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# Recently developed drugs for the treatment of drug-resistant tuberculosis: a research and development case study

Christophe Perrin,[1] Katy Athersuch,[2] Greg Elder,[2] Manuel Martin,[2] Alain Alsalhani[1]

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[1]Access Campaign, Medecins Sans Frontieres, Paris, France
[2]Access Campaign, Medecins Sans Frontieres, Geneva, Switzerland

**Correspondence to**
Christophe Perrin;
Christophe.PERRIN@paris.msf.org

## ABSTRACT

Two drugs with novel mechanisms of action, the diarylquinoline bedaquiline and the nitroimidazole delamanid—as well as pretomanid from the same class of drugs as delamanid—have recently become available to treat drug-resistant tuberculosis (DR-TB) after many decades of little innovation in the field of DR-TB treatment. Despite evidence of improved efficacy and reduced toxicity of multidrug regimens including the two agents, access to bedaquiline and delamanid has been limited in many settings with a high burden of DR-TB and consistently poor treatment outcomes. Aside from regulatory, logistic and cost barriers at country level, uptake of the novel agents was complicated by gaps in knowledge for optimal use in clinical practice after initial market approval. The main incentives of the current pharmaceutical research and development paradigm are structured around obtaining regulatory approval, which in turn requires efficacy and safety data generated by clinical trials. Recently completed and ongoing clinical trials did not answer critical questions of how to provide shorter, less toxic treatment DR-TB treatment regimens containing bedaquiline and delamanid and improve patient outcomes. Voluntary generation of evidence that is not part of this process—yet essential from a clinical or policy perspective—has been left to non-sponsor partners and researchers, often without collaborative efforts to improve post-regulatory approval access to life-saving drugs. Additionally, these efforts are currently not recognised in the value chain of the research and development process, and there are no incentives to make this critical research happen in a coordinated way.

## Summary box

⇒ Various publications in the literature and from the WHO have discussed the need to strengthen the research and development processes for novel antituberculosis drugs and regimens in order to treat the disease more effectively.
⇒ We analysed the development and initial regulatory approval of two antituberculosis drugs, bedaquiline and delamanid, in the current pharmaceutical research and development paradigm and the failure of the approval process to define the drugs' role in multidrug regimens to improve treatment outcomes.
⇒ We recommend inclusion of public health-driven expertise early in the regulatory process; establishment of a legal framework within the regulatory process that would acknowledge societal contributions; and organised, longitudinal inputs from multiple stakeholders into the regulatory process.

## INTRODUCTION

Globally, tuberculosis (TB) is the leading cause of death from a single infectious agent, despite being an infectious disease that can be both prevented and successfully treated. In 2018, there were approximately half a million new cases of rifampicin-resistant TB (RR-TB), including multidrug-resistant TB, multidrug-resistant tuberculosis (MDR-TB) (resistance to both rifampicin and isoniazid), yet only 186 772 of these individuals were diagnosed and even fewer started on appropriate treatment.[1] Only 56% of the 156 071 people enrolled on treatment were treated successfully—a figure that has not changed significantly for decades.[1]

It has been over 6 years since the WHO first recommended the novel drug bedaquiline (Bdq) for the treatment of some forms of RR/MDR-TB in adults in June 2013.[2] In October 2014, the WHO recommended a second new antituberculosis agent, delamanid (Dlm), to treat RR/MDR-TB.[3] These recommendations followed on accelerated and conditional approvals for Bdq from the US Food and Drug Administration (USFDA) in December 2012 and the European Medicines Agency (EMA) in March 2014; Dlm was conditionally approved by the EMA in April 2014. Pretomanid, approved most recently by the FDA in 2019 for treatment of highly drug-resistant forms of TB, is limited to use within a three-drug regimen, including Bdq and linezolid (the BPaL regimen), and will not be discussed here. Given the historically poor rates of treatment success and the high frequency of toxicities from conventional RR/MDR-TB regimens,[4] there has been optimism that WHO recommendations and

subsequent access to these therapeutic agents will significantly improve treatment outcomes.[5 6]

Despite the hope that accompanied regulatory approval, early access to Bdq and Dlm has until recently been slow and problematic in many countries. The reasons for poor uptake are multifactorial and include programmatic, logistic and regulatory barriers. More broadly, preapproval pharmaceutical research and development (R&D) trial design is mostly private sector driven and focused on rapid market authorisation, leaving gaps in evidence to inform clinical practice. Even when trial data are generated with public sector involvement, there is minimal recognition of these efforts in terms of collective decision-making for postapproval access and pricing. This paper aims to analyse these shortcomings through the lens of the current pharmaceutical R&D paradigm.

