

# Hollow Fiber System Model for Tuberculosis: The European Medicines Agency Experience

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**The in vitro hollow fiber system model has been qualified by the European Medicines Agency as a methodology for use in support of selection and development of antituberculosis regimens. More data are expected to be generated in the future to further characterize its value.**

**Keywords.** tuberculosis; PK/PD; in vitro models; EMA; qualification.

This article presents the perspective of the European Medicines Agency (EMA) on the utility of the hollow fiber system model for development of antituberculosis drugs (HFS-TB) based on the recent qualification opinion, and it should be read in conjunction with this opinion and the articles published by the Critical Path to TB Regimens (CPTR) consortium in this supplement. Pasi-panodya et al [1] summarize the use of HFS-TB up to the end of 2012, highlighting the potentialities of this in vitro tool in exploring and characterizing the pharmacokinetic/pharmacodynamic (PK/PD) profile of antitubercular agents in accordance with the human pharmacokinetic profile. In addition, more recent studies [2] have provided significant examples of the utility of this approach in the characterization of regimens and dosages of tuberculosis drugs that would be instrumental in the definition of optimal regimens to be further investigated in clinical trials. The article from Romero et al [3] describes the interactions that occurred between the CPTR consortium and regulatory agencies such as EMA and the US Food and Drug Administration.

## QUALIFICATION OF NOVEL METHODOLOGIES

The EMA acknowledges the challenges associated with drug development resulting in high attrition rates and

promotes the development of new drug development and evaluation tools [4]. As part of this undertaking, the qualification of novel methodologies was established in 2009 with 2 distinct outcomes: the qualification opinion (a method is fit for purpose according to the regulatory standards; opinions published on the EMA website [5]), and the qualification advice (prospective and confidential advice on studies for future qualification). Recently the letter of support, a public statement from the EMA encouraging data sharing and qualification efforts, was introduced as an additional optional outcome from a qualification advice procedure, for methods/biomarkers that show promising preliminary results but are not yet suitable for qualification.

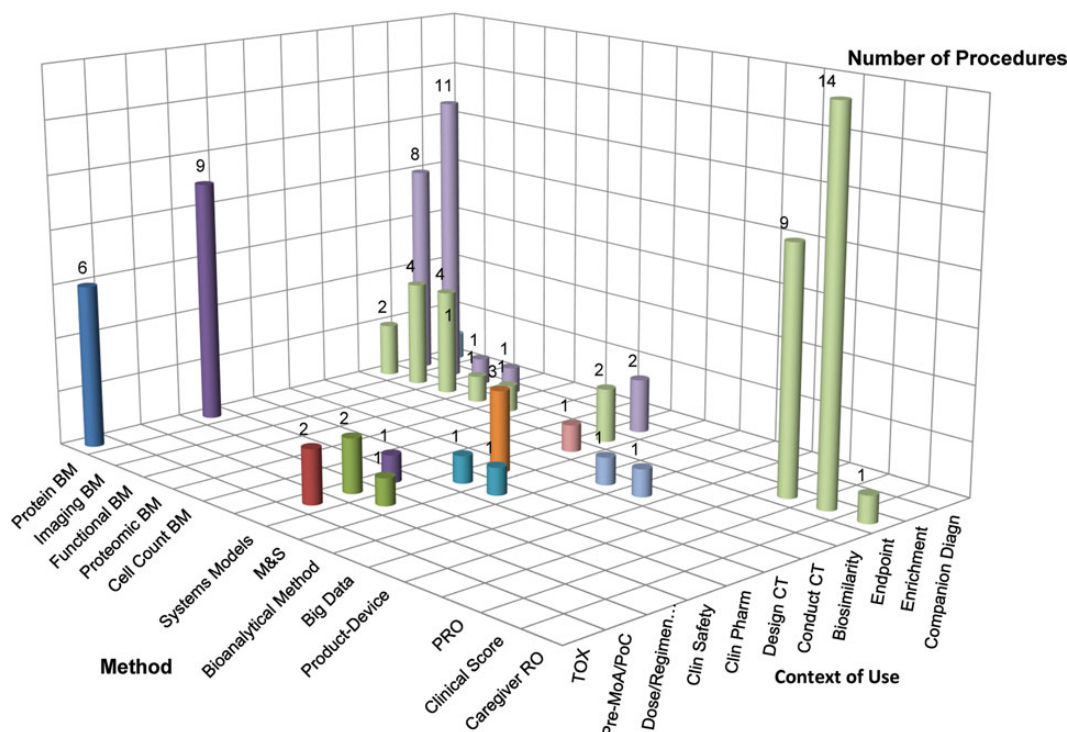
The EMA qualification procedure offers a framework for discussion and data sharing on novel methodologies that span from preclinical biomarkers supporting toxicological assessment, to clinical scores as primary endpoints for phase 3. A qualified method is a method that is accepted by the Committee of Human Medicinal Products (CHMP) to be used in regulatory submissions. In practice, this means that when drug developers are using this method (eg, surrogate biomarkers), they could refer to the already available opinion and preempt any discussions with regulators that may have occurred in the context of a specific development should this method have not been qualified. The EMA experience with biomarker qualification in terms of methods and context of use is discussed in a recent book chapter [6] and shown in Figure 1. The latter is based on internal data on biomarker qualification projects, from the first pilot in 2007 until March 2015. The “method”

