



GRx+Biosims™

Generic + Biosimilar Medicines Conference

Assessment of Risks, Challenges and Opportunities
in Conducting Foreign Bioequivalence PK Studies

Dr. Kumar Ramu
Sr. Vice President & GM, QPS Holdings LLC



Objective

- Insight into conducting PK based BA/BE studies for North America or EU submissions
 - Requirements
 - Timelines
 - Things to consider
 - Future prospects
- Studies conducted in HV or Patients depending on guidance
- Studies being conducted in Foreign Countries like
 - India
 - TW
 - China
 - Eastern Europe
 - South Africa
 - South East Asia (Malaysia)

History

- BA/BE studies were predominantly done in the US before
- Increasing trend over the past 20 years to conduct PK based BA/BE studies for North America/EU submissions in Foreign Countries
- As of the mid 2017 Clin.Trials.Gov indicated only 36% of all clinical studies were done in the USA
 - Brazil, Russia, India, China, East EU, Israel, TW, SA...being the other countries
- By early 2017 >40% of generic drugs imported into the USA were from India
- Indian pharma companies have even lead the generics market with innovation and research, where FDA determines their product to be the RLD in the Orange Book

History (contd.)

- The trend of studies in foreign countries has had its challenges due to quality and ethical issues with some of the CROs
- FDA and DCGI (India) collaboration in mid 2017 helped promote safety and quality of clinical trials in India
- Increased inspections, training and due diligence has helped the trend in the recent years
- Currently >70% of the BE studies for USFDA ANDA submissions are done in India
- Global trials are also much more common now



India

GRx+Biosims™

Study Conduct

- FDA guidance drives the clinical conduct for studies in HV or patients
- Healthy Volunteer Studies
 - Conducted in Phase 1 clinical sites
 - CROs with clinical sites and a wide range of #beds
 - Studies can be for any dosage form
 - Study designs include
 - Cross Over
 - Parallel (drugs with long $T_{1/2}$)
 - Replicate – Partial of Full (Variable drugs)
- Patient Studies
 - Conducted at physicians practice site or as part of a hospital

Approvals to Conduct Study

- CRO applies for approvals on behalf of sponsor
 - Phase 1 trials for NDAs are difficult to get approvals for
- DCGI rule changes in March/April 2019
 - Timelines reduced for Indian companies
 - Timelines of 90 days for foreign submissions, but normally within 50-60 for HV studies
 - Cost for approval increased 20 fold, from \$150 to \$3000
- Regulatory Approvals in India
 - BENOC – Bioequivalence No Objection Certificate
 - NDAC – New Drug Approval Committee (part of DCGI that issues the BENOC for new drugs)
 - T-License – Import Permit
 - EC – Ethics Committee
 - CBN – Central Bureau of Narcotics (for controlled substances)

Submission Documents for Approvals

Category	Documents from the Client
Products marketed in India (>4 year)	Nil
Products marketed in India (1 - 4 year)	Brief Manufacturing Process, Stability (AC/LT, 3 months), Dissolution Comparison Profile, Test & Reference COA & 14 Days sub-acute tox in 2 species (Injectable)
Modified Release (ER) products	Brief Manufacturing Process, Stability (AC/LT, 3 months), Dissolution Comparison Profile, Test & Reference COA & 14 Days sub-acute tox in 2 species (Injectable) Published Literature on PK/PD in healthy / patient population
Products marketed in India (<1 year)	Brief Manufacturing Process, Stability (AC/LT, 3 months), Dissolution Comparison Profile, Test & Reference COA & 14 Days sub-acute tox in 2 species (Injectable) Published Literature on PK/PD in healthy / patient population
Products not marketed in India	Brief Manufacturing Process, Stability (AC/LT, 3 months), Dissolution Comparison Profile, Test & Reference COA & 14 Days sub-acute tox in 2 species (Injectable) Published Literature on PK/PD in healthy / patient population Approval History, Clinical and Non-Clinical Data, HV data with this dosage form

