SUPPLEMENT ARTICLE

Strategic Regulatory Evaluation and Endorsement of the Hollow Fiber Tuberculosis System as a Novel Drug Development Tool

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The first nonclinical drug development tool (DDT) advanced by the Critical Path to TB Drug Regimens (CPTR) Initiative through a regulatory review process has been endorsed by leading global regulatory authorities. DDTs with demonstrated predictive accuracy for clinical and microbiological outcomes are needed to support decision making. Regulatory endorsement of these DDTs is critical for drug developers, as it promotes confidence in their use in Investigational New Drug and New Drug Application filings. The in vitro hollow fiber system model of tuberculosis (HFS-TB) is able to recapitulate concentration-time profiles (exposure) observed in patients for single drugs and combinations, by evaluating exposure measures for the ability to kill tuberculosis in different physiologic conditions. Monte Carlo simulations make this quantitative output useful to inform susceptibility breakpoints, dosage, and optimal combination regimens in patients, and to design nonclinical experiments in animal models. The Pre-Clinical and Clinical Sciences Working Group within CPTR executed an evidence-based evaluation of the HFS-TB for predictive accuracy. This extensive effort was enabled through the collaboration of subject matter experts representing the pharmaceutical industry, academia, product development partnerships, and regulatory authorities including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). A comprehensive analysis plan following the regulatory guidance documents for DDT qualification was developed, followed by individual discussions with the FDA and the EMA. The results from the quantitative analyses were submitted to both agencies, pursuing regulatory DDT endorsement. The EMA Qualification Opinion for the HFS-TB DDT was published 26 January 2015 (available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp).

Keywords. regulatory science; quantitative pharmacology; model-based drug design; drug development tools; tuberculosis.

There is an urgent need for novel treatment regimens for tuberculosis that are safer, optimize treatment duration, and reduce the number of patients with drug-resistant disease. Regimen development strategies require reliable preclinical data that support the informed selection of each new entity to be tested in early combination studies. Furthermore, quantitative pharmacokinetic and pharmacodynamic (PK/PD) information is needed to support informed dose selection for those early clinical combination regimens. Nonclinical drug development tools (DDTs) with demonstrated predictive accuracy for clinical and microbial outcomes are needed to support effective drug development decision making. Furthermore, the endorsement of these DDTs by regulatory authorities is critical for drug developers as it promotes confidence in their use and supports incorporation of data generated by these DDTs in their Investigational New Drug and New Drug Application filings.

The in vitro hollow fiber system model of tuberculosis (HFS-TB), whose methods and engineering are described elsewhere in this supplement [1], is able to recapitulate concentration-time profiles (exposure) observed in patients for a single drug, as well as for multiple drugs tested in combination [2–4]. The HFS-TB supports the evaluation of such drug exposures for ability to kill

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tuberculosis in a variety of physiologic conditions [1]. This quantitative output can be used to inform the selection of optimal drug exposures, drug doses, susceptibility breakpoints, and optimal combination regimens in patients, and to inform the design of nonclinical experiments in animal models, based on Monte Carlo simulations.

This manuscript describes the strategy designed and executed by the Critical Path Institute's Critical Path to Tuberculosis Drug Regimens Initiative (CPTR), which focused on the evidence-based evaluation of the HFS-TB for predictive accuracy [5]. This extensive effort was enabled through the collaborative efforts of the CPTR public–private partnership, which brought together subject matter experts representing the pharmaceutical industry, academia, product development partnerships, and regulatory authorities including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). This team developed a comprehensive analysis plan following the regulatory guidance documents for DDT qualification [6, 7] and engaged in individual discussions with the FDA and the EMA. The analyses [1] were executed, and the results from the quantitative predictive accuracy analyses were submitted to both agencies, pursuing regulatory endorsement for this platform as a DDT. The findings were presented via the Voluntary Exploratory Data Submission (VXDS) mechanism with FDA [8] and via the Qualification Opinion mechanism with EMA's Committee for Medicinal Products for Human Use (CHMP) [7].