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**Figure 1.** Qualification procedures per method and context of use. Abbreviations: BM, biomarker; Clin, clinical; CT, clinical trial; Diagn, diagnostic; M&S, modeling and simulation; Pre-MoA/PoC, preclinical mechanism of action/proof of concept; PRO, patient-reported outcome; RO, reported outcome; TOX, toxicology.

axis represents the different categories of methods submitted for qualification, and the “context of use” axis represents the qualification claims that were sought for these methods. Finally, the number of procedures that discuss the specific method in the specific context of use is represented by the height of the column and indicated on top of each column. For example, 9 qualification procedures were submitted on patient-reported outcomes (PROs). In all of these, the objective was to qualify PROs as endpoints in clinical trials. The objective of this display is not to make exact calculations on how often each method is seen by regulators in qualification procedures, and in which context, but to give a snapshot of the current trends in biomarker qualification. As expected, the main discussions involve the development of biomarkers, clinical scores, and PROs. However, novel methodologies making use of quantitative analyses are also emerging. The HFS-TB model is captured in this analysis as a systems model approach.

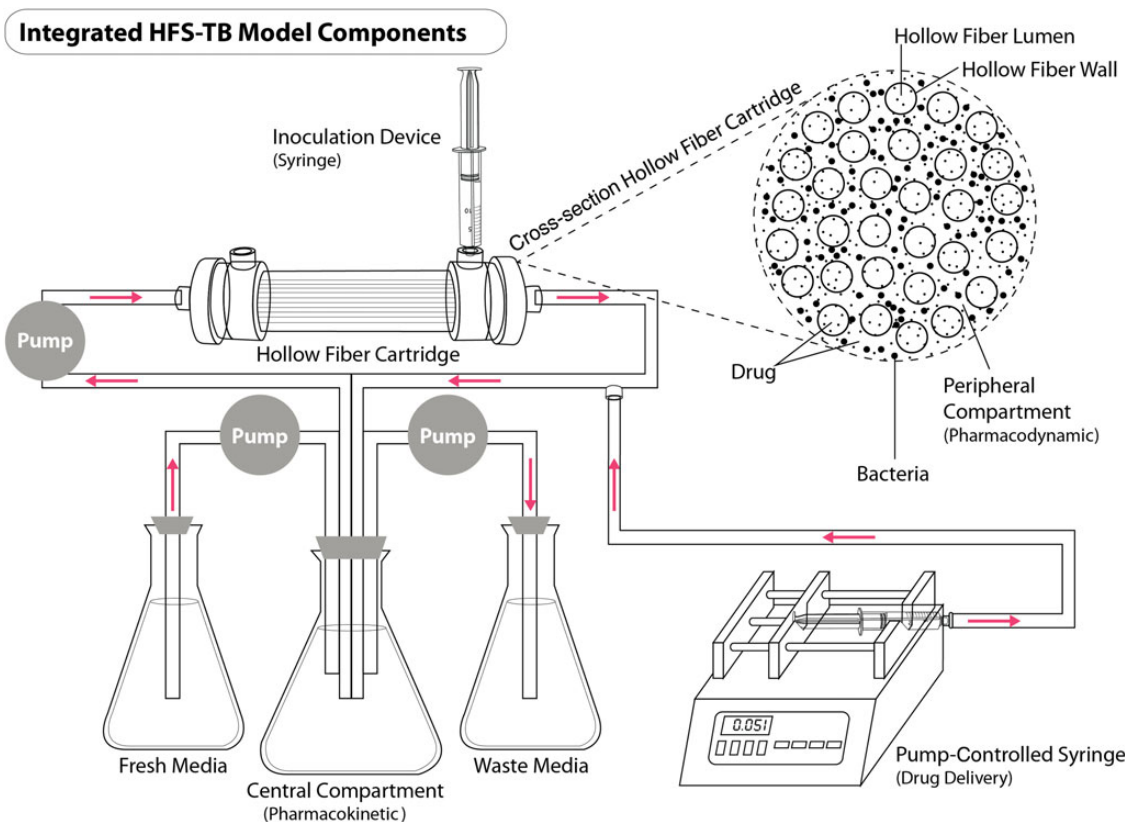
## THE HFS-TB MODEL

It is well recognized that there is a medical need for new drugs and regimens that could shorten treatment duration for both drug-susceptible and multidrug-resistant tuberculosis. However, besides the difficulties in finding new molecules that could

have the necessary profile, we must acknowledge that the process of drug development in the field of tuberculosis is rather lengthy, in particular the conduct of late-stage clinical trials. Therefore, innovative approaches that could streamline and help in rationalizing the development process to increase the chances of success and bring these new treatment options to late clinical development and, ultimately, to patients in a timely manner are warranted.

Under this background, the HFS-TB model was discussed with the EMA. The qualification process involved 2 qualification team meetings and a face-to-face meeting with the applicant. Also, discussions took place in the Scientific Advice Working Party and the CHMP plenary.

The HFS-TB (Figure 2) consists of a pharmacokinetic system that mimics human plasma concentration-time profiles of drugs, first described by Blaser et al [7], and has been extensively used in drug development. The HFS-TB allows *Mycobacterium tuberculosis* to grow in the peripheral compartment of a hollow fiber cartridge. The peripheral compartment is separated from the central compartment by semipermeable hollow fibers, with pore sizes that allow nutrients, drugs, and bacterial metabolites to freely transverse in and out of the peripheral compartment while remaining too small for bacteria to leave the peripheral compartment.



