DR-TB STAT - July 2017 call

20 July 2017

Attendees: Erica Lessem (TAG); Vivian Cox (DR-TB STAT); Jennifer Furin (SWIFT); Ramon Crespo (GDF); Grania Brigden (Union); Christophe Perrin (MSF); Barbara Roth (MSF); Sharonann Lynch (MSF); Shelly Malhotra (TB Alliance); Brian Kaiser (GDF); Dumebi Mordi (MSH); Blessi Kumar (GCTA); Marcia Moepi; Regina Osih (CHAI); Tiziana Masini (MPP); Nataliya Morozova (PIH)

Agenda:

1. General update on DR-TB STAT activities (Erica Lessem, 5 minutes)
2. Quarterly data on global access to new drugs (Erica Lessem, 10 minutes)
3. Presentation and discussion on access to bedaquiline in Ukraine (panel discussion, 20-30 minutes)
4. Wrap up and date for August call (Erica Lessem, 5 minutes)

Minutes: Nataliya Morozova

General Update

- The Union Conference 2017 - DR-TB STAT proposal was accepted – "**Overcoming challenges in the introduction and scale-up of newer drugs for the treatment of multidrug-resistant tuberculosis: lessons from the field**" session at 1030-1200 on Thursday 12 October 2017.
    - The Chairs – Rosa Herrera and Erica Lessem
    - Speakers from: India, Mexico, Papua New Guinea, a patient representative from India, one of the NTP managers from Swaziland
    - The Session discussion - common challenges of using BDQ and DLM in our settings, ongoing barriers in the countries and how to overcome them.
    - Other sessions pertaining to new drugs and the shorter regimen that might be of interest are:
        1. "Programmatic implementation of BDQ and DLM: experiences in drug procurement, technical assistance, clinical management, and drug safety monitoring" workshop at 1130-1730 on 11 October 2017; USAID chairs.
        2. "Accelerating the uptake of new diagnostics, medicines, and regimens to eliminate TB through improved guidance and coordination" workshop at 0800-1400 11 October 2017; GDI/GLI chairs.
        3. "Implementing novel drugs and regimens for the treatment of MDR-TB: a skills building workshop" workshop at 0800-1400 11 October 2017; V Cox, E Rutta, and C Hewison chairs.

- DR-TB STAT switched to quarterly reporting on new drugs and shortened regimen. The July 2017 report has been sent as an attachment to the meeting invite. Not many countries are reporting on the shortened regimen. Until robust data received from the countries, we will report on the use of BDQ and DLM.

Quarterly data on global access to new drugs - Erica Lessem (TAG)

- The July 2017 Global Report provides the numbers of patients on BDQ and DLM in countries who reported to DR-TB STAT
  - India: BDQ – 567 patients, DLM – 51 patients. Most of them are on compassionate use.
  - Kazakhstan: BDQ – 196, DLM – 103, thanks to the interventions of Partners In Health endTB Project
  - Russia: BDQ – 1444; DLM – 18. Otsuka made an announcement, they are licensing DLM (Deltyba) to R-Pharm in Russia to manufacture and commercialize the drug in Russia and other CIS countries. The timeline is not clear because there is no trial on DLM in Russia
  - South Africa: BDQ – 6723; DLM - 81

