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.

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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...
Conventional regulatory pathways could delay vaccine licensure and utilization for many years, potentially leaving high-risk populations vulnerable to ongoing 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 [4]. 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
meningococcal group B vaccine for the EU. The lethal potential of meningococcal disease and demonstrated safety of the meningococcal vaccines played a key role in determining the acceptability of this approval route [20].

3. Principles of adaptive licensure

There is substantial debate on the concept of adaptive licensure [15], defined as using a progressive, staged licensure process where there is a sense of urgency for introducing a product to save lives. Adaptive Licensing should not be viewed as enabling a less rigorous product development plan but as requiring closer interaction between regulators, industry, academia and the general population to ensure that the process works to the ultimate advantage of those who receive novel medicines. The process is, in part, predicated on an “acknowledgement of an acceptable level of uncertainty” [5]. For example, a novel TB vaccine being evaluated in a phase 2 efficacy trial will have already demonstrated a reasonable safety and efficacy profile following assessment in phase 1 and early phase 2 studies [4]. However, in the absence of a correlate of protection, “benefit” can only be assessed in a large and lengthy efficacy trial based upon clinical endpoints [4]. Accordingly, adaptive licensing of a TB vaccine may require each relevant regulatory agency to determine the risk/benefit between the level of uncertain efficacy of the product and the endemic disease burden acceptable to permit a conditional licensure under this regulatory approach.

There are many challenges and substantial resistance to adapting novel licensing strategies. Although adaptive licensing is being discussed by regulators, there is currently no formal acceptance of this regulatory pathway among the world’s major regulatory bodies. For this to be achieved, there will be a need for all stakeholders to accept trade-offs and risk. For example, manufacturers may need to accept that the first approvals will initially have a more limited indication reflected in their labeling during a period of expanded clinical evaluation. It will be important to clarify whether an adaptive licensure strategy is feasible under current legislation guiding the major regulatory agencies. Additionally, it will be important to consider whether an adequate means exists to assess post-marketing data and if there are regulatory resources to implement such an approach. Since WHO “prequalification” of vaccines is likely to be pursued by TB vaccine developers to enhance global distribution [21], it would be useful to clarify whether conditional approval through an adaptive licensure process would qualify for WHO prequalification. Approval may also be granted based on “limited use” and while potentially easier in certain populations in non-endemic countries; it may be difficult to define this population in a TB endemic area. Lastly, if the introduction of a new TB vaccine includes replacing the BCG vaccination in infants, the new vaccine would need to show non-inferiority or superiority to the existing BCG vaccine which may not be feasible in a smaller phase 2 efficacy study [2,3].

4. Statistical requirements for licensure based on a vaccine efficacy study

In the absence of a validated correlate of protection, licensure of a TB vaccine would need to be based upon efficacy against a disease endpoint [2–4]. Since vaccine efficacy from randomized clinical trials is described by a point estimate and a confidence interval (CI), a narrow CI around the point estimate increases confidence that the vaccine efficacy is precise, but requires larger studies. In the US, the lower bound (LB) of the 95% CI is the preferred criterion for assessing vaccine efficacy by the FDA, reflecting a more conservative standard than the point estimate. This is important given potential for widespread administration of vaccines to healthy persons. Within the Center for Biologics Evaluation and Research (CBER) of the US FDA, an internal guide for assessment of vaccine efficacy suggests that the LB of the 95% CI should be: (i) at least two-thirds to three-quarters of the point estimate of efficacy (e.g., for a point estimate of 60%, the LB of the 95% CI should be 40%–45%) and (ii) substantially above 0. There are situations, however, potentially relevant to novel TB vaccines, where:

→ lower efficacy estimates may be acceptable for a disease causing high morbidity/mortality, as well as limited/difficult therapeutic or preventive alternatives and where public health considerations support use of a vaccine demonstrating moderate efficacy;

→ wider CIs may be acceptable if the sample size required to narrow the CI around the point estimate makes the trial infeasible (e.g. in situations of relatively low disease incidence, or long duration to reach clinical endpoints);

Could a phase 2 efficacy trial sized to show statistical significance with the LB of the 95% CI being only slightly above zero be adequate for licensure by regulatory agencies like the FDA or the Medicines Control Council (MCC) of South Africa? Features that would likely be required for licensure studies include use of pre-defined endpoints with prior validation of diagnostic methods and the use of the to-be-marketed product, with lot-to-lot consistency studies also being conducted.