Submission Documents for Approvals

- **EC**
 - Study protocol
 - Informed Consent (English + other local languages)
 - Investigator CV
 - Recruitment Advertisement, if any
- **CTRI**
 - Brief Study Synopsis
 - DCGI and Ethics Committee Approval letter



Approvals for Patient Studies

- BENOC + T-License (DCGI)
- EC application and approval for each PI/site
 - Submit 21 days prior to EC meeting
 - EC meets every 4 – 6 weeks
 - Approval 1 week after meeting
- IP shipment can be initiated after DCGI approval
- CTRI (Clinical Trial Registry of India)
 - Online registry done in parallel with IP shipment
- Site Initiation after all approvals
- Site Selection based on
 - PI experience
 - Language not being a barrier
 - ICH/GCP compliance
 - US/EU training
 - Availability of subjects

Approvals Needed and Timelines

#	Category	Approval time in Days		
		T-License (DCGI)	BENOC* (DCGI)	EC (IRB)
1	Drugs (IR) – manufactured/marketed >4 years in India	20	Not required	30-45
2	Drugs (IR) – manufactured/marketed >1 - <4 years in India	90	90	30-45
3	Drugs (IR) – manufactured/marketed <1 years in India	90	90	30-45
4	Drugs (ER) – dose marketed in India	90	90	30-45
5	Combination drugs/505b2 - drug & dose marketed in India	90	90	30-45
6	BA/BE study in Patients - drug & dose marketed in India**	90	90	30-45
7	Drugs – not marketed in India (considered new drug) – HV***	120	120	30-45
8	Drugs – not marketed in India (considered new drug) – Patients***	120-180	120-180	30-45

T-License and BENOC approvals go together (DCGI)

Filing for BENOC & EC approvals done in parallel

**DCGI approvals happening in 50-60 Days for most cases*

***CTRI registry takes an additional 30 days after DCGI approval for patient studies*

****BENOC for New Drugs reviewed by NDAC within DCGI*

Each clinical site for patient studies has its own EC

CBN approval for controlled substances is an additional 30-40 days after DCGI approval

Things to Consider

- **IP Shipment**
 - Within a week after approvals (EC/DCGI)
- **Blood Volume**
 - 430 mL/subject/study
 - Same as 1 Unit or bag of blood/subject/study = 430 mL
 - 3 month interval between studies
 - But less of an issue today with highly sensitive bioanalytical methods
- **Gender**
 - Normally 100% men
 - Possible to have women (10-15%) with an extra charge
- **Biologics (in HV or Patients)**
 - Conducted at physicians practice site or as part of a hospital

Things to Consider (contd.)

- Languages
 - All documents in English
 - ICF - English, Hindi + 1 or 2 local ones
- Controlled substances
 - Selected ones can be done in India – but limited
 - Additionally CBN approval required
 - DEA process to ship outside USA
- Regulatory Inspections
 - FDA
 - BA audits are surprise
 - Clinic audits are planned and study is notified on arrival
 - EMA/MHRA/WHO
 - Study specific audits
 - Planned audits with approx. 90 days notice

Dermal Studies

- **Topical (Creams & Lotions)**
 - Vaso-Constriction Studies
 - Blanching studies
 - Skin color is less of an issue (though you can find HV that will mostly comply with Fitzpatrick scale of 3, with some 2s')
 - These studies are being done in India
- **Transdermal**
 - PK and Adhesion studies
 - Can be done as skin color is less of an issue
 - Irritation/Sensitization studies
 - Cannot be done in India
 - Skin color is a limitation
 - Two distinct Climatic conditions is a limitation (at least most of the time)
- Need extensive trained personnel to perform these studies

Indications/Therapeutic Areas for Patient Studies

- PK Studies
 - Oncology
 - CNS
 - Respiratory
 - Pharmacoscintigraphy
 - Dermatology
 - Postmenopausal
 - Endocrinology
- Clinical End Point Studies
 - Ophthalmic
 - Infectious Diseases
 - Diabetes
 - Respiratory
 - Dermal
 - Gynecology
 - Psychiatric



