DRUG PRODUCT REGISTRATION IN SEMI-REGULATED MARKET

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REVIEW ARTICLE

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ABSTRACT:

There found a diversity of regulatory requirement in Semi regulated market. This region consists of mainly the countries from Asia pacific, Latin America, Eastern Europe, Africa and Gulf countries. Countries from Asia pacific and Gulf have somewhat harmonized their regulatory environment through The Association of Southeast Asian Nations (ASEAN) and Gulf Co-operation Council (GCC) organizations, ROW countries yet to be harmonized regulations in their respective regions.

The urgent requirement to rationalize & harmonize regulation was required by instance of rising cost of health care, research & development and to meet the public requirement for safe and efficacious treatments to patient in need. ICH committee has given priority to harmonize the format of reporting data for quality, safety and Efficacy in the application dossier.

The commercial significance of ROW markets is increasing globally. It is crucial that pharmaceutical companies keep up-to-date with the latest regulatory developments to ensure their place on the ROW market.

This paper favors the regulatory processes for gaining marketing authorization in ROW countries in terms of technical data requirement for the dossier.

Key words: DRA, ASEAN, GCC, BMR, ROW, CIS, DMF, TSE/BSE, ICH, FP.

Introduction

- Drug Regulatory Affairs is constantly evolving and growing and is the one which is least impacted during the Acquisition and Merger, and also during recession. Global harmonization in standards has led to consistent approach in regulatory submissions and hence its review.
- Systematic formulation development acts as a back bone for any dossier preparation in export registration
- There are different requirements in different countries for registration It is difficult for any company to develop product for each region Therefore; we need to consider majority of requirements during technical data submission which will help in export registration.
- Enormous diversity of regulatory requirements are there, however, harmonisation occurs as clusters in some Semi regulated countries e.g. ASEAN, Gulf

Pharma Market is divided into:

1. **Regulated Market:** US, EU (UK, Germany, France, Ireland, Sweden etc.), Japan, Canada, Australia, New Zealand, South Africa
2. **Semi regulated Market: (ROW Countries):**

(a) **Asia** (Sri Lanka, India, Bangladesh,; **ASEAN**: 10 Countries group - Philippines,

Vietnam Singapore, Malaysia, Thailand, Indonesia, Laos, Cambodia, Brunei Darussalam, Myanmar

(b) **African countries** (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe etc)

(c) **Middle East countries** (Gulf Co-operation Council countries i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE)

(d) **Latin America** (Mexico, Brazil, Panama, Peru, Guatemala, Argentina, Chile, Dominican Republic)

(e) **CIS** (common wealth of independent states): Russia, Ukraine, OFSUs (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirghizstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan etc.)

Difference from Regulated Market

Degrees of implementation are different.

Intensity of audits/ inspections is different and similarly penalties for GMP violations are different. Regulated market guidelines are very clear and are to be adhered to 100%

Recent Queries raised by various ROW markets

- Computation of batch size.
- Chromatograms during method validation for assay and impurities.
- Complete supporting data for process validation
- Cleaning validation report
- Reconstitution Stability (For oral suspensions):
- Preservative content and microbial limits
- Redispersibility and rheological properties
- Particle size distribution

Registration Requirements for Rest of the World

Administrative Documents:-

- Certificate of Pharmaceutical Product
- Product Permission
- Manufacturing License
- WHO-GMP Certificate
- Free Sale Certificate/Export Certificate
- Artwork (Carton, Label & Package Leaflet)

Chemistry, Manufacturing & control documents

API DMF Open part – Following data should be available in Open Part

- Nomenclature
- General Properties
- Name of the Manufacturer and Site of manufacture
- Route of Synthesis, flow diagram in brief
- Structural Elucidation
- Impurities
- Specifications and Method of Analysis
- Container Closure System
- Stability testing – Retest period & Storage

API Specification and Method of Analysis & COA of API by the Applicant

Justification for Impurity Limits

The following factors to be considered while fixing the specification limits

- API impurity limits data (COA)
- Check ICH requirements.
- Check pharmacopoeial limits, if any.
- API stability data.
- Finished product stability data etc.

Manufacturing Formula & Process

- Manufacturing Formula
- Description of manufacturing/packaging

- Scale, Equipment by type, capacity, process parameters for steps (e.g. time, temp, pH), Environmental conditions, e.g. Relative Humidity for Hygroscopic materials
- Description of In process controls/test
- Flow Diagram- Indicate critical steps , In-process controls
- Master formula
- Batch manufacturing Record – Copy of the Master BMR or Completed BMR
- Process Validation Protocols and /or reports-3 batches process validation reports and /or protocol is to be submitted. 3 Batches should be of the same size and should be similar to the batch size mentioned above in the manufacturing formula.
- Formulation & Development is required for some countries like Russia, Ukraine, Algeria, Kenya, ASEAN etc.

Batch Analysis

- Results of at least one batch should be given. It should be preferably of the batch of which the samples will be submitted for registration. OR It can be of the latest batch, as required by the agency in the respective country. It should be given as certificate of analysis.