## GAPS IN KNOWLEDGE: DATA FOR REGULATORY APPROVAL VERSUS CLINICAL USE

Bdq, a diarylquinoline antimycobacterial agent developed by Janssen Pharmaceuticals, received accelerated approval from the USFDA based on phase IIb data generated by a randomised controlled trial (RCT) of multidrug backbone therapy with Bdq versus placebo.[7] The Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB (STREAM) trial stage 2 open-label RCT serves as the phase III study for Bdq, with study results expected in 2022.[8] In addition to STREAM stage 2, Bdq is a component of several ongoing clinical trials (table 1). Dlm, developed by Otsuka Pharmaceutical Japan, is the first in a new class of TB drugs called nitroimidazoles. The EMA based its conditional approval in 2014 on phase IIb RCT data,[9] in January 2019, the final results of the phase III trial for Dlm were published.[10] As with Bdq, Dlm continues to be studied in several ongoing clinical trials (table 2).

Bdq continues to be investigated in at least 10 phase II and III trials—Dlm in at least six—with public actors as both sponsors and collaborators. In addition, academic institutions, National TB Programs, non-profit organisations and scientific consortiums are conducting retrospective and prospective observational studies to produce data on the safety and effectiveness of Bdq and Dlm when used programmatically; these significant public investments add to the body of evidence for policy guidance and provide much-needed guidance for clinicians on appropriate clinical use of the medicines. Bdq and Dlm both received initial regulatory approval based on studies that looked at adding one drug to the 'standard of care' or an optimised background regimen. The evidence, thus, generated for market authorisation was focused on whether the drug was active against TB and did not address the pressing need of how it could be optimally used within novel shorter, less toxic treatment regimens and improve patient outcomes. In addition, soon after approval, clinical management uncertainties (table 3) arose as experience with each drug increased through observational studies, compassionate use/clinical access programmes, ongoing trials and programmatic use.

## RESPONDING TO THE NEED FOR CLINICALLY RELEVANT EVIDENCE ON THE USE OF NOVEL DRUGS

Organisations providing TB/RR-TB treatment such as Médecins Sans Frontières (MSF) and Partners In Health (PIH) as well as individual countries and research institutions, recognised that programmatic trials to generate clinical evidence optimising use of the newer drugs were necessary. Despite initial regulatory approval of Bdq and Dlm, treatment regimens still consisted of multiple drugs of which some were likely ineffective. There was also growing awareness that the current 20–24 month treatment duration was likely unnecessary, yet there was no evidence on what a shorter duration could be and whether the novel drugs would allow treatment shortening. MSF and PIH engaged in a clinical trial in order to design new fully oral, shorter MDR-TB treatment regimens containing Bdq, Dlm or both, which could markedly improve treatment outcomes: Expand New Drugs for TB (endTB) trial is a randomised, controlled, open-label trial of five 39-week injectable-sparing experimental regimens for fluoroquinolone susceptible, pulmonary RR/MDR-TB. Each of the experimental regimens will be compared for non-inferiority to a standard-of-care control, with randomisation adapted to treatment response.[11] The US$90.4 million multicountry trial will randomise 750 participants with the primary endpoint assessed at 73 weeks. Second, the 33.1 million USD MSF TB-PRACTECAL (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen[s]) trial is a multicentre, open label, multiarm, randomised, controlled, phase II-III trial evaluating short treatment regimens containing Bdq and the additional novel drug pretomanid in combination with existing and repurposed anti-TB drugs.[12]

A broader lack of coordination among all trialists, partners and countries involved in generating data needed for clinical use of Bdq and Dlm has led to a loss of efficiencies, including several competing prioritisations of research questions, inconsistent data quality with variable outcome measurements and inconsistent support for regional research collaborations.[13–15] Perhaps most important is how and when the real-world evidence (RWE)[16] being generated is used by national TB programmes and the WHO to produce progressive DR-TB management guidelines. Despite this, there are commonalities among clinical research initiatives who are worth highlighting: the decision to study a regimen or regimens, rather than a single drug; the choice of less rigid, innovative trial designs to reduce the gap between phase II and phase III trials and reduce the time for study completion and availability of results and allowing the use of interim data for policy guidance consideration, such as the sharing of Dlm data from the endTB observational study with Otsuka and WHO.

