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COMMENT

Novel licensure pathways for expeditious introduction of new tuberculosis vaccines: A discussion of the adaptive licensure concept

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SUMMARY

The ultimate goal of vaccine development is licensure of a safe and efficacious product that has a well-defined manufacturing process resulting in a high quality product. In general, clinical development and regulatory approval occurs in a linear, sequential manner: Phase 1 – safety, immunogenicity; Phase 2 – immunogenicity, safety, dose ranging and preliminary efficacy; Phase 3 – definitive efficacy, safety, lot consistency; and, following regulatory approval, Phase 4 – post-marketing safety and effectiveness. For candidate TB vaccines, where correlates of protection are not yet identified, phase 2 and 3 efficacy of disease prevention trials are, by necessity, very large. Each trial would span 2–5 years, with full licensure expected only after 1 or even 2 decades of development. Given the urgent unmet need for a new TB vaccine, a satellite discussion was held at the International African Vaccinology Conference in Cape Town, South Africa in November 2012, to explore the possibility of expediting licensure by use of an "adaptive licensure" process, based on a risk/benefit assessment that is specific to regional needs informed by epidemiology. This may be appropriate for diseases such as TB, where high rates of morbidity, mortality, particularly in high disease burden countries, impose an urgent need for disease prevention. The discussion focused on two contexts: licensure within the South African regulatory environment – a high burden country where TB vaccine efficacy trials are on-going, and licensure by the United States FDA –a well-resourced regulatory agency where approval could facilitate global licensure of a novel TB vaccine.

1. Background

TB remains a leading cause of morbidity and mortality in most of the developing world [1]. The emergence of extensively drug-resistant TB (XDR-TB) and disease rates that are slow to decline despite the implementation of TB control programs of varying effectiveness, in regions where the epidemic hits the hardest, make a compelling argument for the expeditious introduction of a novel preventive vaccine [1,2]. The only vaccine currently licensed for prevention of TB is BCG, which has variable protective benefit in the prevention of pulmonary TB, with waning protective benefit over time and little or no effect on repeat administration [2,3]. The need for improvement is clear and several new vaccines are under development [3]. Many important steps are currently underway that may lead to a novel TB vaccine, but important downstream requirements are just beginning to be addressed. Among them is vaccine manufacturing, which will need to be scaled up with substantial modifications to formulations and presentations for administration of the vaccine prior to routine use. Most importantly there is an expectation that efficacy will be confirmed in large phase 3 trials, perhaps in different regions [4]. This work may take years following completion of a successful phase 2 study, even utilizing an adaptive phase 2/3 trial design, which permits prespecified changes in certain specific aspects of the conduct of a

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study, based on the results of interim evaluations previously discussed with and agreed to by relevant regulatory authorities [4].

Conventional regulatory pathways could delay vaccine licensure and utilization for many years, potentially leaving high-risk populations vulnerable to on-going pathogen exposure and development of disease. In light of this challenge, the concept of "adaptive licensure" has been invoked in an effort to create a more flexible and potentially more efficient regulatory pathway to licensure [5]. Adaptive licensure is distinguished from adaptive design [4] as the former refers to the creation of a new regulatory pathway while the latter addresses the actual conduct of a specific clinical trial. Conceptually, adaptive licensure offers the potential for permitting early access to new vaccines in specific countries under careful regulatory control while providing opportunities for development of additional information on the safety and efficacy of the vaccine to permit the future widening of the product's indication [5,6]. For example, after a successful phase 2b trial and initiation of confirmatory clinical trials, an adaptive licensure approach could be used to allow early, limited licensure of a vaccine. This limited licensure would be conditional on subsequent submission of final data from these trials. An early approval of this type would:

- Provide access to a novel vaccine for specific populations, e.g. adolescents
- Simultaneously allow completion of a more robust phase 3 efficacy study or an effectiveness study with controlled use in selected areas with enhanced surveillance
- Include safety data of the vaccine from target populations closely monitored at an early stage of use

Such a process has not been extensively explored with regulators to date. In addition, a number of critical questions about the adaptive licensure mechanism need to be addressed, including: [1] would this approach require implementation of a new regulatory policy or does the relevant regulatory body already possess the required authority? [2] How should efficacy, effectiveness and safety be assessed utilizing an adaptive licensure approach? [3] What groups should be involved in planning and implementing an adaptive licensure strategy? [4] While an adaptive licensure process might be desirable for high TB disease burden countries such as South Africa, where efficacy trials are predominantly conducted, registration by this process could impact licensure in other countries or regions. These questions and other topics were addressed at a satellite meeting of stakeholders attending the International African Vaccinology Conference in Cape Town, South Africa, in November 2012 [7]. Discussions focused upon the main challenges to be considered when considering a novel regulatory strategy, such as adaptive licensure, for a novel TB vaccine.

