GLOBAL VIEW ON REGULATORY AFFAIRS

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Global Regulatory Affairs – Simple or Complex??

How people think things are

How things really are

Few critical challenges faced by the Industry which requires steps towards Harmonization:

1. Faced paced actions of FDA and the anticipated actions on product extensions – Complexity of COPPs
2. Nitrosamine Risk assessment and vendor support
3. Compendia Harmonization Challenges
4. Data and Reference product requirements in harmonized product development
5. Complex Generics and Paradigm shift on the requirement of Q1+Q2 and Now Q3 Similarity
6. IIG Evaluation and potential RTR concerns
7. RLD labelling updates and its impact on timely ANDA approval
Regulatory Harmonization – Need of the Hour

Image Credit: www.fdli.org
Fast paced actions from US FDA during COVID & Anticipated impact on Product Extensions

Approvals / Tentative Approvals – 948 ANDAs
- Includes 72 1st time gRx
- 35 gRx with CGT Designation (17 CGT Approvals if Q1 FY 2020)

Responded to 3,711 Controlled Correspondences
121 Requests for product development and pre-ANDA meetings

Reference: 2020 OGD Annual report
Certificate of Pharmaceutical Product - CPP

Emerging Market Health Authorities – CPP Expectation
Product to be approved and being commercial in the country of origin (where the product is manufactured)

Definition of CPP –
Certificate for a Pharmaceutical Product is an evidence of GMP, Quality, Safety, Efficacy review and approval by a competent Health Authority.

When would a CPP be required
• A recipient authority could require a CPP when it does not undertake a full review of QSE data submitted for registration

Is it possible to obtain a CPP from a certifying authority that is not the country where the manufacture of the finished product takes place?
• Yes, the GMP declaration in the CPP will refer to assurance of GMP for the product approved in the certifying country at the stated site, even if the manufacturing site is in a different country than the issuing authority

Is it necessary for the CPP to come from the country where the Finished product manufacture takes place
• No, although the Scheme was set up assuming that the certifying country was also the country where finished product manufacture takes place, there is scope within the Scheme for CPPs to be issued by other authorities that can provide independent assurance of the GMP compliance status
Certificate of Pharmaceutical Product- CPP

**WHO –**
1. If the CPP is made available from a competent authority (High surveillance) then the Importing Country Health Authority *need not undertake a full review of QSE* data submitted for registration
2. Proof of **GMP compliance** for the site where the product is manufactured

**Health Authorities –**
1. Proof that the product is approved and commercial
2. The product is actually consumed and safe in the Population of the exporting country where it is manufactured

Complex process to get CPP for the products which are US/EU extensions to Emerging markets/NCE/NDA in India
Certificate of Pharmaceutical Product- CPP

1.2
• Is this product licensed to be placed on the market for use in the exporting country? (Yes/No)

1.3
• Is this product actually on the market in the exporting country? (Yes/No)

1.2 & 1.3
- Yes
  • Argentina, Mexico
  • Colombia, Peru
  • Ecuador, Malaysia
  • Philippines, Vietnam
  • Myanmar, Kazakhstan
  • UAE, Thailand
  • Singapore, Indonesia
  • Cambodia, Sri Lanka
  • Taiwan, Dominican Republic
  • Jamaica, Egypt, Iraq

1.2 & 1.3
- Yes/No
  • Brazil
  • Hong Kong
  • Laos
  • Tanzania
  • Maldives

1.2 & 1.3
- No/No
  • Russia
  • Ukraine
  • Kenya
  • Georgia
  • Belarus
  • Azerbaijan
**Nitrosamine Risk Assessment**

<table>
<thead>
<tr>
<th>N-Impurity</th>
<th>USFDA</th>
<th>EMEA</th>
<th>Health Canada</th>
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<tr>
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<td>√</td>
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</tr>
<tr>
<td>NMPA</td>
<td>√*</td>
<td>√*</td>
<td>√*</td>
</tr>
<tr>
<td>MeNP (1-methyl-4-nitrosopiperazine)</td>
<td>-</td>
<td>-</td>
<td>√*</td>
</tr>
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</table>

**Timeline for Risk Assessment**
- March 01, 2021
- March 31, 2021
- March 31, 2021

**Timeline for Confirmatory testing**
- ASAP
- ASAP
- October 1, 2022

**Changes to MA**
- 3 Years from Guidance (Sept ‘23)
- September 26, 2022
- October 1, 2022

*Included in latest published guideline

**Frequent updates from various HA on additional known N-Imp as more and more information is shared with the Agencies is a challenge from both API Supplier’s assessment as well as internal Risk Assessment by the MAH – Scope of a Harmonized Approach**
### Compendia Harmonization Challenges