METHODS

Analysis Plan and Overall Regulatory Strategy

As described by Gumbo et al [5], a comprehensive analysis plan was developed, with the ultimate goal of completing a quantitative predictive accuracy and bias analysis, based on data from 3 systematic literature searches that were performed to identify HFS-TB experiments and clinical studies evaluating the same drugs as in the HFS-TB experiments (with and without a time correlation). Based on the Critical Path Institute's 10-year-long experience with DDT projects, discussions with regulatory authorities were initiated very early in the process. Both the FDA and EMA were kept informed of the regulatory discussions with each agency, and the review process was simultaneous but not joint. Following the comprehensive analysis plan, a systematic literature search was performed to identify HFS-TB experiments that were followed by clinical studies evaluating the same drugs as in the HFS-TB experiments (published at least 6 months apart).

Regulatory Pathway With FDA

Aimed at informing a subsequent biomarker qualification discussion, which would be led by the Office of Translational Sciences with input from the Division of Anti-Infective Products, the Office of Biostatistics, and the Office of Clinical Pharmacology, the regulatory strategy was designed around a VXDS and its associated face-to-face meeting with the FDA [9]. The approach for the HFS-TB platform, taken in agreement with the FDA, allowed a more flexible discussion and outcome than would have been possible under the DDT Qualification Programs, which are applied to qualification of animal models, biomarkers (with a qualified context of use), and clinical outcome assessment measures. The steps to submit to the VXDS program are as follows: (1) Discuss the scope of the proposed VXDS with FDA; (2) if deemed appropriate, briefing documents can then be submitted, followed by (3) a meeting with FDA scientists, if requested, approximately 6–8 weeks following document submission.

Regulatory Pathway With EMA

EMA also agreed on the value of the proposed analysis, and suggested the biomarker qualification process as the most appropriate avenue for regulatory endorsement of the HFS-TB platform. According to the EMA guidance document for the Qualification of Novel Methodologies in Drug Development [8], the results of formal regulatory reviews by the Scientific Advice Working Party (SAWP) can take the form of qualification advice, in which the sponsor is given guidance and asked to perform additional work for a future submission, or their review can result in the issuance of a qualification opinion, which constitutes the formal regulatory qualification of the proposed novel methodology and recommendations for use [10]. In contrast to the FDA process for qualification of DDTs, the scope of the EMA process is somewhat broader, thus allowing a formal qualification opinion to be obtained. The steps for submission of qualification advice or opinion with EMA are as follows: (1) Applicant submits a letter of intent and draft briefing package to EMA's qualification team. (2) The briefing package is reviewed and discussed and a background summary and list of questions and comments from the EMA qualification team and other experts is created and sent to the applicant. (3) Applicant submits a final briefing package incorporating feedback received from EMA (step 2). (4) The applicant and EMA qualification team will have a face-to-face SAWP meeting to discuss the proposed development method. (5) The SAWP will recommend whether the procedure will be eligible for a qualification opinion or a qualification advice. (6) Based on SAWP's recommendation, the CHMP will discuss and adopt the qualification advice for future studies or discuss the qualification opinion as appropriate. (7) If CHMP drafts a qualification opinion, the draft qualification opinion and assessment report and the basis for its regulatory acceptance are released for 6 weeks of public consultation. (8) Based on public comment and consultation from the scientific community, the CHMP will decide if the proposed innovative development

method should render a final, positive CHMP qualification opinion. (9) The final CHMP qualification opinion and grounds for acceptance will then be made publicly available on the EMA website 15 days after the final CHMP opinion is issued [11].

Predictive Accuracy Analysis

As described by Gumbo et al [5], predictive accuracy and bias were evaluated for HFS-TB experiments for clinically relevant drug concentrations and/or exposures in patient studies published at least 6 months subsequently. Accuracy was defined as follows (see Gumbo et al [5] for more complete details):

$$A = 100\% - \left(\frac{1}{n} \times \left[\sum_{i=1}^{n} \left|\frac{T_i - P_i}{T_i}\right| \times 100\right]\right), \quad (1)$$

where n represents the number of trials or experiments, T_i represents the observed values in the clinical trial, and P_i represents the predictive values in the HFS-TB experiment.

In turn, bias was defined as:

$$B = \sum_{i=1}^{n} \frac{(T_i - P_i)}{n}. \quad (2)$$

RESULTS

The predictive accuracy analysis yielded a robust mean accuracy of 94.6% (95% confidence interval [CI], 8.7–22.5), with no significant bias in any direction (−0.1% [95% CI, −2.5 to 2.2]). Thus, in the case of the random model, there was no significant bias in either direction.