**Table 1** Key recently completed and ongoing trials testing bedaquiline as a single drug or as part of a multi-drug regimen for drug resistant tuberculosis

| Bdq trials (clinical trials identifier) | Phase | Description | Sponsor (funding source*) | Number enrolled† | Study start date | Primary completion date | Study completion date |
|---|---|---|---|---|---|---|---|
| IMPAACT 1025/1026S (NCT00042289) | IV | Pharmacokinetic properties of antiretroviral therapy, tuberculosis drugs and hormonal contraception during pregnancy and postpartum in HIV positive and HIV negative women | NIAID Collaborator: NICHD | 1786 | March 2003 | September 2020 | September 2020 |
| ACTG 5267 (NCT00992069) | I | Safety, tolerability and effect of single-dose Bdq and efavirenz in healthy volunteers | NIAID | 37 | December 2009 | December 2010 | December 2010 |
| NCT01012284 | I | Safety, tolerability, and effect of single-dose Bdq in patients with moderate hepatic impairment | Tibotec BVBA | 16 | January 2010 | January 2011 | January 2011 |
| TMC207-CL002 (NCT02216331) | I | Open-label trial to evaluate PK interaction between rifapentine or rifampicin and single-dose Bdq in healthy volunteers | TB Alliance (GATB) | 32 | March 2010 | May 2010 | May 2010 |
| TMC207-CL001 (NCT01215110) | II | Dose ranging trial to evaluate the EBA, safety, tolerability and PK of Bdq in smear positive pulmonary TB | TB Alliance (GATB) | 68 | April 2010 | August 2010 | September 2010 |
| C208/C209 (NCT00449644) | IIb | Open-label trial with 6 months of Bdq in addition to a background regimen for smear-positive pulmonary MDR-TB | Janssen Pharmaceuticals | 241 | September 2009 | March 2011 | January 2013 |
| NC-001 (NCT01215851) | IIa | Evaluation of EBA for different combinations of Bdq, moxifloxacin, pretomanid and pyrazinamide for pulmonary DS-TB | TB Alliance (GATB) | 85 | October 2010 | May 2011 | August 2011 |
| NCT01341184 | I | Evaluation of effect of rifampin or rifabutin on single dose PK of Bdq in healthy volunteers | NIAID Collaborator: CWRU | 33 | October 2011 | May 2012 | May 2012 |
| NC-003 (NCT01691534) | IIa | Evaluation of EBA, safety, and tolerability of combinations of Bdq, clofazimine, pretomanid, and pyrazinamide for newly diagnosed DS-TB | TB Alliance | 105 | October 2012 | April 2013 | May 2013 |
| *USFDA accelerated approval December 2012* | | | | | | | |
| NC-005 (NCT02193776) | IIb | Open-label trial to evaluate efficacy, safety and tolerability of combinations of Bdq, moxifloxacin, pretomanid, and pyrazinamide during 8 weeks of treatment in newly diagnosed smear positive pulmonary DS-TB or MDR-TB | TB Alliance (GATB) | 60 (MDR) | October 2014 | February 2016 | February 2018 |
| Janssen Japan Trial (NCT02365623) | II | Open-label, single-arm, multi-centre trial to explore safety, efficacy, and PK of Bdq for pulmonary MDR-TB | Janssen Pharmaceuticals | 6 | February 2015 | November 2018 | November 2018 |
| NiX-TB (NCT02333799) | III | Study of Bdq, pretomanid, and linezolid in XDR-TB and MDR-TB for 6 months with option of 9 months | TB Alliance (GATB) | 109 | March 2015 | February 2019 | August 2020 |
| NeXT-5001 (NCT02454205) | II/III | Open label RCT of 6–9month fully oral shorter regimen with Bdq, linezolid, levofloxacin, ethionamide/high dose isoniazid, and pyrazinamide | UCT Collaborators: South African universities | 300 | November 2015 | December 2020 | August 2021 |
| **STREAM stage 2** (NCT02409290) | **III** | **Comparison of a 6-month and 9-month Bdq-based regimen against the WHO and 'Bangladesh' regimen** | **IUATLD (USAID) Collaborators: MRC, ITM, LSHTM, Rede TB** | **588** | **April 2016** | **December 2021** | **August 2022** |
| C211 (Paediatric) (NCT02354014) | II | Evaluate PK, safety, tolerability and activity of Bdq in combination with MDR-TB therapy for HIV uninfected children and adolescents | Janssen Pharmaceuticals | 60 | May 2016 | February 2025 | July 2025 |
| DELIBERATE (ACTG 5343) (NCT02583048) | II | Study of drug-drug interactions and combined QT effects of bedaquiline and delamanid | NIAID | 84 | August 2016 | January 2019 | February 2021 |
| Expand New Drugs for TB (endTB) (NCT03259269) | -- | Non-interventional, prospective, observational cohort study to examine the safety and efficacy of Bdq and delamanid used individually in routine, multidrug regimens for treatment of MDR-TB | PIH Collaborators: MSF-F, HMS, IRD, Epicentre | 2600 | February 2016 | September 2020 | September 2020 |
| TASK-002 (NCT03032367) | I | Randomised, open-label, cross-over study comparing the bioequivalence of Bdq administered in whole tablet form vs Bdq administered in crushed (experimental) form in healthy adult volunteers | IMPAACT | 24 | November 2016 | December 2016 | January 2017 |