Taiwan

GRx+Biosims™

Study Conduct

- FDA guidance drives the clinical conduct for studies in HV or patients
- Healthy Volunteer Studies
 - Conducted at CRC (Clinical Research Centers) in hospitals or at a qualified teaching hospital
 - CROs don't own the clinic
 - Studies can be for any dosage form, design, including 505b2 and NDAs
- Patient Studies
 - Conducted at hospital sites
 - Depends on the patient pool
 - PI resources
- Inspections
 - Study specific
 - Planned

Submission Documents for Approvals

- IRB (EC)
 - BE Protocol
 - Clinical Study Synopsis in Chinese
 - ICF in Chinese
 - Brief Introduction of IP
- TFDA (Taiwan FDA)
 - Trial registered in the Taiwan Clinical Trial Network
 - All docs submitted to EC
 - IP Information and drug registration status in Taiwan
 - CMC data including assay, content uniformity, Dissolution profile of T & R along with methods and details
 - Information on Bioanalytical Method Validation or supporting literature

Submission Documents for Approvals

- IP Import Permit
 - Approvals (EC/TFDA)
 - IP Amount
 - Study flow chart depending on study design from protocol



Approvals Needed and Timelines

#	Category	Approval time in Days		
		EC (IRB)	TFDA	Import Permit
1	Drugs marketed in TW – BA/BE studies	45		30
2	Drugs not marketed in TW (NDAs) – BA/BE studies	45	90	30
3	Drugs not marketed in TW – non BA/BE studies (need CTA)*	45	45	30

**Studies like SAD/MAD PK/PD, DDI, food effect, PK in special populations, bridging studies*

Almost all drugs are marketed in TW; so Generics will fall under #1

Filing for TFDA & EC approvals done in parallel

Each clinical site has its own EC

Import permit application made after EC/TWFA approvals

Things to Consider

- IP Shipment
 - Import permit application needed - ~30 days
 - Application made after EC/TFDA approval
 - Shipment within a week after that
- Clinical Conduct
 - At Clinical Research Centers in a hospital or at a qualified teaching hospital
 - Max # beds is 40
 - Volunteer pool is a shared resource with most major CROs in Taipei area
- Clinical Monitoring
 - Sponsor or CROs monitor the site



China

GRx+Biosims™

Study Conduct

- FDA guidance drives the clinical conduct for studies in HV or patients
- Healthy Volunteer Studies
 - Conducted at CRC (Clinical Research Centers) as part of hospitals
 - CROs don't own the clinic
 - Studies can be for any dosage form, design, including 505b2 and NDAs
- Patient Studies
 - Conducted at hospital sites
 - Depends on the patient pool
 - PI resources
- Inspections
 - Study specific
 - Planned

Submission Documents for Approvals

- IRB (EC)
 - BE Protocol in Chinese
 - Clinical Study Synopsis in Chinese
 - ICF in Chinese
 - Brief Introduction of IP
 - GMP Certificate
 - IB in Chinese
 - Additional docs specific to IRB at hospital
- NMPA (National Medicinal Products Association, CFDA)
 - All docs submitted to EC
 - All major documents in Chinese
 - IP Information
 - Dissolution profile of T & R along with methods and details
 - Information of Bioanalytical Method Validation

Submission Documents for Approvals

- **IP Import Permit**
 - Approvals (EC/NMPA)
 - Approved clinical protocol
 - IP Specs and Amount
- **Genetic Office Approval**
 - Applicable to foreign sponsors
 - Application made after EC/NMPA approval
 - Application to be done by the clinical (hospital) site



Approvals Needed and Timelines

#	Category	Approval time in Days			
		EC (IRB)	NMPA	Import Permit	Genetic Office
1	Drugs marketed in China – BA/BE studies	20-60		≤30	~20
2	Drugs not marketed in China – BA/BE studies	20-60	60	≤30	~20
3	NDA	20-60	12-16m	≤30	~20