Differences in the Pharmacopoeial standard preferences and specifications

**EU and other regions viz. Russia/Ukraine/South Africa** are more inclined towards **BP and Ph. Eur**

Where as **Latam/Asian** countries are towards – **USP standards**

**Example – USP and Ph. Eur Monograph of Clobetasole Propionate** -

<table>
<thead>
<tr>
<th>Related substance</th>
<th>USP</th>
<th>Ph Eur</th>
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<tbody>
<tr>
<td>Betamethasone 17 propionate</td>
<td>Not listed</td>
<td>0.20%</td>
</tr>
<tr>
<td>Clobetasol delta 16</td>
<td>Not listed</td>
<td>0.30%</td>
</tr>
<tr>
<td>1,2 dihydroclobetasol propionate</td>
<td>Not listed</td>
<td>0.20%</td>
</tr>
<tr>
<td>21 chloro-16B-methyl 3,0 dioxopregn 1 - 4 diene -17 ylpropanoate</td>
<td>Not listed</td>
<td>0.30%</td>
</tr>
<tr>
<td>Each unknown impurity</td>
<td>1.00%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Total impurities</td>
<td>2.50%</td>
<td>1.00%</td>
</tr>
<tr>
<td><strong>SOR</strong></td>
<td>+98°C to 104°C in Dioxane</td>
<td>+112°C to +118°C in Acetone</td>
</tr>
<tr>
<td><strong>Loss on drying</strong></td>
<td>NMT 2.00 %</td>
<td>NMT 0.5%</td>
</tr>
</tbody>
</table>
Leveraging Data from US/EU Development Program to Emerging Markets

**Facility Audits** — Health Authorities which do not recognize USFDA/PICS need Physical audits – ANVISA, SFDA (Saudi Arabia), Kenya and other African countries

**OSDs - Dissolution Data**
- Comparative Dissolution profile, Multi media against US and Local RLD
- Dissolution development report as OGD recommendations are used for US
- Dissolution media with Surfactant - US follows USP or OGD recommendation; whereas Emerging countries prefer to have dissolution profiling data without surfactant

**Stability Studies** –
- 3 batches – Zone IVB
- In-use – Considering the US market prefers Bottle/container packs

**AMVs: Brazil Specific** -
- Site AMVs API & FP with use of Pharma standards, Linearity in Triplicate etc.
- **Forced Degradation** to be part of Assay & Related Substances in API & FP AMVs (min 10-30% degradation or 10 days with Acid/Base/Heat/Light/Oxidation/Humidity/Metal Ions to be performed & % degradation to be reported)

**Process validation protocol and Report** –
With Challenge studies – Initial application

**Pre-clinical / Clinical**
Overviews and Summaries, Module 4 and Module 5 as per ICH TOC
Acceptance of Global Reference Product for BE Studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Brazil</th>
<th>Mexico</th>
<th>Malaysia Philippines</th>
<th>Thailand</th>
<th>Ukraine Colombia Peru Ecuador</th>
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<td>🧄</td>
<td>😞</td>
<td>🧄</td>
</tr>
</tbody>
</table>

Confidential
Unique Country Specific Guidelines – Challenge in Global Harmonization

COUNTRY SPECIFIC GUIDELINES-
- **Russia** needs analytical methodologies as per Russian Pharmacopeias / EAEU methodologies.
- **Brazil** needs AMV’s as per RDC 166, which needs repetition of most of the analytical parameters and Forced degradation using reference standards.
- Due to difference in local RLDs, need to generate the In-vitro data among the Global RLD and Local RLDs

PRIMARY PACK- Marketing need
For Emerging markets usually the necessity is of unit dosage ie Strip/blisters unlike that of US, where the preferred commercial pack is container.

LABELLING REQUIREMENTS – Branded or Generic
Emerging markets works on branded generics, hence each market has different trade names based on local trade mark clearance. Making it difficult to have same pack/brand across the globe.
Emerging requirements of Q1/Q2 and **Q3 Similarity and going beyond…**

**Q3 In Vitro approach for Q1 and Q2 formulations**
- Cyclosporine Emulsion (2013)
- Difluprednate Emulsion (2016)

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**Stepping Forward: Integration**

- Expand Q3/characterization approaches to nasal and inhalation products
- Go beyond Q3
  - Q1/Q2/Q3 approaches limits formulation flexibility and could limit generic competition
  - Non Q1-Q2 products often need an in vivo component of BE
    - PD measures, direct sampling or systemic PK are alternatives to clinical endpoints
    - Modeling and simulation is critical to the interpretation of in vivo data (especially PK) for locally acting products

**Other concerns – BE Guidance updates and RLD Updates**
- GRx company followed the Product Specific guidance for a NTI with a passing BE study however during review phase the applicant had to re-perform the BE study in line with expectations of a NTI drug product
- Frequent or last minute RLD labeling updates has impacted many recent gRx approvals