Continued

**Table 1** Continued

| Bdq trials (clinical trials identifier) | Phase | Description | Sponsor (funding source*) | Number enrolled† | Study start date | Primary completion date | Study completion date |
|---|---|---|---|---|---|---|---|
| endTB (NCT02754765) | III | Open-label, non-inferiority, multi-country RCT evaluating the efficacy and safety of new combination regimens for MDR-TB treatment | MSF-F (Unitaid) Collaborators: PIH; HMS; Epicentre; ITM; Ministries of Health | 750 | December 2016 | July 2023 | September 2023 |
| TB-PRACTECAL (NCT02589782) | II-III | Multi-centre, open-label, multi-arm RCT evaluating short treatment regimens containing Bdq and pretomanid in combination with existing and re-purposed drugs for pulmonary MDR-TB treatment | MSF-N (Government of Netherlands, private donors) Collaborators: LSHTM; TB Alliance; UCL; DNDi; STPHI; eResearch; WHO; THINK; Ministries of Health; LSTM | 630 | January 2017 | September 2022 | December 2022 |
| InDEX (NCT03237182) | IV | RCT comparing treatment success of a gene-derived individualised drug-resistant tuberculosis regimen to a standard tuberculosis regimen based on South African National Tuberculosis guidelines | CAPRISA | 448 | June 2017 | December 2021 | July 2022 |
| P1108 (DAIDS ID 11884) (NCT02906007) | I-II | Evaluate the safety, tolerability, and pharmacokinetics of Bdq to treat MDR-TB in HIV-infected and HIV uninfected infants, children, and adolescents | NIAID | 72 | August 2017 | September 2022 | March 2023 |
| ZeNiX-TB (NCT03086486) | III | Evaluate the efficacy, safety, and tolerability of various doses and durations of linezolid plus Bdq and pretomanid after 26 weeks of treatment for either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB | TB Alliance (GATB) | 180 | November 2017 | February 2021 | February 2022 |
| SimpliciTB (NCT03338621) | II-III | Treatment for MDR-TB with Bdq, pretomanid, moxifloxacin, and pyrazinamide for 26 weeks or 6 months | TB Alliance (GATB) | 450 | July 2018 | February 2021 | February 2022 |
| BCH_PPK003 (NCT03625739) | -- | Observational, prospective cohort study to establish population PK models of each anti-tuberculosis drug in children by nonlinear mixed effect modelling | Beijing's Children Hospital Collaborators: Shandong University; Robert Debré Hospital; Rennes University Hospital | 800 | July 2018 | October 2026 | December 2026 |
| BEAT-TB (NCT04062201) | III | Open label, multi-centre, randomised controlled trial to compare efficacy and safety of 6 months bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine compared with current 9-month South African standard of care for rifampicin resistant TB | Wits Health Consortium (USAID) Collaborators: University of California; University of Cape Town; PHRU | 400 | August 2019 | March 2023 | March 2023 |
| endTB-Q (NCT03896685) | III | Open-label, non-inferiority, multi-country RCT evaluating the efficacy and safety of new combination regimens for treatment of fluoroquinolone-resistant MDR-TB | MSF-F (Unitaid) Collaborators: PIH; HMS; Epicentre; ITM; Socios En Salud, Peru; IRD; USF | 324 | April 2020 | May 2024 | July 2024 |

The table does not include planned/non-recruiting trials, trials evaluating diagnostics, or pre-clinical trials; the Phase III regulatory required trial for bedaquiline is listed in bold.
*If different from the trial sponsor as a complementary or complete source of funding.
†Or estimated participant enrolment if the trial is planned or ongoing.
ACTG, AIDS Clinical Trials Group; TB Alliance, Global Alliance for TB Drug Development; Bdq, bedaquiline; CAPRISA, Centre for the AIDS Programme of Research in South Africa; CWRU, Case Western Reserve University; DNDi, Drugs for Neglected Diseases Initiative; DS-TB, drug sensitive tuberculosis; EBA, early bactericidal activity; endTB, Evaluating Newly Approved Drugs for MDR-TB; GATB, Global Alliance for TB Drug Development; HMS, Harvard Medical School; IMPAACT, International Maternal Paediatric Adolescent AIDS Clinical Trials Network; InDEX, Individualised M(X)DR-TB Treatment Strategy Study; IRD, Interactive Research and Development; ITM, Institute of Tropical Medicine; IUATLD, International Union Against TB and Lung Disease; LSHTM, London School of Hygiene and Tropical Medicine; LSTM, Liverpool School of Tropical Medicine; MDR-TB, multidrug-resistant tuberculosis; MRC, Medical Research Council; MSF-F, Médecins Sans Frontières-France; MSF-N, MSF-Netherlands; NIAID, National Institute of Allergy and Infectious Diseases; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; PHRU, Perinatal HIV Research Unit of the University of the Witswatersrand; PIH, Partners In Health; PK, pharmacokinetics; pre-XDR-TB, pre-extremely drug-resistant tuberculosis; RCT, randomised, placebo-controlled trial; STPHI, Swiss Tropical and Public Health Institute; STREAM, Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB; THINK, TB and HIV Investigative Network; UCL, University College London; UCT, University of Cape Town; USF, University of San Francisco; WHO, World Health Organization; XDR-TB, extremely drug-resistant tuberculosis.