- GDF Orders:
  - BDQ orders from GDF: 13,825
  - DLM orders from GDF: 3,238
- Additional updates on shortened regimens and new drugs – Jennifer Furin (SWIFT)
  - A lot of countries have not started using shortened regimens because of high rates of resistance to one or more drugs in the regimen
  - South Africa has 936 patients on shortened regimen
  - Vietnam stopped enrollment on BDQ because the drug is not registered in the country. They need to bring it under operational research conditions. The original cohort was defined only as 100 patients, so now that they have enrolled 100, they don't have a mechanism for enrolling more patients.
  - DLM in South Africa – fewer than 20 patients started on DLM clinical access program. Otsuka has been promising to register DLM since February 2016. The latest update – they need a local company to do a registration. They hope to register DLM in South Africa by the end of the year.
    - [Update since call: Otsuka has now filed for registration in South Africa]
- Question and Comments
  - Erica Lessem - Can DR-TB STAT do anything to address the Vietnam situation?
    - Answer – Jennifer Furin – the NTP wants to start using the drug regularly, but the Ministry of Science and Technology controls the number of patients the NTP can enroll, they see this as an operational observational cohort, i.e. research. We could push Janssen to register BDQ in Vietnam and DLM as well.
      - [update since call: Janssen has filed for BDQ registration in Vietnam in 2016; we will check with them on status]
  - Vivian Cox –lack of WHO pre-qualification of the new drugs has been another barrier for not to use the drug in Zimbabwe
    - Zimbabwe started the 3rd patient on BDQ.
    - Erica Lessem – new WHO pre-qualification fee structure may be a barrier for pursuing PQ– we hope to work out a process with WHO for smaller

volume products (especially for pediatric formulation for SLD or other products, which have no reference originator so can't go for SRA approval). For BDQ and DLM – ether WHO pre-Q or SRA approval can be done.

- Christophe Perrin (MSF) – Zimbabwe signed an agreement with WHO to be part of collaborative registration procedures. They can register the drug through a pilot project. Janssen is working in 7 African countries through the WHO collaborative registration. It will need to add Zimbabwe in the list. It will help the country without being pre-qualified by WHO since this process can also rely on SRA approval
- Vivian Cox – in Zimbabwe we discussed Section 75, a waiver to import BDQ and DLM. The issue of WHO pre-qualification is a reason not to continue to grant waivers and move towards registering the drugs. They do not need to wait for Phase III data results to be known for either drug. It would be good if they can join the collaborative registration process.

<u>Presentation and discussion on access to bedaquiline in Ukraine</u> (panel discussion)

- Neither BDQ, nor DLM is available under routine access in Ukraine.
- BDQ access - Christophe Perrin (MSF)
  - There is a need for registration of the DR-TB drugs to be imported and dispensed in Ukraine.
  - The main issue for BDQ in the country - Ukraine is part of Pharmstandard footprint, Janssen is working with Pharmstandard to get money to fund Phase III clinical trial, then Pharmstandard could have the right to register and supply BDQ in all CIS countries, including Ukraine.
  - Pharmstandard should be registering BDQ in Ukraine, but they might not be able to. Janssen for business reason could not be a license holder in the country. They know the issue should be resolved as soon as possible.
  - Novartis went ahead with registration of clofazimine with current available data. On June 23rd clofazimine was registered through a fast track approval. A fast track approval system can be used for registering other drugs.
- Questions and Comments:
  - Is Ukraine still able to get drugs through GDF, while they try to resolve the issue?
    - Answer – Erica Lessem - Ukraine does not have a waiver mechanism to import and distribute the drug. It appears that under some small programs in Kiev, some patients can access the drug. There is no legal mechanism to distribute the drug before it is approved. There is no compassionate use pre-approval access mechanism in the country. Part of it is legal and regulatory complication from the country side, but registration would solve that.
  - Christophe Perrin – there was an order for 200 treatments of BDQ placed last month
  - Ramon Crespo (GDF) – According to the report, 200 bottles were received at the end of June and cleared customs in July.
  - Christophe Perrin - It is hard to get final information from Ukraine. It could be that they have identified a one-off solution, but it is precarious.

- Erica Lessem – It might be for a limited number of patients. It would not be possible to use for a routine programmatic use for the country without registration.