Results From FDA Regulatory Pathway

As described in the HFS-TB regulatory strategy timeline (Figure 1), on 20 February 2013 a letter of intent statement was submitted to FDA followed by a teleconference on 27 February 2013. During this teleconference, the FDA acknowledged the value of performing a quantitative prediction accuracy and bias analysis for the HFS-TB platform. The analysis plan was agreed upon and the decision was made to pursue the following strategy for the regulatory endorsement of the HFS-TB platform by FDA: (1) Upon completion of the analysis plan, a comprehensive briefing package would be submitted to the agency; (2) after FDA completed the review of such package, a subsequent meeting would be held to discuss the specific results of the analysis.

CPTR followed this path as suggested by FDA. Subsequently, when the analyses were completed, a comprehensive VXDS briefing document was submitted to FDA on 16 October 2013 followed by a VXDS meeting held on 15 November 2013. As a result of this meeting, the FDA both encouraged the CPTR team to submit comments to the docket for the guidance document on tuberculosis drug development and suggested a co-publication strategy in relevant peer-reviewed journals (FDA official communication to CPTR, 15 November 2013). At FDA's recommendation, comments were submitted by the CPTR team on 4 February 2014 to the FDA Docket FDA-2013-D-1319-0001 on the FDA's draft guidance entitled "Guidance for Industry–Pulmonary Tuberculosis: Developing Drugs for Treatment" dated November 2013, and the present series of articles was created, accompanied by FDA's editorial in this supplement [12].

Results From EMA Regulatory Pathway

As shown in Figure 1, a comprehensive briefing document was submitted to EMA with a request for qualification opinion on 24 February 2014. A qualification opinion rather than qualification advice was requested based on the robust data and analyses

Figure 1. Graphic description of the regulatory strategy timeline for the hollow fiber system of tuberculosis model. Abbreviations: FDA, Food and Drug Administration; LOI, letter of intent; SAWP, Scientific Advice Working Party; VXDS, Voluntary Exploratory Data Submission.

supporting the HFS-TB model and informal conversations with EMA around the benefits of this model. Additionally, CPTR believed the results presented in the briefing package supported endorsement for use. A meeting with the EMA's SAWP was held on 6 May 2014, during which the results were thoroughly discussed. SAWP had subsequent discussions, after which the decision was made to recommend to the CHMP that a positive qualification opinion be issued. Once the CHMP evaluated and reviewed the recommendation by SAWP, a draft qualification opinion was published on EMA's website on 18 November 2014 for a 6-week public comment period that concluded on 9 January 2015. On 26 January 2015, the final qualification opinion was published by EMA [10]. The qualification opinion highlights the broad applicability of the model both to the design of appropriate studies and to the interpretation of data from clinical studies, in all stages of development. However, it should be noted that use of the HFS-TB is not considered to be a mandatory requirement, but is intended to encourage rational drug development approaches and building of a knowledge base.

DISCUSSION

Although the regulatory endorsements by FDA and EMA followed different pathways, it is envisioned that both types of endorsement will be effective in facilitating adoption of this tool by sponsors in the field of tuberculosis. A critical success factor for future enrichment and expansion of the HFS-TB model is that data generated by sponsors will be shared with CPTR, as well as the sharing of clinical trial data in these stages. Thus, as additional information accrues regarding optimal endpoints for different populations, including biomarkers and disease severity measures, the quantitative approach applied for the HFS-TB platform will be instrumental in building next-generation modeling and simulation tools for TB drug development. Indeed, DDTs are continuously evolving, and predictive accuracy needs to be validated using a wide variety of data sets. This has led to the development of a plan with the following deliverables: (1) comprehensive standard operating procedure and laboratory manual documents for tuberculosis experiments on the HFS-TB platform and (2) additional experimental work to evaluate the drug regimen tested as part of the Rapid Evaluation of Moxifloxacin in Tuberculosis program and the pretomanid, moxifloxacin, and pyrazinamide regimen under several different conditions (log-phase growth, intracellular infection, and semidormant bacilli).

This work has also spurred interest in other CPTR teams that plan to apply an equivalent strategy to quantify the predictive accuracy of other preclinical animal models, with the goal of integrating the findings from in vitro and in vivo platforms for a more informed decision-making process to support the transition from preclinical to clinical stages of tuberculosis drug regimen development.

Notes

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