2. Application of existing mechanisms for expedited licensure to vaccines

Several mechanisms have been developed to overcome limitations to accessing investigational products. For example, compassionate use and expanded access programs have long allowed infrequent pre-licensure use of life-saving medicines [8]. Beyond compassionate use mechanisms, existing regulatory pathways to licensure of a new medicine can differ considerably depending on the urgency of the medical need. When there is a serious unmet medical need that is potentially treatable with the new medicine, the development and approval processes may be shortened significantly by making use of a number of regulatory options existing within traditional regulatory pathways [8]. At the United States (US) Food and Drug Administration (FDA), these options include: (i) fast track designation; (ii) priority review designation, and (iii) breakthrough therapy designation [9,10]. Additionally, the accelerated approval regulations (21 CFR 601 Subpart E for biological products) permit a vaccine developed to prevent or ameliorate a serious or life threatening illness, such as TB, to be granted licensure based on efficacy data from a surrogate endpoint shown to be reasonably likely to predict clinical benefit [11]. Licensure under the accelerated approval pathway may be conditional, whereby the sponsor may be required to conduct post-marketing trials to verify and describe the drug's clinical benefit [11]. For neglected tropical diseases that are not typically endemic to the U.S. such as TB, a US FDA guidance document also discusses principles for developing vaccines to protect against global diseases [12,13]. In the European Union (EU), European Medicines Agency (EMA) regulatory mechanisms include: (i) Conditional Approval; (ii) Exceptional Circumstances, and (iii) Accelerated Assessment [14]. In the EU, Conditional Approval is similar to the accelerated approval regulation used by the FDA but the circumstances are less specifically prescribed. Many regulatory agencies also have mechanisms for providing early advice on product and clinical plans which is particularly important for the clinical testing of novel vaccines for global diseases like TB [13,14].

In addition to these official mechanisms for making important medicines more readily available, the approval process itself may also reflect the human element of care and concern. For example, in 1996 the FDA approved one of the first protease inhibitors for HIV in just 6 weeks, significantly faster than the officially mandated timeline for priority review (6 months) and certainly much faster than the average approval time [15]. The rapid approval of new drugs for the treatment of AIDS continues to demonstrate the type of flexibility that regulators can provide when there is a serious need for expediency [15].

Regulatory schemes that provide needed medicines to the patient most expeditiously are generally associated with some type of abbreviated or provisional approval, typically based on phase 2 or early phase 3 clinical data, using surrogate markers or a less rigorous clinical outcome [16]. The availability of a clinically confirmed surrogate endpoint, the strength of the early clinical data in demonstrating a positive risk/benefit profile, and the extent to which the product addresses an unmet medical need are factors often considered by regulatory agencies in deciding whether a vaccine may be licensed before confirmatory clinical efficacy trials are completed [11,13]. This is particularly important when such trials may take many years to complete or may not be feasible [4–6].

Decisions regarding licensure necessarily include assessments of the risk/benefit ratio of the product from a national perspective since, for example, the expedited availability of a vaccine may be more important to an endemic region than other parts of the world where the risk of disease is low. Mechanisms to accelerate licensure of new medicines may be less familiar to those working with vaccines than those working with medicines for very sick patients, such as oncology products [17] and HIV therapeutics [15]. However, since FDA recently approved bedaquiline [18] for treatment of MDR-TB on the basis of phase 2 data utilizing the accelerated approval process, and the EMA is making an assessment under a similar conditional licensure process for both bedaquiline and delamanid [18,19], mechanisms to advance product approval and introduction are already proving to be important to the TB field.

There are examples of vaccines where efficacy has proven to be difficult to demonstrate in controlled clinical trials. These include meningococcal conjugate vaccines, for which immunogenicity was considered adequate initially for group C vaccines in the UK [20] and subsequently for combined group A, C, Y and W135 vaccines in the United States. The FDA Vaccines and Related Biological Products Advisory Committee has advised that licensure on the basis of immunogenicity would suffice for a novel group B meningococcal vaccine and such data has been used to approve a