A critical issue for the first registration of a new vaccine, particularly for global diseases like tuberculosis, is the selection of efficacy thresholds sufficient for licensure. These thresholds will be dependent on local public health exigencies. Prudence should guide against setting a low efficacy threshold to mitigate the risk of licensing a vaccine with low efficacy creating an unacceptable risk/benefit situation (harm could outweigh good), thereby eroding public trust. When selecting an efficacy threshold, it will be essential to guard against creating unmet expectations, a situation that could arise if a low efficacy threshold were to be selected and the use of the vaccine had little to no effect on the public health problem against which it was targeted. Such a situation could reduce confidence in regulatory agency assessments or in vaccine use in general. Assessments of future vaccines may also be compromised because studies comparing vaccines head to head can be very large relative to placebo controlled trials, and non-inferiority designs introduce potential for “creep” toward less efficacious vaccines, when each subsequent vaccine produced demonstrates non-inferiority to the lower margin of the efficacy spectrum. Such a situation could result in high costs to society to implement and pay for vaccination programs of marginal benefit. Also, there are potential opportunity costs if licensing of improved vaccines is delayed. Additional factors that might be considered in selection of an efficacy threshold for approval include: a) previous regulatory decisions regarding products of a similar class, or those addressing similar public health challenges; b) preceding data in phase 2 studies that support reasonable estimates of efficacy; c) potential public health impact (e.g., effect on morbidity/mortality); and d), feasibility issues for designing a sufficiently sized study to demonstrate efficacy with high confidence.

5. Current regulatory pathways for accelerating approval of important new medicines in South Africa

The challenges of expedited licensure in high disease burden developing countries where most of the TB vaccine trials are conducted are numerous. In large part, this is because regulatory systems in such countries are typically less well-resourced and therefore less developed than those in low disease incidence, economically-advantaged countries. The South African Regulatory
Authority, the MCC, is probably the most advanced agency in Africa with experience in the review and oversight of clinical trials. Under South African regulation, however, no mandate for conditional or adaptive registration of medicines exists. To allow for use of an unregistered medicine in the country, a mechanism under Section 21 of Act 101 is available. An applicant applies for, and the Council may authorize, the sale of a specific quantity of unregistered medicine to particular individuals for up to six months (for each authorization) [22]. This mechanism is also available for medicinal products in clinical development for which data on product manufacturing quality are available. Therefore Section 21 approvals allow for the off-label sale and use of investigational products and require that the details of every person treated are recorded, and that such data, including adverse reaction data, is directly reported to the Registrar of Medicines. However, this reporting process is unlikely to be applied as rigorously and monitored as thoroughly as would be required for adaptive licensing, especially for a widely-used vaccine. Therefore an adaptive licensure process, as currently being explored, is very difficult to envisage in the current South Africa context. Furthermore, the MCC, like most regulatory agencies, is unaccustomed to registering vaccines that have moderate levels of efficacy (VE ~ 50%), which may well be the case for a TB vaccine. Unless indirect economic benefits (hospitalization, treatment cost savings, deaths averted) are explicitly elucidated, the MCC ordinarily considers risk-benefit to the individual rather than primarily public health considerations. For vaccines of lower efficacy, the safety/reactogenicity issues become more important, and consequently, risk-benefit must be very clearly demonstrated.