**Table 2** Key recently completed and ongoing trials testing delamanid as a single drug or as part of a multi-drug regimen for drug resistant tuberculosis

| Dlm trials (clinical trials identifier) | Phase | Description | Sponsor (funding source*) | Number enrolled# | Study start date | Primary completion date | Study completion date |
|---|---|---|---|---|---|---|---|
| -- | Pre-clinical | Investigated the properties of OPC-67683 against TB in vitro and in mice | Otsuka Pharmaceuticals | -- | -- | -- | 2006 |
| -- | Pre-clinical | Investigated the sterilising activity of OPC-67683 against drug-tolerant TB in the Bactec model | Otsuka Pharmaceuticals | -- | -- | -- | 2007 |
| NCT00401271 | IIa | Evaluate the safety, efficacy and PK of four oral doses of Dlm in patients with uncomplicated, smear-positive pulmonary TB | Otsuka Pharmaceuticals | 54 | November 2006 | March 2007 | March 2007 |
| 204 (NCT00685360) | II | Multi-centre RCT to evaluate safety and efficacy of Dlm at 100 mg BD, 200 mg BD or placebo for 56 days with an optimised background regimen to treat MDR-TB | Otsuka Pharmaceuticals | 481 | April 2008 | June 2010 | June 2010 |
| 208 (NCT02573350) | II | Multi-centre, uncontrolled, open-label trial extended the administration of Dlm for an additional 6 months among MDR-TB patients who completed Trial 204 | Otsuka Pharmaceuticals | 213 | March 2009 | October 2011 | October 2011 |
| NCT01131351 | II | Multi-centre, uncontrolled, open-label dose escalation trial to evaluate the safety and tolerability, PK, and efficacy of oral Dlm when administered BD to MDR-TB patients refractory to treatment with an optimised background regimen of anti-TB medications | Otsuka Pharmaceuticals | 10 | February 2010 | May 2011 | May 2011 |
| **213 (NCT01424670)** | **III** | **Safety and efficacy of Dlm or placebo for 6 months in combination with optimised background regimen for 18–24 months** | **Otsuka Pharmaceuticals** | **511** | **September 2011** | **May 2014** | **July 2016** |
| 232 (Paediatric) (NCT01856634) | II | Pharmacokinetic and safety trial of Dlm to determine the appropriate dose for paediatric MDR-TB HIV negative patients | Otsuka Pharmaceuticals | 37 | June 2013 | December 2017 | December 2017 |
| 233 (Paediatric) (NCT01859923) | II | Safety, efficacy, and pharmacokinetic study of Dlm in paediatric patients with MDR-TB | Otsuka Pharmaceuticals | 37 | July 2013 | January 2020 | January 2020 |
| *EMA conditional approval April 2014* | | | | | | | |
| MDR-END (NCT02619994) | II/III | Compares efficacy of a treatment regimen including Dlm, linezolid, levofloxacin, and pyrazinamide for 9–12 months with a control arm of a standard treatment regimen including injectables for 20–24 months for treatment of quinolone sensitive MDR-TB | Seoul National University Hospital Collaborators: Korean University Hospitals; Korean Institute of TB; NMC-S; KCDC; Korean University | 238 | January 2016 | June 2021 | June 2021 |
| Expand New Drugs for TB (endTB) (NCT03259269) | -- | Non-interventional, prospective, observational cohort study to examine the safety and efficacy of bedaquiline and Dlm used individually in routine, multidrug regimens for treatment of MDR-TB | PIH Collaborators: MSF-F, HMS, IRD, Epicentre | 2600 | February 2016 | September 2020 | September 2020 |
| DELIBERATE (ACTG 5343) (NCT02583048) | II | Study of drug-drug interactions and combined QT effects of Bdq and Dlm | NIAID | 84 | August 2016 | January 2019 | February 2021 |
| endTB (NCT02754765) | III | Open-label, non-inferiority, multi-country RCT evaluating the efficacy and safety of new combination regimens for MDR-TB treatment | MSF-F (Unitaid) Collaborators: PIH, HMS; Epicentre; ITM; Ministries of Health | 750 | December 2016 | July 2023 | September 2023 |
| InDEX (NCT03237182) | IV | RCT comparing treatment success of a gene-derived individualised drug-resistant tuberculosis regimen to a standard tuberculosis regimen based on South African National Tuberculosis guidelines | CAPRISA | 448 | June 2017 | December 2021 | July 2022 |
| IMPAACT 2005 (Paediatric) (NCT03141060) | I/II | Evaluation of pharmacokinetics, safety, and tolerability of delamanid in combination with an optimised background regimen for MDR-TB in HIV-infected and HIV-uninfected children with MDR-TB | NIAID | 48 | January 2018 | June 2022 | November 2022 |

