Biosimilars Development & Commercialization Experience

HETERO BIOPHARMA LTD
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INTRODUCTION

- A similar biologic product is similar in terms of quality, safety and efficacy to an approved reference product based on comparability
- India emerging as a key player in Biosimilars
- In about a decade, India has seen a robust growth in Biosimilars
- India has released Biosimilar guideline in 2012 and revised subsequently in 2016
- This guideline provides Regulatory Pathway for development, manufacturing and commercialization of biosimilars
- Biosimilars represent a major change/paradigm shift in terms of innovation, new indications, cost and competition
- Biosimilars have large potential commercial opportunities
Hetero Biopharma Experience in India

- Hetero Biopharma Biosimilar Products developed and commercialized as per following major milestones
  - Clone/cell line development
  - Product development
  - Pre-clinical studies
  - Clinical studies
  - Commercialization
  - Post Marketing Surveillance or phase IV studies
Product Development

- Hetero Biopharma Biosimilar Products are produced in Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology; CHO cell line most widely used cell line
- Master cell bank (MCB) and working cell bank (WCB) manufactured under GMP environment
- MCB & WCB are characterized for identity and safety parameters
- Extensive comparative biosimilarity studies were performed against innovator product
- Process development – upstream & downstream development
- Analytical methods development for lot release testing & biosimilarity establishment
- Stability studies for Biosimilar products performed under real time real temperature and accelerated conditions
Product Development

- Biosimilar products are analysed as per in-house specifications
- Extensive characterization using Reference product (at least 3 lots of Reference product)
- Process validation, viral validation and method validation studies have been performed
- Non-infringing process and materials used all through the process & product development
Pre-clinical development

- Preclinical (in vivo toxicological studies) were conducted to show safety between the biosimilar and reference product in rodent species (mice & rats)
- Extensive toxicological investigations were undertaken before a biosimilar taken to the clinical evaluation stage
Clinical development of Biosimilars

- Clinical studies (Phase III) were conducted with reference product to demonstrate PK/PD, efficacy and safety including immunogenicity
- All clinically relevant and sensitive study population, endpoints, sample size and study duration are chosen to confirm similarity and ruled out clinically meaningful differences
- Clinical study was conducted at internationally accredited CRO’s
- Phase IV studies been initiated for all commercialized products with large number (at least 200) of patients in India
Regulatory pathway in India

IBSC: Institutional Biosafety Committee
RCGM: Review Committee on Genetic Manipulation
DCGI: Drug Controller General of India

Reference: Indian similar biologic guideline (2016)
### HETERO Biosimilars

- Commercialized products in India

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Product</th>
<th>Indication (Category)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Darbepoetin alfa</td>
<td>Nephrology and Oncology</td>
<td>Commercialized in 2014</td>
</tr>
<tr>
<td>2.</td>
<td>Rituximab</td>
<td>Oncology and Rheumatology</td>
<td>Commercialized in 2015</td>
</tr>
</tbody>
</table>
Conclusion

- Hetero Biopharma experience in Biosimilars development complying as per Indian and some of the global regulatory guidelines
- The regulatory guidelines will continue to evolve as we get more experienced and biosimilars continue to come to the market
- Awareness of the deviations between biosimilars and innovator products in terms of efficacy, safety and immunogenicity is essential for proper prescription and safety of the patients
- Biosimilars are answer to save medication costs and increase population coverage especially in emerging and under developed countries