vaccine, Vaxchora, was in late phase development, CBER accepted the sponsor's position that clinical field study(ies) in the target population (cholera-naïve travelers to endemic areas) would be infeasible. In this case, the sponsor provided evidence and analysis indicating that a study powered to demonstrate efficacy in the target population would be too large because the attack rate is so low. If sponsors believe that clinical endpoint field study(ies) for their candidate vaccines are infeasible, they are encouraged to support their assertion with information and data that could include multiple lines of evidence, such as the epidemiology/geography/seasonality of disease, clinical manifestations and natural history of disease, characterization of the target population, availability of other preventive and/or therapeutic options, standard-of-care in the region where studies could be conducted, predicted efficacy of the vaccine, and sensitivity/specificity/accuracy of available diagnostic tests.

Whether a CHIM can be used for the primary study(ies) to demonstrate effectiveness of an investigational vaccine will also depend on the strengths and limitations of the model in the specific context of clinical development (e.g., indication being sought, intended population). Perhaps the most important fundamental issue that sponsors should address is the question of how well the CHIM recapitulates wild-type infection and/or disease. Considerations include:

1. the extent to which the route of administration of the challenge inoculum reflects the natural exposures that lead to infection in the field;
2. how well the challenge strain(s) reflects the diversity of clinically relevant strains in circulation;
3. the relevance of the clinical outcomes observed in the model, considering that ethical and/or safety considerations may limit the spectrum of disease manifestations that can be induced in the CHIM; and
4. the degree to which pre-existing immunity may impact response to the investigational vaccine and/or manifestations of infection in the CHIM model [19].

In a case where the sponsor proposes to use a CHIM as the sole source of effectiveness data to support licensure, those data will be required to meet FDA's standard for substantial evidence of effectiveness [20]. (It is important to note that the topic of demonstrating safety of an investigational product is beyond the scope of this

paper. Sponsors are encouraged to consider this issue when planning clinical development, because on their own, CHIM study(ies) necessary to support effectiveness of an investigational product are unlikely to be sufficient to establish safety for the purpose of a licensure application.) Substantial evidence consists of adequate and well-controlled studies, the attributes of which are described in regulations and guidance (21CFR314.126). Typically, more than one adequate and well-controlled study is required because of the importance of independent substantiation of experimental results. For vaccines, there are examples where one efficacy study was sufficient to support a licensure application, in part because vaccine trials are frequently very large, they demonstrate consistency across subject subgroups, and they are designed to demonstrate highly significant results, both clinically and statistically. With respect to the CHIM approach, one efficacy study could potentially be sufficient, particularly if it were designed to demonstrate effectiveness in more than one subgroup and/or at more than one time point after vaccination, but this should not be assumed, as this decision is necessarily case-by-case and must consider many factors.

Even when efficacy data derived from an adequate and well-controlled controlled human infection study have been accepted to support licensure, the limitations of the CHIM may have implications for product labeling. For example, since the primary data for effectiveness for Vaxchora® were from a cholera challenge study conducted in healthy cholera-naïve volunteers in the U.S., these data did not establish the effectiveness of the product in persons living in cholera-affected areas and persons with pre-existing immunity. Section 1.1 of the U.S. package insert for Vaxchora® describes limitations of use regarding the effectiveness of Vaxchora in these populations, and CBER's Summary Basis for Regulatory Action (SBRA) explains the rationale for this approach in detail [7].

4.2. Bridging studies

Due to the complex safety and ethical issues frequently associated with their use, controlled human infection studies are typically conducted in healthy adults. When the proposed indication of the vaccine includes a population that differs in clinically important variables (e.g., age, previous exposure to the relevant disease) from the one in which efficacy was established, a strategy for bridging effectiveness of the product to these populations may be necessary. In this case, it is important to consider an appropriate immune marker to evaluate when designing controlled human infection studies. Such considerations will inform the timing of blood draws and clinical testing, ensure that samples are stored appropriately to enable specific types of assays, and guide the approach to assay validation. The goal is to develop data demonstrating a statistically rigorous association between immune markers measured by a well-validated assay and clinically meaningful outcome(s) following infection.

Bridging studies should be of sufficient size to evaluate prespecified statistical success criteria for demonstrating adequacy of immune responses in the new population compared with those in the population in which efficacy was established. It is important to note that a bridging study intended to evaluate immune responses may not be of adequate size to demonstrate safety in the relevant population. Therefore, additional studies may be required to achieve an adequate safety database to support licensure.

5. Summary

Prior to initiating development of a CHIM, significant consideration should be given to selection of the challenge strain(s) to ensure the ability to terminate infection, if treatable, and to balance virulence with ability to provide informative value. Microbial purity to ensure lack of contaminating pathogens, and consistency of dosing to ensure administration of a dose shown to be tolerable in the trial, should be demonstrated. Safety and effectiveness in the context of challenge with a known pathogen relies on establishing potency within a narrow range and stability of the challenge inoculum over time to consistently provide the appropriate dose and therefore a consistent attack rate. In the US, CHIM studies are required to be conducted under IND. Federal regulations regarding the safety and protection of human subjects apply to these studies. Systematic monitoring, recording, and reporting of safety data following challenge is an important aspect of conducting CHIM studies. CHIMs can enhance development of an investigational vaccine at various stages during development. The decision to develop a CHIM to provide primary or supportive evidence of effectiveness of a product may depend on the feasibility of conducting a field efficacy study and on the strengths and limitations of the challenge model. Because of the complex considerations related to the use of CHIMs to support development of investigational vaccines, early and frequent interactions between FDA and vaccine sponsors are crucial to enhance efficient product development.

Declaration of Competing Interest

None.

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