Given these considerations, the prospects for adaptive licensure in South Africa will be limited, particularly as long as Section 21 approvals remain the sole mechanism. Currently under discussion by the MCC is a proposed Investigational Medicinal Product Application (IMPA) procedure for South Africa allowing for pre-registration consultations with a technical expert committee of the MCC [23]. The intention is to provide a mechanism for interaction between product developers and the MCC that will guide product development and facility design, and facilitate compliance with the regulations governing the registration of medicines for use in the country. Use of this mechanism would be limited to biological and other medicines that have not been previously submitted for registration to the MCC or to any other regulatory authority and for which registration may be sought from the MCC in the future. The IMPA would, therefore, be accessible to local manufacturers and developers of biological medicines, including vaccine developers, where the major part of the clinical development will be in a South African population.

Initiatives in other regulatory settings for discussion of product development strategies, novel regulatory mechanisms and potential harmonization across regulatory agencies for the registration of TB vaccines, include the pre-IND consultation procedure of the FDA [24], the Scientific Advice and Protocol Assistance procedures of the EMA [25] (which are also applicable for products to be assessed under EMA article 58 of regulation 726/2004 [26]), the Developing Countries’ Vaccine Regulators Network (DCVRN) [27], the African Vaccine Regulators Forum (AVAREF) [28] and the Health Canada Progressive Licensing Project [29]. These regulatory initiatives offer sponsors of novel TB vaccines a number of advantages, including opportunities for discussions on developing a licensing plan and opening dialogue amongst sponsors, developers, regulators and health authorities, and the chance to make a plea for harmonization among these different stakeholders [21].

A number of challenges have resulted from this discussion on adaptive licensure and the role of regulatory authorities in expediting the review and introduction of vaccines for TB. Overcoming these challenges will require innovative strategic plans that address regulatory challenges in both emerging countries like South Africa and nations with stringent regulatory agencies (SRA) like the US. This will be particularly difficult for eventually implementing “non-traditional” approaches such as adaptive licensure. As discussed in this article, one strategy is to use the resources of a stringent regulatory authority such as the US FDA to work with regulatory agencies (RA) in countries endemic for global diseases like the MCC in South Africa to complement the strengths of both agencies in assessing the data associated with the regulatory submission including the clinical trial data and the proposed plans for conditional approval. Strategies for fostering communication and collaborations among SRAs and RAs have been documented in a number of publications focused on information sharing among regulatory bodies and strengthening the capacity of less-well-resourced RAs in developing countries to tackle the review of complex biological vaccine products under a reasonable timeframe. Moran et al., for example, focuses on the training and exchange of information between SRAs and RAs, called “twinned-review” [30], while Maiga et al. comments on the importance of the World Health Organization initiatives like the African Vaccine Regulatory Forum in harmonizing the regulation of vaccines in Africa [31]. The AVAREF has reviewed an adaptive trial protocol for TB vaccines and a summary of their comments is published in Rustomjee et al. [4]. In addition, a series of reports by the Global Health Technologies Coalition which represents non-profits and product development partnerships developing products for neglected diseases provides a number of recommendations on how US policy could bolster the role of the US FDA in global health [32] Also, a report by the Centers for Global Development [33] recommends a two — prong approach to streamlining the introduction of products for neglected diseases focusing on changes to clinical development and harmonization of regional regulatory pathways. As pointed out in a review [34], a global regulatory science agenda which encompasses strengthening of laboratory-based regulatory science and inclusion of adaptive trial designs and other less traditional approaches to evaluating vaccines for global diseases is an important part of the Decade of Vaccines Collaboration and the Global Vaccine Action plan. Therefore, for the most part, strategies to address the obstacles to the potential licensure pathways outlined in this report exist and the main challenge remains in finding the resources and political mechanisms for implementing change within regulatory bodies needed for efficient approval and introduction of new products for neglected global diseases.

In summary, the potential for expediting licensure of a TB vaccine using “Adaptive Licensure” appears challenging, both in South Africa and the USA. Nonetheless, it is widely accepted that the critical importance of developing and introducing an improved TB vaccine should lead all stakeholders to work to establish the most efficient possible route to licensure for the introduction of a novel vaccines for tuberculosis.

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