Continued

**Table 2** Continued

| Dlm trials (clinical trials identifier) | Phase | Description | Sponsor (funding source*) | Number enrolled# | Study start date | Primary completion date | Study completion date |
|---|---|---|---|---|---|---|---|
| NCT03678688 | I/II | Evaluate the safety, tolerability, pharmacokinetics, and efficacy of multiple oral doses of OPC-167832 in subjects with uncomplicated, smear-positive DS-TB (Stage 2 with DLM) | Otsuka Pharmaceuticals<br>Collaborator: Bill and Melinda Gates Foundation | 125 | October 2018 | February 2022 | April 2022 |
| PHOENIx (NCT03568383) | III | Compare efficacy and safety of 26 weeks of Dlm vs 26 weeks of isoniazid for preventing confirmed or probable active TB during 96 weeks of follow-up among high-risk household contacts of adults with MDR-TB | NIAID<br>Collaborator: NICHD | 5610 | June 2019 | September 2026 | September 2026 |
| BEAT-TB (NCT04062201) | III | Open label, multi-centre, randomised controlled trial to compare efficacy and safety of 6 months bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine compared with current 9 month South African standard of care for rifampicin resistant TB | Wits Health Consortium (USAID)<br>Collaborators: University of California; University of Cape Town; PHRU | 400 | August 2019 | March 2023 | March 2023 |
| endTB-Q (NCT03896685) | III | Open-label, non-inferiority, multi-country RCT evaluating the efficacy and safety of new combination regimens for treatment of fluoroquinolone-resistant MDR-TB | MSF-F (Unitaid)<br>Collaborators: PIH; HMS; Epicentre; ITM; Socios En Salud, Peru; IRD; USF | 324 | April 2020 | May 2024 | July 2024 |

The table does not include planned/non-recruiting trials, trials evaluating diagnostics, or trials for treatment of TB infection; the Phase III clinical trial for delamanid is listed in bold.
*If different from the trial sponsor as a complementary or complete source of funding.
Dlm, delamanid; PK, pharmacokinetics; RCT, randomised, placebo-controlled trial; BD, twice daily; MDR-TB, multidrug-resistant tuberculosis; NMC-S, National Medical Centre, Seoul; KCDC, Korean Centre for Disease Control and Prevention; NIAID, National Institute of Allergy and Infectious Diseases; endTB, Evaluating Newly Approved Drugs for MDR-TB; MSF-F, Médecins Sans Frontières-France; PIH, Partners In Health; HMS, Harvard Medical School; ITM, Institute of Tropical Medicine; InDEX, Individualised M(X)DR-TB Treatment Strategy Study; CAPRISA, Centre for the AIDS Programme of Research in South Africa; IMPAACT, International Maternal Paediatric Adolescent AIDS Clinical Trials Network; National Institutes of Health; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; PHRU, Perinatal HIV Research Unit of the University of the Witswatersrand.

It can be argued that the dichotomy of regulatory approval versus policy recommendation for a TB drug is unnecessary, since the key is good quality data: both RWE and clinical trials can and should contribute to regulatory approval, the quality of evidence in WHO recommendations and interpretation by clinicians and programmes. However, the traditional motivations of industry, regulators and clinical trials that are primarily aimed at securing market entry are different from pragmatic research initiatives to optimise use of new agents. Additionally, the pathway towards regulatory approval of a DR-TB drug is better defined than the framework necessary to receive normative body policy guidance. For the phase III trial of Dlm, the primary trial end point of time to sputum culture conversion differed from the WHO defined outcomes of interest in clinical care (cure, completion, failure, lost from treatment, death) and reflects the different perspectives of the WHO versus that of researchers and regulatory agencies: the role of regulators is to safeguard people from harm from individual products, while WHO subsequently makes recommendations of how to best improve health outcomes.

