Scaling-up manufacturing capacity of novel HIV therapeutics: reality check

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Medicines Patent Pool

Long-acting formulations for HIV: Current Landscape

Oral Delivery

Islatravir (NRTTI)

Implants

Tenofovir Alafenamide

Subcutaneous Delivery

Lenacapavir (Capsid Inhibitor)

Intramuscular Delivery

CABOTEGRAVIR
RILPIVIRINE

Approved

Intravenous Delivery

Broadly neutralizing antibodies

Transdermal Delivery

Microarray patch of Cabotegravir

Vaginal Delivery

Dapivirine Ring

Approved

Long-acting formulations: Viewpoint of Generics

Contents of the dossier for submission

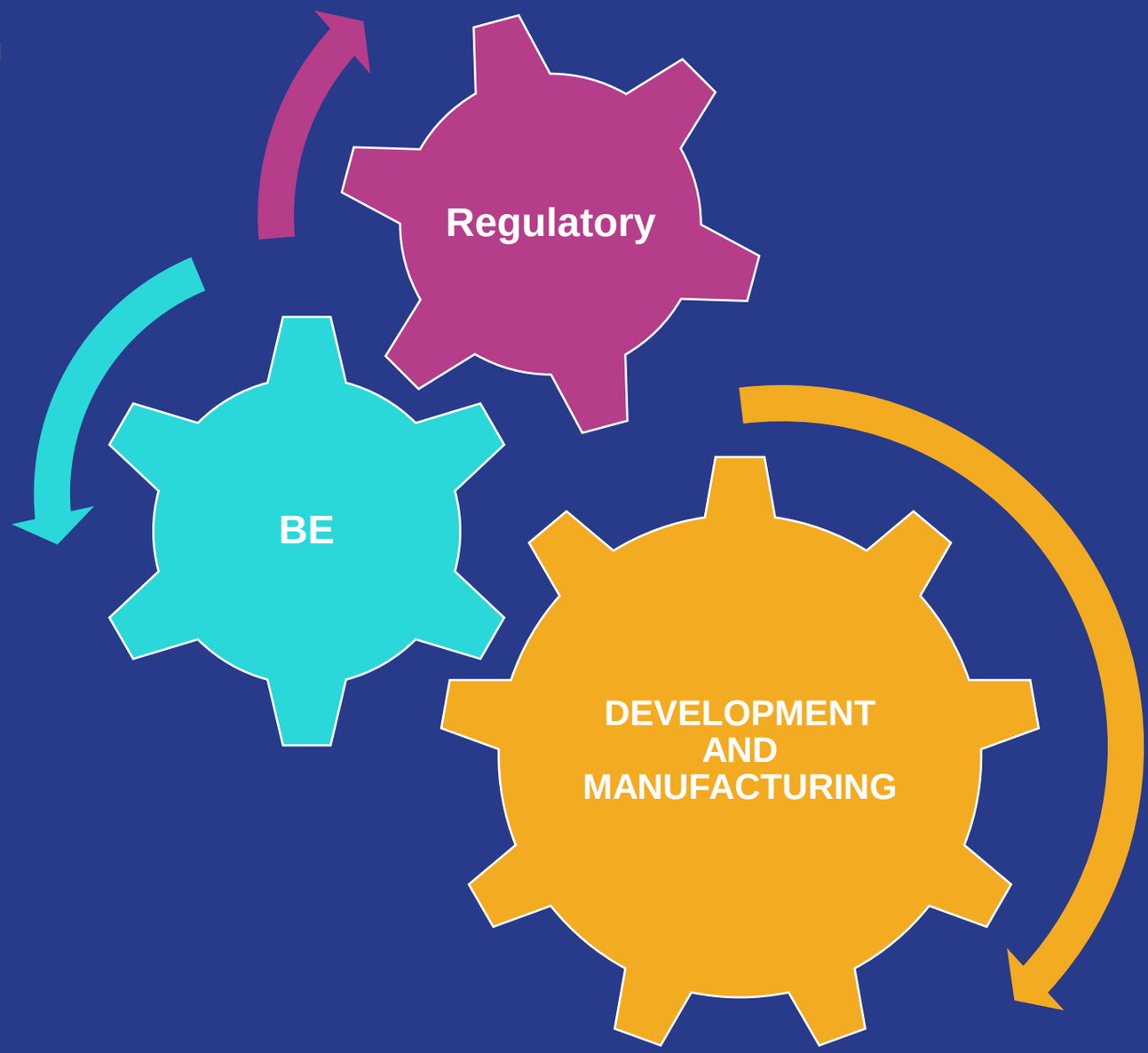
Originator

- Chemistry
- Manufacturing
- Controls
- Labelling
- Testing
- Animal Studies
- Clinical Studies
- Bioavailability

