Terms of the Global TB Drug Pipeline

The Working Group on New TB Drugs (WGND) global TB drug pipeline is intended to track the progress of new candidate drugs under active development for the treatment of tuberculosis. The WGND maintains an online detailed database of compounds, candidates, and clinical trials. The database includes information on active compounds and on past development efforts that have paused or been withdrawn. The WGND also tracks compounds for latent TB, compounds in use presently, and host-directed therapies. Only trials overseen by stringent regulatory health agencies are included.

Compounds/candidate drugs depicted on the primary downloadable PowerPoint slide are new chemical entities in active development for tuberculosis treatment (see section V. below). Approved TB drugs and marketed antibiotics with activity against *Mycobacterium tuberculosis* (M. tb) infection (active and latent) are not depicted but are tracked by the online WGND database. Additional slides depicting ongoing clinical trials of regimens may include existing drugs.

I. Drug Development Terminology

1. Compound - a singular chemical entity identified as active against M. tb or under active development for potentiating another chemical entity against M. tb.
2. Regimen - treatment comprising two or more compounds
3. Trial- A study in humans conducted to test the safety and/or efficacy of a compound or regimen.
    a. Active Trial- a trial where subjects are currently enrolled and being followed.
4. Discovery - Investigation of potential chemical entities for development as a medical treatment.
    a. Hit to Lead - a stage in early discovery wherein bactericidal activity is identified through screens to identify promising hits which are then optimized into lead compounds
5. Preclinical Development
    a. Lead Optimization- the process by which a series of lead compounds are optimized for efficacy, selectivity and drug-like properties such as bioavailability.
    b. Drug Candidate- a single chemical entity identified by name and declared as a candidate drug with animal model efficacy data.
    c. GMP/GLP toxicology is the critical commitment phase for synthesis of the active pharmaceutical ingredient, oftentimes using Good Manufacturing Practices and for safety toxicology testing most often using Good Laboratory Practices.
6. Clinical- The multi-phase trials in humans to evaluate compounds or regimens.
    a. Phase 1- A phase where trials, usually with 20-100 participants, are conducted to explore safety, tolerability, pharmacokinetics, dosing in humans and drug-drug interactions of experimental drugs.
    b. Phase 2- A phase where trials, usually with several hundred participants, are conducted to assess short or intermediate term efficacy, safety and tolerability of experimental drug alone or in combination and identify optimal therapeutic dose(s) to inform go/no-go decisions for phase III.

c. Phase 3- A phase where trials, usually with 300-3,000 participants, are conducted to provide confirmatory evidence showing new treatment is safe and efficacious and considered sufficient to allow for registration if positive.

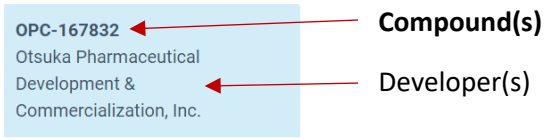
7. Trial Site- The location where clinical trials are conducted, which meet criteria set out by regulatory agencies.
8. Developer- Pharmaceutical company, non-profit organization, academic institution, government entity, foundation or other agency that is leading the development of a compound or regimen.

II. WGND Pipeline Filters

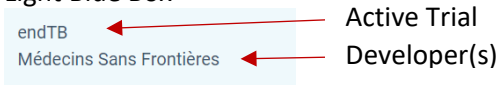
1. Advancing- a compound, regimen or trial in any given phase of development that is actively progressing through drug discovery or clinical development. During clinical testing, a compound or regimen's advance to a new phase is captured only after first patient in takes place.
2. Marketed- Drugs that have received market authorization for TB or are available on the WHO essential medicines list.
3. Repurposed- Drugs that are already approved by a stringent regulatory authority for treating a particular disease or condition, that are being studied for safety and efficacy of treating an unrelated disease or condition.
4. NCE- 'New chemical entity'- a compound for TB that has not been approved by a stringent regulatory authority for any indication.
5. Trials for Market Approval- Efficacy/safety studies required by stringent regulatory authorities prior to marketing or for removal of the Conditional Approval Status.
6. Biologic- an intervention that originates in a living organism and is administered as a therapy to enhance the eradication of Mycobacterium tuberculosis.
7. GLP- 'Good Laboratory Practice'- a set of principles intended to assure the quality and integrity of non-clinical laboratory studies.