## INTRODUCTION TO THE REGULATORY PROCESS FOR NEW MEDICINES

At the starting point of a typical regulatory process, a developer approaches the regulator for authorisation to pursue the clinical development of a medicine based on an agreed preclinical data package. As the product advances in clinical development, more knowledge and data are generated. When the clinical development is deemed successful in meeting the requirements agreed with the regulator, the developer compiles and submits data in a registration application to the regulator with a view of marketing it on its approval; the developer, hence, becomes an applicant for marketing authorisation and if granted a marketing authorisation holder. Data generated throughout the development process are typically compiled in a dossier called the common technical document (CTD).[17] The CTD constitutes the main regulatory document submitted by the developer as part of the registration application. The CTD includes data on manufacturing and control of the product and the preclinical and clinical studies. For a developer to be able to include any of these data in a CTD, it must have generated the data itself or have signed bilateral agreements with the respective entities having generated the data to allow such use.

In the current regulatory system, it is ultimately the marketing authorisation holder of the new product that makes all the key decisions with regards to clinical and industrial developments and the regulatory pathway within the possible options. Once market authorisation is granted, it is the market authorisation holder who decides where and when the product will be manufactured and sold, at what price or prices, and in what quantities. Understanding these aspects of decision-making is paramount when considering the place and value of

Table 3 Clinical management uncertainties for bedaquiline and delamanid after regulatory approval.

| Clinical management decision | Clinical trial design | Implications for clinical management |
|---|---|---|
| Duration of use | Phase II trial design limited the duration of the drug under investigation to 24 weeks; drug duration was chosen for ease of endpoint analysis rather than optimal duration to maximise treatment outcomes | WHO guidance initially limited use of Bdq and Dlm to 24 weeks; clinicians were unable to prolong duration for patients requiring extension of Bdq or Dlm beyond 24 weeks due to resistance or intolerance to other second line medications, which can contribute to high rates of culture reversion and treatment failure[25] |
| Use in special populations | Children, adolescents, and pregnant women excluded from eligibility in Phase II trials, with time delay between adult and paediatric new drug investigations | Despite an USFDA pregnancy category B rating for Bdq (animal studies fail to show a risk to the fetus), there is ongoing reluctance to use the drug in pregnancy, due to the lack of data and subsequent WHO recommendation for its use; the delay between adult and paediatric new drug investigations means most children and adolescents in need of novel MDR-TB drugs will not receive them[26] |
| Drug–drug interactions | Potential additive toxicities, most notably QT prolongation with Bdq, Dlm, the fluoroquinolones, and clofazimine, required further investigation at the time of regulatory approval, leaving questions regarding the concurrent use of multiple QT prolonging agents, how to design an appropriate clinical monitoring schedule with electrocardiography, and whether patients should be hospitalised for close monitoring when starting treatment | WHO redefined pharmacovigilance requirements in 2015 in order to strengthen the monitoring and management of patients on Bdq and Dlm,[20] requiring significant investment at country level to establish and maintain monitoring systems |
| Combination use of Bdq and Dlm | Phase II trials did not allow for concomitant use of the two drugs | For patients with severe patterns of resistance, with few treatment options remaining, the use of novel drugs in combination was a necessity for many patients prior to WHO's recommendation on combination use in 2017[27–29] |

Bdq, bedaquiline; Dlm, delamanid; TB, tuberculosis.

contributions to the regulatory process—usually in the form of clinical data—by entities that are *not* product sponsors.

## REGULATORY VALUE VERSUS CLINICAL VALUE IN THE R&D PROCESS

It is inherent to how most pharmaceutical companies function that industry will seek the most efficient way to achieve market authorisation. However, this does not necessarily generate the evidence needed by health practitioners to use the newly approved product in clinical practice. When evidence generated by the developer to support regulatory approval fails to inform the needs of practitioners and patients, the burden of generating the missing evidence falls on actors who are not part of the formal regulatory and R&D processes, as shown in the case of Bdq and Dlm. The clinical knowledge gap left by Bdq and Dlm developers was the primary reason behind the engagement of MSF and other TB not-for-profits in the conduct of clinical trials: there was a true disconnect between evidence needed to achieve regulatory approval and evidence that practitioners involved in day-to-day care would consider essential.

The regulatory process is not merely about teasing out 'good' drugs from 'bad' drugs; it can also be viewed by some, including developers, as a value-generating process. The closer a medicine gets to market authorisation, the more *commercial value* it accrues. Because progressing through the regulatory process is a function of the evidence that is submitted to the regulator, any evidence that is part of the regulatory submission also acquires, *de facto*, a *regulatory value*. Following this logic, evidence that is not part of the regulatory process—no matter how essential it may be from clinical or programmatic perspectives—has no regulatory value because it is not a part of the data package agreed on between the developer and the regulator. In the cases of Bdq and Dlm MSF and other not-for-profit partners generated data post-conditional marketing approval, independently of the market authorisation holders and using commercial products that were bought from companies as approved medicines. Therefore, these studies have never been part of the post-marketing obligations imposed by

regulators on authorisation holders as part of the conditional approvals process.