Filing for NMPA & EC approvals done in parallel

Each clinical site has its own EC

Import permit application made after EC/NMPA approvals

Genetic Office application made after EC/NMPA approvals

Things to Consider

- IP Shipment
 - Import permit application needed - ~30 days
 - Application made after EC/NMPA approval
 - Shipment within a week after that
- Clinical Conduct
 - At Clinical Research Centers in a hospital
 - Max # beds is 60
 - Volunteer availability is not an issue
- Clinical Monitoring
 - CROs monitor the site
- Chinese Documents
- Genetic office approval



Eastern Europe

GRx+Biosims™

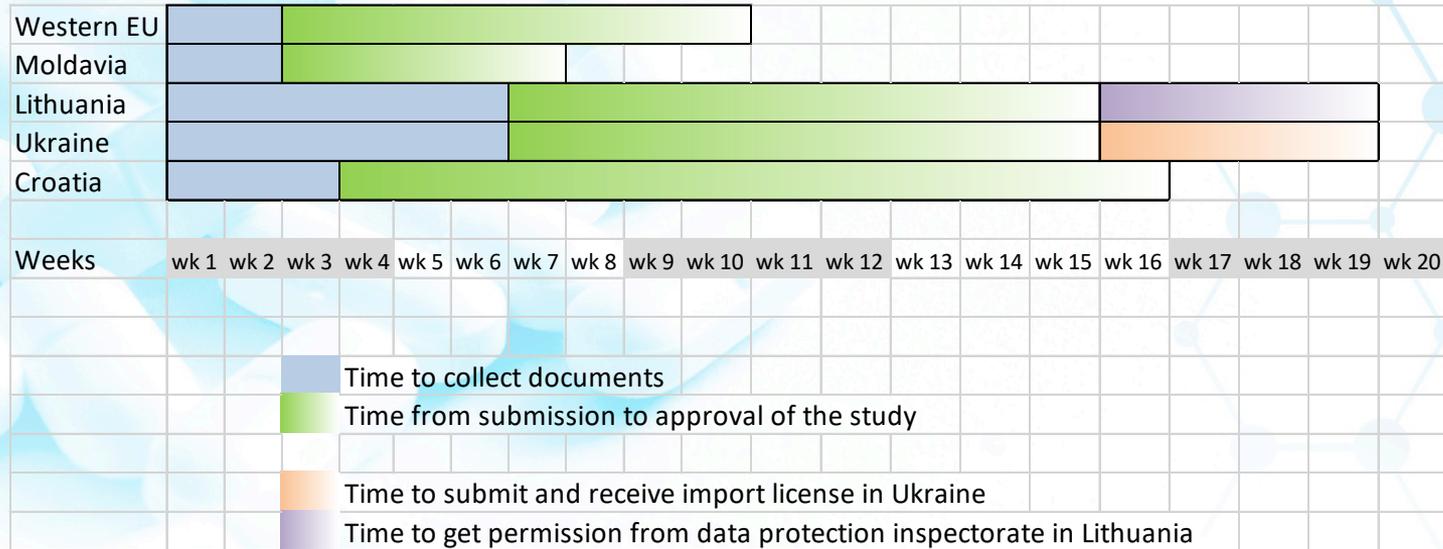
Study Conduct

- PK studies in HV and patients can be done in **Eastern Europe (CEE)** countries like for e.g.
 - Moldavia, Lithuania, Ukraine, Croatia
- Doing a generic PK BE study in HV has less benefit to volunteers - recruitment but also approval by the authorities can be hurdles
- There are some well-established Phase I units delivering high quality work
- The approval timelines comprise the timeframes for ethics approvals as well as approvals from the competent authorities

Study Conduct (contd.)

- There is no central submission process – like the EU
- Approvals needed from the specific countries local authorities (e.g. ministry of health) and the EC
- Special approvals in certain countries for certain patient population
- Countries may need import licenses
 - Licenses differ among countries
 - Could depend on compounds/product

Approvals Needed and Timelines



Approval times vary among the countries



South Africa



GRx+Biosims™

Study Conduct

- PK studies in HV and patients can be done in **South Africa**
- There are some well-established Phase I units delivering high quality work
- The approval timelines comprise the timeframes for ethics approvals as well as approvals from the competent authorities
- SA GCP guidelines updated in 2014 into law
- Guidance for quality and conduct of BE studies released in 2019
- Additional approval needed for biologics

Study Conduct (contd.)