III. Pipeline Key

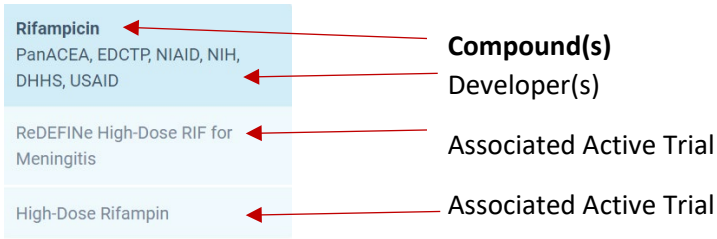
1. Medium Blue Box



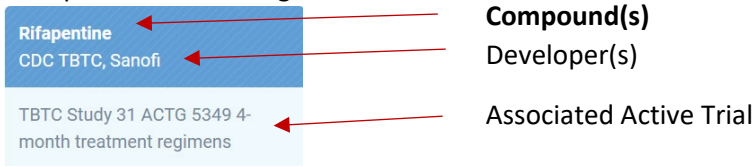
2. Light Blue Box



3. Grouped Medium Blue + Light Blue Boxes

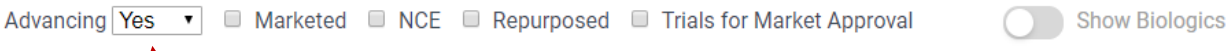


4. Grouped Dark Blue + Light Blue Boxes

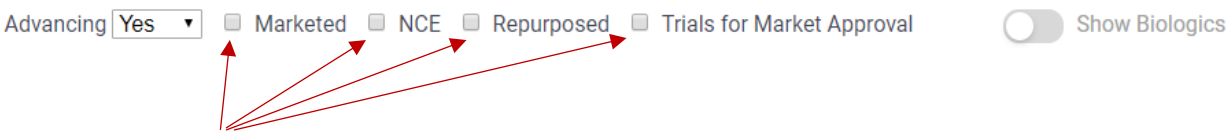


IV. Pipeline Filter Options

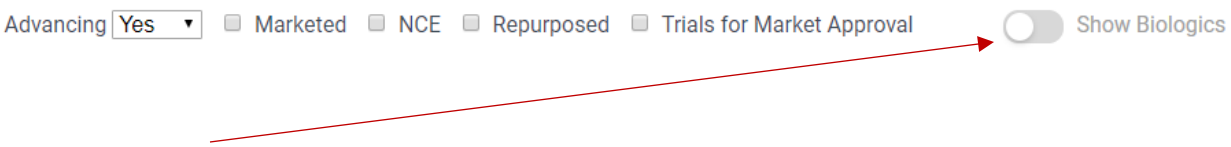
The online Global TB Drug Pipeline has interactive filters to create a dynamic set of views. As seen below, a user can choose to click on a drop-down menu next to advancing, choose one to four different filter options (Marketed, NCE, Repurposed or Trials for Market Approval), and choose a toggle to see Biologics in the pipeline.



- Drop-down menu to view advancing, non-advancing, or either



- By clicking any one of these four filters, you can manipulate the pipeline to view only those projects that are included in that filter. Or by clicking two or more filters, the pipeline will display projects that apply to either or both filters.



- By clicking the toggle next to “Show Biologics”, any biologic projects will appear on the pipeline.

V. Global TB Pipeline Downloadable PPT

The WGND provides a downloadable PowerPoint covering current new candidates for the treatment of TB. Compounds/candidates depicted in the first online PowerPoint slide are new to development for tuberculosis treatment (since around 2001) and are in active development. Active development can include substantial sponsor investment in the candidate development plan, funding obtained to support translational research, recent publications substantiating anti-TB activity or promising drug-like features, progression into a new phase of development, or regulatory filings or approvals. This slide is updated in the Fall before the UNION conference, on World TB Day, and as the WGND is informed of major advances by the developers or in public presentations. Compounds/candidates that have shown no new advances (publications, new funding, advances in pipeline, licensure, etc.) in the previous year are removed from the TB drug pipeline.

VI. Notice of Pipeline Updates

Updates to the Global TB Drug Pipeline are voluntary submissions by the sponsors or follow-up from a WGND representative with study directors. If no response is received from the study director(s) and no publicly released update has appeared in the prior year, projects may be labelled “not advancing” or removed from the Global TB Drug Pipeline.