## INCREASING CONTRIBUTION OF NON-PROFITS IN LATE-STAGE AND POSTMARKETING R&D

The examples of Bdq and Dlm are not isolated cases. The contribution of not-for-profit organisations has been essential to generating clinical evidence of safety and efficacy in late-stage development of USFDA-approved medicines in the last decade.[18] In the case of MSF, this has been particularly prominent, in recent years, in areas such as TB and Ebola. In addition to these 'thematic' niches, a more systemic trend can be observed in the regulatory process with an increasing number of medicines approved based on limited clinical data.[19] By their very design, these early approvals that explicitly accept a higher level of uncertainty warrant enhanced monitoring and postmarketing evidence collection by public health actors. As an example, the use of Bdq and Dlm after their respective accelerated/conditional approvals was subjected to strict safety monitoring protocols requiring considerable human and material resources on the health systems side.[20] In short, not-for-profit institutions are increasingly becoming active in the process of evidence generation within the R&D process, with the increasingly shared responsibility to share data with the WHO as part of their process of WHO policy updates,[21] or by collecting valuable postmarketing and observational evidence that informs an improved use of the product or which may lead to its withdrawal. Contributions may also be indirect where special provisions meant to compensate for limited clinical data for a medicine with early market entry, such as safety monitoring, are supported by medical care providers instead of by the market authorisation holder. These situations warrant extra effort and resources—both financial and human—from public health systems and non-profit institutions, and not the market authorisation holder.

This participation, however, has not resulted in a better position for these not-for-profit entities in the decision-making about further R&D and regulatory steps, including availability, pricing and access: in the specific cases of Bdq and Dlm, controlled or observational studies conducted by not-for-profits were not even initiated by the time the conditional/accelerated regulatory approvals were granted, nor were they part of the clinical development commitments made by respective market authorisation holders as part of the conditional/accelerated approval processes.[22 23] Bdq and Dlm—although initially used programmatically within standard of care regimens that served as a basis for their regulatory approvals at the time of their early market entries—are now being investigated by partners, product development partnerships and academic institutions primarily in clinical trials with novel regimens containing the two drugs as part of a patient-centred and programme-centred approach (tables 1 and 2). Since these studies, financed and conducted by not-for-profit entities, were never part of the clinical development plan validated upfront or postconditional/accelerated approvals by regulatory authorities, they have minimal regulatory value to date. The consequence of not-for-profit entities not being part of the formal process is that their essential contribution, despite its undeniable public health value and its high cost to the not-for-profit public health community,[24] falls outside the *regulatory value chain*. Consequently, it can not be used, in legal terms, to exert the essential 'checks and balances' role of public health actors in the R&D and regulatory processes. Nor can it be put forward, again legally speaking, as an argument for a wider access or more affordable price.

## WHAT NEEDS TO CHANGE: A REGULATORY PROCESS THAT PROVIDES FOR AND RECOGNISES NOT-FOR-PROFIT ACTORS' CONTRIBUTIONS

There needs to be a general acknowledgement in the medical R&D community that we are moving increa singly towards a collaborative model of drug development, where costs and risks are shared among a number of stakeholders. Moreover, early regulatory approvals result in a *de facto* shifting of the burden of generating essential additional safety and efficacy data from market authorisation holders to healthcare organisations. Therefore, it is imperative that regulatory authorities capture this plurality and task shifting, alter their processes in a manner that formally integrates the inputs and contributions of all stakeholders, including not-for-profit ones and prioritise the participation of independent clinical practitioners and healthcare organisations from the outset. The inclusion of public health-driven expertise early on in the regulatory process when optimal clinical development plans are established should increase the likelihood that these plans better reflect the needs of patients and practitioners and, hence, better respond to public health imperatives of the society. In the event where developers are not able or willing to conduct some of the essential studies, not-for-profit organisations willing to take them up will do so in a fully acknowledged and coordinated manner, as part of the R&D process and as recognised by regulators. Additionally, given that developers do not have a commercial incentive beyond regulatory approval, incentives or financing should be considered to ensure that critically needed research is done. This also applies to post-marketing studies and RWE generation when early access regulatory pathways are being pursued. In order for this to happen, one option could be to establish a legal framework within the regulatory process that would acknowledge the societal contributions, such a framework would entail clinical development programmes that better reflect public health needs. Moreover, it will lead to the legal enactment of societal contributions, as opposed to calling on the companies' good-will or 'moral' acknowledgement of these contributions. This legal enactment can then be leveraged to obtain enforceable

access provisions from product market authorisation holders such as price and supply strategy.

In order for such changes in the market authorisation process to take place, longitudinal inputs from multiple stakeholders will be needed. Efforts to create and sustain regular dialogue—through webinars, symposiums or meetings—will need leadership and commitment from the TB community if the regulatory process is to better serve the needs of those suffering from tuberculosis and other priority infectious diseases.

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