**Figure 2.** Diagram of hollow fiber system for tuberculosis (HFS-TB). In vitro hollow fiber pharmacodynamic infection model of *Mycobacterium tuberculosis* that simulates human pharmacokinetics. The pharmacokinetic compartment consists of a central compartment of the hollow fiber system composed of the central reservoir, the inner lumen of the hollow fiber capillaries, and the oxygen-permeable flow path connecting the central reservoir to and from the hollow fibers. The peripheral compartment is the space outside the hollow fiber capillaries that is enclosed by an impermeable plastic encasement.

The sponsor performed literature searches to identify publications, including (1) HFS-TB studies and Monte Carlo simulations (search A); (2) clinical studies for tuberculosis drugs published prior to the HFS-TB studies (search B); and (3) clinical studies published at least 6 months after the HFS-TB publication (search C).

Standard evidence-based medicine criteria were used to evaluate the quality of clinical studies. As a second step [8, 9], the sponsor attempted to determine the level of correlation between HFS and clinical/microbiological outcomes in patients with tuberculosis, as well the forecasting accuracy of the HFS-TB output in a retrospective fashion.

The exercise was retrospective and conducted in a relatively small number of studies and drugs, without access to raw data; therefore, there are some inherent limitations around the strength of evidence derived from such analysis. Nonetheless, the value of HFS models as has emerged from submitted data has been acknowledged. Moreover, it is recognized that HSF models are being used more and more frequently in the development of antimicrobial agents, and in particular for antibacterial agents, as a valuable tool for PK/PD profiling and as relevant supportive evidence in the context of regulatory activities [10].

Based on this overall weight of evidence, the CHMP agreed to qualify the HFS-TB models [11].

## QUALIFICATION OPINION

Among the potential benefits that could derive from employing HFS-TB during the various stages of development of tuberculosis drugs and regimens, the possibility of using this tool to better define combinations of drugs that could provide additive or synergistic rapid bactericidal/sterilizing activity without causing emergence of resistance turns into a major advantageous feature. The insight that could be gathered on the activity on different mycobacterial populations, including intracellular activity, and the definition of PK/PD targets and doses to be tested in clinical trials are also important aspects for which HFS-TB is expected to be highly useful. These aspects would be particularly relevant to decrease the amount of doses and regimens to progress further in clinical development. Also, HFS-TB in combination with Monte Carlo simulations could produce estimates of target attainment once sufficiently extensive data on the human pharmacokinetics are generated,

contributing to understanding of the exposure–response relationship.

