OPEN DISCUSSION 2

Clinical Considerations

Kimberly Struble kicked off the discussion by affirming FDA openness to new ideas for BE assessment of LAI formulations. Attendees voiced specific concerns about the current approach to BE determination and highlighted challenges posed by LA formulations. Throughout the discussion, there was a sense of urgency to leverage this group's expertise and collaborate to design new methodologies and hold discussions with the FDA as well as regulatory agencies in other countries and global stakeholders.

"What is the alternative approach to evaluating [BE] ... The FDA is inviting some of this novel thinking in order to move forward"

We need a new set of target parameters to determine BE for LAI formulations

LAIs behave differently. BE for short-acting formulations cannot be used as a place holder.

- LAIs exhibit release-dependent PK.
- Massive inter-individual variability is inherent in LAI products.

Concern about missing opportunities for generic approval if BE confidence bounds are too rigid (i.e., 85-125%).

- Need to allow for therapeutic equivalence if BE is not met.
  - ◊ Example: BE study is conducted in a slightly different population; Drug absorption curve is similar to the innovator but does not meet confidence bounds for BE due to more variability.
- FDA. A built-in safeguard via modeling the Ka to prove we aren't giving up any efficacy based on some variability not accounted for in traditional BE.
  - ◊ Virtual BE studies or a supplemental package could be very helpful.
- There is a precedent for applying criteria to drugs with very wide inter-individual variability that are wider than traditional BE.

Bayesian approach.

- FDA Office of Generic drugs just wants applicants to show that the two formulations are the same given the inherent biological variation.
- BE based on priors (PK data from the existing formulation) and what you think you know about the proposed generic formulation.
  - ◊ If we can craft a line through the PK curve, and the line for the innovator and proposed generic are the same, that is sufficient for BE, even if there is variability in the data.
  - ◊ A statistical test would not be used to say the formulations are different – They are not.

pAUC and inferring BE.

- A challenge is that a small difference in a LAI formulation can have a profound impact over a 2-3m dosing interval.
  - ◊ The terminal half-life is going to look different.
  - ◊ Many LAI products have multi-modal PK.
- **How long does it take to figure this out?**
  - ◊ It is obvious when you have a full dataset (i.e., CAB), and you can draw a line through it.
  - ◊ With BE, you are collecting a small piece of data (pAUC) at the point of making a decision. **You cannot just extrapolate from here.**
  - ◊ Example of multi-dose olanzepine: Each dose has a different PK (i.e., Same formulation over time in the same individual).
- Fundamental research is needed to understand how much of the terminal half-life we need to collect to have confidence in a BE determination.

Different parameters are needed, but regulators do not change quickly

Generic ARV products will need to meet BE criteria for the foreseeable future.

- If BE is not met, there may still be an opportunity to prove equal activity via a clinical trial.

Could we influence BE study duration for CAB-LA or are we talking about more in the future?

- CAB-LA BE studies are set to begin in 2025.
- A simple change in methodology might be possible, but a radical proposal will take time.

Call to action to design innovative methodologies for BE

If we don't do it, no one will.

- Generic companies are conservative; They need support.
- We have many ideas and experts in this room. Let's study designs, put ideas together, and have conversations with the FDA to generate some of these concepts.
- FDA is looking for innovation from people like us.

Don't wait. There is no more compelling time than right now.

- FDA sounds receptive to change now, then it will go down the traditional path.
  - ◊ Do not miss this opportunity to impact the path in a positive direction.
- If we cannot make LEN and CAB-LA available for PrEP where most of the infections are, then we are basically giving up.

There is a precedent for proposing new methodology to FDA.

- In recent years, the Forum for Collaborative Research has proposed new methodology to the FDA for DAA trials and studies on PrEP and background infection rates.
- The Office of Generic Drugs has been open to different methods.
  - ◊ Need to show that your method has the correct predictive power.
  - ◊ The statistical analysis plan and underlying assumptions need to be completely and thoroughly laid out.

Getting generics into LMICs extends beyond FDA – need buy-in from other agencies and interested parties.

- Need to convene additional meetings to educate a mass amount of people at the same time and foster discussion.
  - ◊ Regulators, key opinion leaders, and purchasers in other countries.
  - ◊ New methodologies could be foreign territory for many.
  - ◊ Include access to modelers and statisticians and this group to explain some of the concerns and how we will work through them.
- Potential shorter term targets for engagement:
  - ◊ PQ and FDA-tentative approval will open procurement with PEPFAR and Global Fund.
  - ◊ License for CAB-LA requires PQ or SRA approval (FDA-tentative approval, sometimes EMA and article 58).

Negative consequences of ARV drug resistance are huge

The frequency of resistance mutations depends on duration of failure.

- Resistance profiles are limited in clinical trials due to early detection.
- In clinical practice, people fail for longer periods.

Administration issues can impact drug concentrations and resistance.

- Especially when drugs are supplied on a larger scale.

Concern around the idea of informed consent (Before BE criteria met) and follow-up.

- If we give patients a "bad" or under-performing formulation, then we have selected a number of integrase mutations in those patients.