- Approvals needed (all done in parallel)
 - SAHPA (health authority)
 - EC
 - Import license
- SAHPA (South African Health Products Authority, called MCC before)
 - Meets 4 times a year
 - Approval times range from 12 – 20 weeks (90-120 days)
- Regulatory authorities like to see justification/rationale to conduct study
 - Sponsor is planning to market the drug in S.A.
 - Drug in the trial is for a disease that is prevalent in S.A.
- Doing a generic PK BE study in HV has less benefit to volunteers - recruitment and approval by the authorities can be hurdles



Why S.A.

- Infrastructure
 - Facilities
 - Research
 - Diversity in population
 - Experience
 - Regulations well defined
-
- Global patient trials are more common in S.A.





South East Asia (Malaysia)

GRx+Biosims™

Study Conduct

- PK studies in HIV and patients can be done in **South East Asia (SEA)** countries like for e.g.
 - Malaysia, Thailand, Singapore, Philippines, Indonesia, Vietnam,...
- Malaysia is seeing an increased attention to conduct clinical studies
- There are some well-established Phase I units that can conduct clinical trials
 - Ministry establishments, private hospitals and medical teaching hospitals
 - Established medical centers and sites
- Sites inspected by FDA and EMA

Regulatory Approvals

- **Registration of Clinical Trial**
 - All the clinical trials must be registered with National Medical Research Register (NMRR)
- CTA submitted to Drug Control Authority (DCA) and EC in parallel
- **Independent Ethics Committee (IEC/IRB) Approval**
 - The IRB structure depends on the location or type of facility conducting the research
 - Most university hospitals have their own local IRB/IEC
 - There are 13 IRBs/IECs in Malaysia registered with the NPCB
 - Research conducted at ministry of health (MOH) hospitals fall under central IRB which is Ministry of Health Medical Research and Ethics Committee (MOH MREC)
 - Research conducted at non-ministry of health (MOH) hospitals use local IRBs like Penang Ethics Committee or that from universities and private hospitals
 - Clinical trials conducted at these sites have to be approved by the respective IRB/IEC

Regulatory Approvals

- Agencies within DCA
 - National Pharmaceutical Control Bureau (NPCB) regulates drug clinical trials
 - National Pharmaceutical Regulatory Agency (NPRA) ensures its conduct
- CTIL (Import License)
- Application made to NPRA in parallel
- Sponsor/CRO with a permanent address in Malaysia needs to apply
- The NPRA screens the application dossier for completeness before handing them over to the DCA for a decision to be made

Approvals Timelines

- CTIL/CTX application is processed within 45 days (30 working days)
- MREC/IEC approval takes 75 days (50 working days)
- Once approval is granted by both the DCA and MREC/IEC, the NPRA issues the CTIL/CTX and regulatory approval letters to begin the clinical trial
- The average timeline for regulatory and IRB approval is about 3-4 months

Indications/Therapeutic Areas for Patient Studies

Cardiovascular disease and Stroke

Endocrinology

Influenza and Pneumonia

HIV/AIDS

Tuberculosis

Diabetes

Gastroenterology

Respiratory

Oncology



Why SAC (Malaysia)

- Infrastructure
- Facilities
- Diversity in population
- Research Experience
- Regulations well defined
- They have an established healthcare system
- Government supportive of Malaysian clinical research
- Regulatory and ethics submission in English and in parallel
- Quick start-up timelines as clinical trial agreement
- Many Investigators are GCP trained
- Diverse population



Future

GRx+Biosims™

Future of Clinical Trials

- Increased # of Clinical Studies in these regions
- Including 505b2, Injectable, Biologics
- Patient PK studies on an increase
- Quality CROs
- Increased regulatory inspections
- Increased global regulatory knowledge and oversight
- Clinical trials Infrastructure
- Volunteer availability including treatment naïve
- Increased awareness in the community (cell phones)
- Skilled Investigators
- Experienced quality staff, many with US/EU training/influence
- Extensive FDA and EMA end to end submissions capability