Managing Risks and Benefits in Medicines Systems:

The Example of Dolutegravir

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April 3RD 2019

The Global Fund

Quality Assurance Team

Mission

Enable procurement of the health products complying to internationally-recognized norms and standards, assure continuity of supply, and facilitate access to innovative products through policies, communications with countries, data sharing and compliance verification exercise

Value driver	Description of value
Safety	• Ensure products procured with GF funds are safe, efficacious and of assured quality
Access	• Support introduction to innovative products through Expert Review Panel (ERP) process
Availability	• Work to ensure continuity of supply
Compliance	• Guarantee that products procured with GF funds adhere to GF internal policies and guidelines

In full alignment with TGF 2022-2017 Strategy :
Maximize impact against HIV, TB and Malaria

Recalling the event

- A preliminary analysis of an on-going observational study in Botswana has identified a potential safety issue with the HIV antiretroviral medicine Dolutegravir (DTG)

- The preliminary findings identified 4 cases of neural tube birth defects out of 426 women who became pregnant while taking DTG. This rate of approximately 0.9% compares to a rate of 0.05% seen among women treated with EFV-based ARV and 0.09% among HIV-negative women.

- Neural tube defects are birth defects that can occur early in pregnancy when the spinal cord, brain and related structure do not form properly

- Preliminary data from the aforementioned study seem to suggest that the potential safety issue arises from a women's exposure to DTG at the time of conception rather than during pregnancy.

Current environment in 2018

- DTG is a very promising medicine
  - Faster action
  - Less toxic
  - More robust – High barrier to resistance
  - Potential to be cheaper - 270m USD per year in savings
  - Potential increase in treatment for same funding for 5 million people

- Dolutegravir is an US FDA, EMA and WHO approved antiretroviral medicine used in combination with other ARVs medicine to treat HIV.

- As per Global Fund's Quality Assurance policy DTG is eligible for procurement with GF funds because stringently assessed

- As consequence Drug safety communication from Major regulators providing safety recommendations on the use

- The same has been forwarded to all GF recipients via QA Information Notice

Experience gained from Dolutegravir / 1

- ✓ Innovative medicines usually bring added benefits (cost, efficacy) but also uncertainty
- ✓ This uncertainty is inherent to the limited knowledge gained through the development of the medicine including Clinical Trials, on a limited population, and recruitment criteria not considering all types of patients (pregnant women, MultiTh).
- ✓ Robust regulators such as FDA & EMA supplement their marketing authorization with specific plan to manage risks (RMP) based on the remaining uncertainty, e.g. registry exposure, post-authorization safety studies (PASS), …
- ✓ Robust regulators can rely on operational Pharmacovigilance systems intensified for innovative molecules, allowing for early identification of safety signals
- ✓ Where innovative products are marketed in mature health systems, health practitioners and personal are trained, patients informed on risks