Excipients

- For Excipients of natural origin microbial limits should be specified
- For Human or Animal origin TSE/BSE certificates from the manufacture should be incorporated
- Information on Adventitious Agents should be provided, such as Asbestos in Talc
- Permitted & approved Colors and Flavors should be used.
- Excipients not in compendia are generally not recommended. Some standard mixtures comprising excipients in Pharmacopoeia are allowed (e.g. Opadry Colors). In such cases table with composition of such mixtures and specifications with test form the supplier should be provided
- For Excipients described in compendia, copy of Monograph along with copies of the methods referred to in monograph but not appearing in monograph should be provided.
- Current Pharmacopoeial monograph is always applicable. Details of any specifications additional to monograph should be provided.(e.g. particle size, residual solvents)
- Excipients Certificate of Analysis tested against the full set of specifications.

Finished product Specification and Method of Analysis

- If not as per Pharmacopoeia specifications should be prepared as per ICH Q6A. Methods of Analysis should be described in details
- If based on Pharmacopoeia additional product related specifications should be included as in-house specifications (e.g. Description, Hardness, Friability, Average weight, Dimensions, Identification of colorants, MLT). Copy of the Monograph is acceptable in some countries. Methods of the additional tests should be given.
- If a test is based on a compendia monograph, a copy of the monograph + any methods referenced in the monograph must be submitted.
- Details of any specifications and test methods additional to those in the Pharmacopoeia must be submitted.

Method Validations for FP and API

- In few countries Validation of analytical methods is still not mandatory if the Pharmacopoeial method is followed.
- Non-Compendial method needs to be validated if required by the Agency.

Stability Data and Stability Protocol

- Ability of pharmaceutical product to retain its property within specified limits throughout shelf-life
- The stability programme includes sample size, test interval, storage conditions, specific methods and container closure system
- Stability studies should include testing of those attributes of the Finished product that are susceptible to change during storage and are likely to influence quality, safety and efficacy
- Testing should cover the physical, chemical, biological and microbiological attributes, preservative content and functionality tests (e.g. Nebulizer).
- Microbial limits at release and end of shelf life. Dissolution limit should be same as for release.
- API used shall preferably be of different batches.
- Stability to be performed on each individual strength & container size of drug product, unless bracketing or matrixing is applied.
- In conclusion Shelf life should be proposed / concluded including the storage condition.
- Generally 3 batches (2 pilots, 1 smaller) data is required to be submitted.
- A pilot scale batch is generally, one tenth of a full production scale or 100,000 units, whichever is larger
- Recent modification of 30°C/70%RH condition to 30°C/65%RH – an attempt at a single long-term global testing condition
- Testing frequency and storage conditions should as per the ICH guidelines
- Stability data as per Zone: {Acc.: 0, 1, 2, 3 & 6 months; Long term: 0, 3, 6, 9, 12, 24 & 36 months}
- Local stability requirements for different countries is given below:-

Attribute Market	Number of Batches	Stability Condition Long Term	Min Duration-ACC	Min Duration-Long Term
FWA & CA	**3**	**Zone II**	**3 m**	**3-6 m**
ASEAN	**3**	**Zone IV(b)**	**6 m**	**12 m**
LATAM	**3**	**Zone IV**	**6 m**	**6 m, Vene-12 m**
Mid-East	**3**	**Zone IV;Jordan-Z-III**	**6 m**	**12 m, SL, Jordan-24m**
CIS	**3**	**Zone II**	**6 m**	**6 m**

Packing Material

- Packing material should be suitable for storage, transport and compatible.
- For Primary packing material detailed specifications and method of analysis including Identification for material of construction required.
- For Secondary packing material specifications and method of analysis required
- Printed packing material and PIL specimens and /or colored artworks Certificate of Analysis & Batch Packaging record required

Bioequivalence

- Compares the systemic exposure profile of a test product (Generic) to that of a reference product (Innovator Brand)
- For the test product to be bioequivalent it should exhibit the same rate and extent of absorption as the reference product
- Required for Tablets, Capsules and Oral Suspensions etc
- It can be waived for aqueous oral solutions, parenteral solutions or solutions which are locally applied and locally acting, for example eye drops topical products inhalators or nasal spray products.
- If Bioequivalence study is not available then multimedia, multipoint comparative dissolution profile data of the product with innovator product should be submitted. Data should be complied the requirement for F2 factor.

Pharmacological, Toxicological data

- Published References on Toxicological & Pharmacology studies are attached in the dossier
- Published data on clinical trials and references are attached in the dossier

Registration fees- Registration fees should be paid as per the requirements of the Agency of importing country

Other requirements

- Working Standard and along with certificate of analysis
- Samples of API and Excipients
- Chromatograms, Spectra of the identification tests wherever applicable

Samples

- As per the quality, it is mandatory to submit fresh finished product samples along with the dossier. The quantity of the sample varies as per the requirements of the Agency of importing country.

Summary & Conclusion

- ❖ Any export market demands good quality dossier which can be generated through systematic Formulation Development.
- ❖ The proper planning and execution of Formulation development will help in quality dossier & in answering queries from Regulatory authorities.
- ❖ Since the world is divided in the drug approval procedures with technical data as described above, it is important especially for the generic manufacturers, to carefully judge the market need, Development Cost, target regions, & regulatory requirements before the development of drugs. Hence it is critical to plan and co-ordinate all the activities for successful launch of product in the market on time.
- ❖ Due to vast difference in Regulatory requirements it is impractical to get global marketing approval at same time and launch the product at once in all regions. Hence, one should carefully understand and define the clear regulatory strategy by looking at the target regions, different patent terms and its extension, various application possibilities, data requirements, potential timeline for marketing launch in different regions. This eliminates unnecessary studies, minimizes the delay in drug approvals and subsequent launch, and reduces overall cost of development.

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