The intended revision of the EMA guidance on the evaluation of medicinal products indicated to treat disease due to *M. tuberculosis* [12] will cover, among other things, an update of the section on the use of PK/PD data for rational dose selection for new agents and regimens, including models that can take into account the effects of growth phases and intracellular accumulation. HFS-TB is recognized as being an important promising model for such purposes, as reflected in the recent qualification opinion.

The opinion also highlights that the HFS-TB model cannot substitute for preclinical animal or clinical data, although it could reduce requirements by targeting and optimizing experiments. It is also clear that the HFS-TB model cannot be used to drive inferences and support regulatory claims, but could support submissions and benefit–risk assessment in an overall weight-of-evidence approach.

## FUTURE STEPS

As this qualification was based on a retrospective analysis of literature data, it is considered important to prospectively collect and analyze data on the performance of the HFS-TB model. In addition, as experience with HFS-TB grows, it will be important to consider the reproducibility of the method and any operational issues related to the test performance. The need to standardize and establish/communicate good practices for HFS-TB models was identified and agreed on by the applicant.

## CONCLUSIONS

The use of the HFS-TB model is encouraged by regulators, as reflected in the recent qualification opinion.

The qualification is a dynamic field, and as the sponsors gain experience with the use of the method, more data will be submitted to the regulators to reassess and optimize the context of use. In addition, wider implementation of the method will enable and require the development of good practices. Because in the future the HFS-TB model may become more widely used for the selection of regimens and dosages of antitubercular agents, it is imperative that new prospective data are systematically collected, analyzed, and reported to the regulatory bodies.

## Notes

**Disclaimer.** The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Pasipanodya J, Nuermberger E, Romer K, Hanna D, Gumbo T. Systematic analysis of hollow fiber model of tuberculosis experiments. *Clin Infect Dis* **2015**; 61(suppl 1):S10–7.
2. Drusano GL, Neely M, Van Guilder M, et al. Analysis of combination drug therapy to develop regimens with shortened duration of treatment for tuberculosis. *PLoS One* **2014**; 9:e101311.
3. Romero K, Clay R, Hanna D. Strategic regulatory evaluation and endorsement of the hollow fiber tuberculosis system as a novel drug development tool. *Clin Infect Dis* **2015**; 61(suppl 1):S5–9.
4. European Medicines Agency. Road map to 2015. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101373.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf). Accessed 30 June 2015.
5. European Medicines Agency. Novel methodologies webpage. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000319.jsp&mid=WC0b01ac0580022bb0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0). Accessed 30 June 2015.
6. Manolis E, Koch A, Deforce D, Vamvakas S. The European Medicines Agency experience with biomarker qualification clinical proteomics. *Methods Mol Biol* **2015**; 1243:255–72.
7. Blaser J, Stone BB, Zinner SH. Two compartment kinetic model with multiple artificial capillary units. *J Antimicrob Chemother* **1985**; 15(suppl A):131–7.
8. Gumbo T, Pasipanodya JG, Nuermberger E, Romero K, Hanna D. Correlations between the hollow fiber model of tuberculosis and therapeutic events in tuberculosis patients: learn and confirm. *Clin Infect Dis* **2015**; 61(suppl 1):S18–24.
9. Gumbo T, Pasipanodya JG, Nuermberger E, Romero K, Hanna D. Forecasting accuracy of the hollow fiber system model of tuberculosis for clinical therapeutic outcomes. *Clin Infect Dis* **2015**; 61(suppl 1):S25–31.
10. European Medicines Agency. Draft concept paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99) and conversion to a CHMP guideline. Available at: [http://www.ema.europa.eu/ema/doc\\_index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500162135&murl=menus/document\\_library/document\\_library.jsp&mid=0b01ac058009a3dc](http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500162135&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc). Accessed 30 June 2015.
11. European Medicines Agency. Final qualification opinion. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2015/02/WC500181899.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/02/WC500181899.pdf). Accessed 30 June 2015.
12. European Medicines Agency. Concept paper on revision of the addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to *Mycobacterium tuberculosis*. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/11/WC500177902.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177902.pdf). Accessed 30 June 2015.