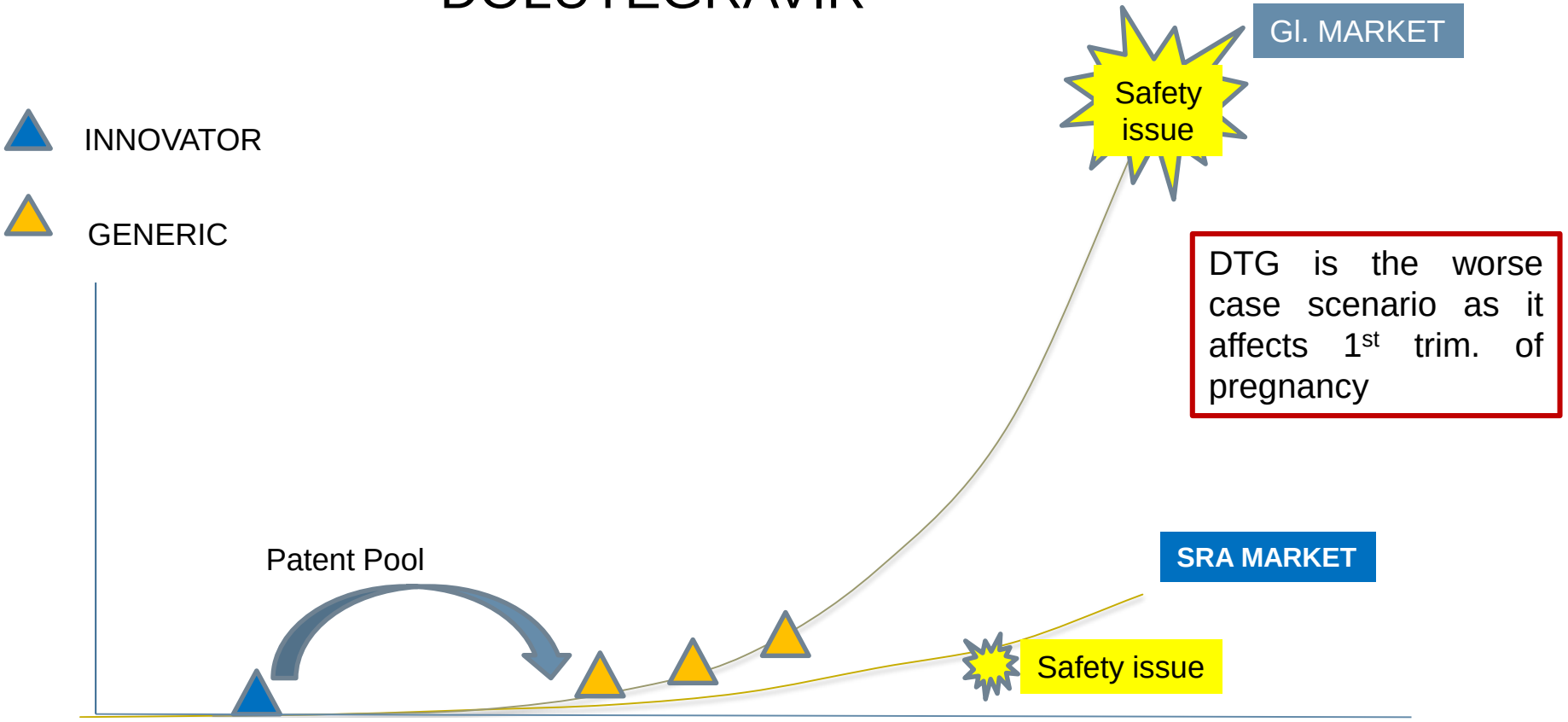
Experience gained from Dolutegravir / 2

- ✓ GF through grant funds improves to a great extend the access to innovative products for an increased number of patients
- ✓ Some of these innovative medicines may potentially lead to an increased risk of emerging adverse drug reactions only by volume effect which increases the probability for ADRs
- ✓ In most of LMIC where the innovative medicines are provided, regulators are not sufficiently mature and have poor pharmacovigilance systems in place.
- ✓ Moreover Risk management plans similar to those implemented in mature regulatory systems are not always in place and / or may not be adequate to the LMIC country environment e.g. change in the IFU/notice
- ✓ Health care providers are not always trained and patients sensitized to Pharmacovigilance
- ✓ Limiting the capacity to detect safety signals in a timely manner

Experience gained from Dolutegravir / 3

- ✓ In the past, innovative medicines were put first on the market in countries with mature regulatory system and reached LMIC markets at later stage
- ✓ To some extend, developing countries were relying / benefiting on drug safety data collected from Robust regulatory system and assessed by Stringent Regulators
- ✓ At present, numerous novel products are being developed in order to treat diseases which are disproportionally affecting developing countries and are introduced in early in those countries
- ✓ Without intervention, this might increase the number of patients exposed to emerging risks which could seriously undermine the global effort to provide new treatment options to patients

DOLUTEGRAVIR



Concluding Remarks

- No intension to reconsider the GF position to support introduction of innovative health products which is a corner stone of the GF Strategy

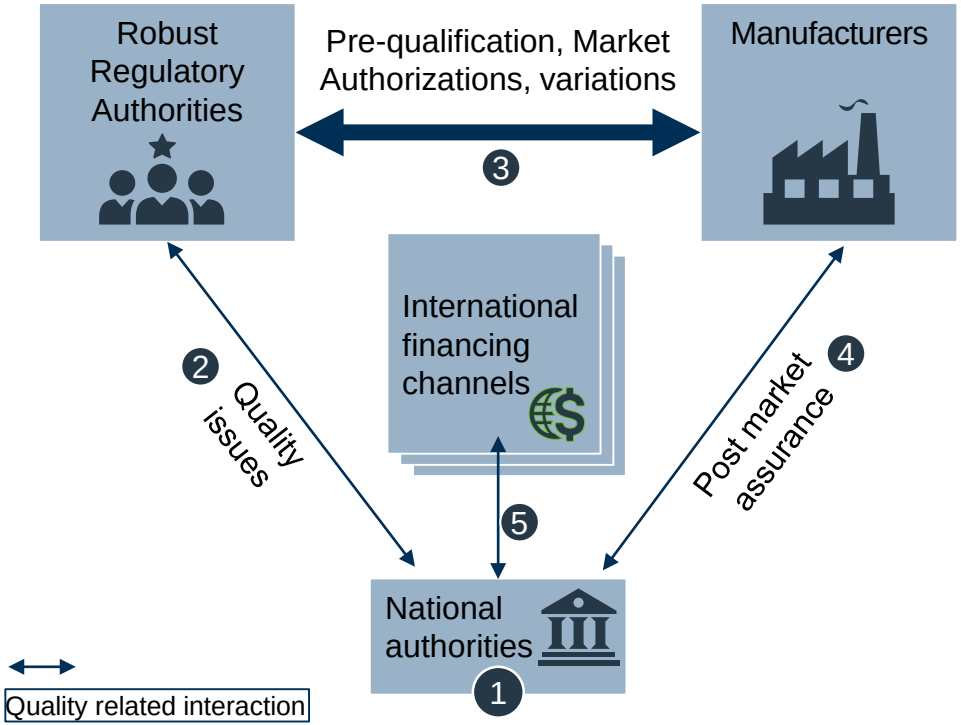
- Quality Assurance should not be seen as a barrier to access but rather as a tool for continuous improvement / risk assessment

- We have to learn lessons based on this example
  - To review our initial assessment of risk triggered by introducing innovative products
  - To reconsider our current practices and further improve our internal processes e.g. communication & sharing information on risks
  - To provide financial support to countries and to external partners such as WHO
  - To sensitize the global community

Thanks for your attention

Concluding Remarks

Communication Challenges in the QA Echosystem



1. **Limited capacity of countries to generate adequate information in a timely manner**
2. **Insuficient quality information from the field reach the SRA to effectively act up**
3. **Manufacturers informing predominantly RRA and only partially countries on quality & safety issues**
4. **Very limited quality information from the field reach the manufacturer**
5. **Limited sharing of information between countries and partners**

Source: GF