Generics

- Chemistry
- Manufacturing
- Controls
- Labelling
- Testing

BIOEQUIVALENCE



Development and Manufacturing Considerations for generics

- **Technical Expertise** : Experience and expertise to develop long-acting formulations

  - *Leveraging from experience of developing Long-acting formulations (antipsychotic, hormones)*
  - *Technology package/Technology transfer/Technology support from originators when needed can accelerate generic development*

- **Equipment and Infrastructure** : Especially where formulation technology is the driver for long-acting properties, and not the properties of the drug *per se*

  - *Leveraging from common technologies used for oral/ophthalmic routes (eg Nanomill, Extrusion etc)*
  - *Funding for specific CAPEX requirements (if required) from donors/funders can be helpful*

- **Novel excipients and devices (proprietary polymers, rare solvents, complex devices)** : Concerns in supply chain security, identifying and characterizing CMAs by analytical tools, additional studies for device performance and equivalence

  - *Originator support in sourcing and characterizing novel polymers and devices can be useful for the generics*
  - *Supplier agreements for novel excipients /devices can help in solving supply chain concerns*

- **Oral Lead In** : Additional development of a solid oral formulation

  - *Generics are equipped to develop standard OSD formulations*

Bioequivalence considerations for generics

- **Biowaivers not possible**

- **BE duration :** Sampling times longer than traditional BE

- **Bioequivalence design :**

  - Parallel Vs Cross Over (Parallel design might not be possible due to long wash out period)
  - Single dose Vs Multiple dose (in some formulations, multiple dose study might be required)

- **Population** : Patients Vs Healthy volunteers , Special population requirements, Pediatrics etc

- **Number of subjects :** High variability expected , thus increased number of subjects

- **Oral Lead In :** Additional BE requirements

  - *Originator tech pack support containing PK data at both single dose and multiple dose (steady state), time to reach steady state, level of accumulation if any, intersubject and intrasubject variability etc can help generics develop an appropriate BE protocol*

  - *Timely availability of Regulatory guidelines for BE : Collaboration between generics and scientific advisory teams of regulatory authorities*

- **Lack of IVIVC :** Establishing IVIVC is challenging for long-acting formulations

  - *Originator and expert group support for any possible IVIVC can enhance the probability of BE success*

Regulatory considerations for generics

- **Regulatory Pathway** : Regulatory pathways for generics
    - *Well defined regulatory pathways (like inclusion in PEPFAR , WHO EOI etc) can help and promote filing of generic products.*
- **Regulatory guidelines on technical aspects :** Availability of BE recommendations, Product monographs
    - *Timely availability of technical guidance from Regulatory authorities on BE, product monographs containing specifications can help generics in developing the product faster*.
- **Regulatory capabilities in LMICs :** Competence of regulatory authorities in LMICs to assess dossiers of complex products
    - *Initiatives to strengthen regulatory capabilities of some LMICs*
    - *Promoting reliance /recognition of Stringent Regulatory Authorities/WHO PQ*
    - *Originator support with preclinical and clinical data in some countries to facilitate generic filing*

Conclusions

- To promote **accessibility and affordability in LMICs,** it is important to have **generic versions** of Long-acting HIV formulations

- **Diverse technologies** are adopted to achieve long-acting formulations : each product will **pose specific challenges** for the generic manufacturers in terms of development, manufacturing, bioequivalence and regulatory aspects. Thus, these products needs to be evaluated and analyzed on a **case-by-case** basis.

- The objective of making these products available in LMICs at affordable price cannot be achieved by the generic players alone. A **collaborative effort** from all stake holders including originators, regulators, policy makers, civil society, donors and funders etc are crucial for success.

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THANKS