- Recent Otsuka announcement in CIS countries
  - Sharonann Lynch (MSF) - Otsuka has given the marketing licensing right of DLM for all CIS countries to R-Pharm. We do not know the price and timeline for registration.
  - Christophe Perrin – Otsuka says R-Pharm has a Ukrainian partner that would be able to be a license holder in Ukraine.. We do not know about the timeline. After the press release was made public, we could clarify that R-Pharm does not have to wait until marketing authorization is granted in the Russian Federation before they can start filing DLM dossiers in all CIS countries. There is no list of priority countries, that needs to be clarified.
  - Erica Lessem – We were in touch with Otsuka after the announcement came out. They say that R-Pharm is a subsidiary in Ukraine, they know this is a priority, but there is no concrete timeline. We do not know what the priority countries are, what the price is. Otsuka Announcement has been sent to DR-TB STAT group during this call. We need to ask both Otsuka and R-Pharm to come up with clear timeline for registering the drug in CIS countries. There is also a potential complication in that it is unclear if Russia will require studies to be conducted in Russia, which Otsuka has not done, which could delay registration by $\geq$ 1 year.
  - Sharonann Lynch – There is no public announcement from Otsuka in terms of price, timeline for registration. Otsuka still needs to submit this product for WHO pre-qualification in order for it to be a part of the WHO collaborative registration platform unless there has been some change.
  - Christophe Perrin – We do not need to go through extra steps of WHO pre-qualification of DLM due to the WHO collaborative registration process. That's good news.
  - Question (Erica Lessem) - Does it need to be an agreement with WHO to participate in the collaborative registration even if they do not need to file with pre-qualification?
    - Answer (Christophe Perrin) – WHO registration collaborative procedure needs country, manufacturer, and WHO should agree on the way forward. For BDQ, it was the matter for WHO and Janssen to agree about the sections that WHO should support countries in the registration process. Janssen published an article about this process. Otsuka always mentioned that it agreed about the process and it should be part of the agreement they signed with the two partners.
  - Next Step - Erica Lessem - We should write a letter to Otsuka (concerning Global registration) and R-Pharm (concerning CIS countries) to find out their timeline. Today was the deadline that Otsuka had to submit a dossier for filing with the Indian Regulatory Authority (DCGI). They have submitted their dossier in Peru, another trial country.
    - [update post-call: Otsuka confirms that the dossier was submitted in India]
  - Question - Shelly Malhotra (TB Alliance) – With the Janssen agreement with Pharmstandard, they have allowed for parallel importation to GDF and some CIS countries, as part of the agreement, the counties that were typically

accessing medicines through GDF (some low and middle-income countries). Will they be able to do that? With the DLM agreement, are the countries still able to access to GDF?
    - Answer - Erica Lessem – We should flag it and find out what the terms are, because a lot countries in the region are procuring through GDF. We need to make sure they are able to.
    - [update post-call: Otsuka confirms that countries will be able to buy through either GDF or R-Pharm]
- Sharonann Lynch – In Ukraine we don't have pediatric FDC being used.
- Shelly Malhotra - I am aware that Ukraine has ordered FDCs. I can find out if they have been delivered.
- Sharonann Lynch – Can you find out if Ukraine is going to use them? Will they be changing their guidelines to include FDCs? Is it possible? Any change of policy?
    - Answer - Shelly Malhotra (TB Alliance) - Many other countries issue an addendum with a dosing table. They do not reissue the overall guidelines.
- Do you have data on consumption?
    - Answer – No, we have data on what has been ordered and sent out.
- Erica Lessem – Should we put pressure on Global Fund, Ukraine to do more? Who should be a target for that?
    - Answer - Sharonann Lynch (MSF) – Absolutely. Global Fund should make clear their expectations. To have pressure from people of influence – WHO, USAID – that would be helpful.
- Ramon Crespo – The drugs arrived in Ukraine and passed clearance on the 4th of July.
- Erica Lessem – Janssen has committed to sharing solution on bedaquiline availability in Ukraine at the Union Conference.

Next DR-TB STAT call: **17 August 2017, Thursday,** at 11:00am EDT, agenda to follow