Complex Generics

**Traditional Generics**
- API Compendial requirements
- Same Dosage Forms
- PK Study for BE
- Dissolution Similarity
- Adequate Stability
- Adequate Specifications

**Faster APPROVAL**

**Complex Generics**
- API Characterization
- Formulation Similarity
- Clinical End Point studies
- Device compliance
- Complex Peptides
- Advanced characterizations
- Device Formulation interactions

**Sluggish APPROVALs**

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**Equivalence Determination**

“Simple” vs “Complex”

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**Reference:** Overview of Complex Generics Regulatory Perspective on Bioequivalence; Xiaohui (Jeff) Jiang, PhD, 4th PQRI-FDA Conference on Advancing Product Quality; April 9 -11, 2019
## Complex web of IIG Compliance

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Number of entries in IID</th>
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<tbody>
<tr>
<td>Oral</td>
<td>6395</td>
</tr>
<tr>
<td>Topical</td>
<td>1598</td>
</tr>
<tr>
<td>IV and IV (Infusion)</td>
<td>830</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>358</td>
</tr>
<tr>
<td>Vaginal</td>
<td>247</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>238</td>
</tr>
<tr>
<td>Transdermal</td>
<td>191</td>
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<tr>
<td>Nasal</td>
<td>155</td>
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<tr>
<td>IM</td>
<td>336</td>
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<tr>
<td>Sublingual</td>
<td>148</td>
</tr>
<tr>
<td>Rectal</td>
<td>137</td>
</tr>
<tr>
<td>Respiratory (Inhalation)</td>
<td>50</td>
</tr>
<tr>
<td>Others</td>
<td>1701</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>12384</strong></td>
</tr>
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</table>
Concomitant Administration and cumulative levels of excipients

### Inactive Ingredients

**Glipizide**

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>UNII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicon Dioxide</td>
<td>ETJ7Z6XBU4</td>
</tr>
<tr>
<td>Lactose, Unspecified Form</td>
<td>J2B2A4N98G</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>OP1R32D81U</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>4ELV7Z65AP</td>
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**Atenolol**

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<tbody>
<tr>
<td>Magnesium Stearate</td>
<td>70097M6I30</td>
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<tr>
<td>Microcrystalline Cellulose</td>
<td>OP1R32D81U</td>
</tr>
<tr>
<td>Sodium Starch Glycolate Type A Potato</td>
<td>5856J3G2A2</td>
</tr>
<tr>
<td>Povidone, Unspecified</td>
<td>FZ989GH94E</td>
</tr>
</tbody>
</table>

**Ranitidine Tablets, USP**

<table>
<thead>
<tr>
<th>Ingredient Name</th>
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<tbody>
<tr>
<td>D&amp;C Red No. 30</td>
<td>2S42T2808B</td>
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<tr>
<td>Hydroxypropyl Cellulose, Unspecified</td>
<td>9XZ8H6N90H</td>
</tr>
<tr>
<td>Hypromellose 2910 (3 MPa.s)</td>
<td>0VUT3PMYS2</td>
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<tr>
<td>Magnesium Stearate</td>
<td>70097M6I30</td>
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<tr>
<td>Microcrystalline Cellulose</td>
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<tr>
<td>Titanium Dioxide</td>
<td>15FIX9V2JP</td>
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<tr>
<td>Triethyl Citrate</td>
<td>8Z98QXD6UM</td>
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<tr>
<td>Propylene Glycol</td>
<td>6DC9Q167V3</td>
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Soliciting inputs from stakeholders

- How can we improve nomenclature?
  - % responses
    - use USP names
    - add synonyms
    - SRS preferred name
    - other

- How should we identify excipient amounts?
  - % responses
    - add MDI
    - clarify %
    - eliminate dosage forms
    - other

IIG and Excipients Levels – What’s acceptable and what’s not? Needs intervention from Industry associations...

Safety v/s Affordability

Reference: Current FDA Perspective on Excipients, NJPhAST Meeting – September 15, 2016, Jeffrey B. Medwid, Ph.D
Key Take Away’s:

• Industry and Health Authorities need to work more closely than ever in the current scenario to bring in Harmonization in all aspects of product life cycle and thereby ensure accessibility to quality affordable medicines across the markets.

• Balance needs to be maintained in ensuring safety as well as affordability.

• Harmonization efforts focused on aligning various compendial monographs.

• Harmonized common template for Nitrosamine Risk assessment would bring in more uniformity in risk assessment.

• ICH / WHO etc. needs to bring in more aspects of drug product development under their ambit as a baseline requirement across geographies.

• Initiatives from ICH/WHO/Industry association in bringing out guidance documents on issues such as product extensions leveraging CoPPs would bring in more predictability in quick availability of Complex drug products to Emerging Markets.