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RECOMMENDATIONS TO RCGM

INCREASING SHARE OF INDIAN BIOSIMILARS IN GLOBAL MARKET – REGULATORY PERSPECTIVE OF SIMILAR BIOLOGICS.

CONTENTS

REGULATORY PERSPECTIVE OF SIMILAR BIOLOGICS: INCREASING SHARE OF INDIAN BIOSIMILARS IN GLOBAL MARKET

1 HARMONISATION AND INDUSTRY GUIDANCE DOCUMENTS

1 There is an urgent need for harmonization of the Indian guidelines with the international guidelines to streamline the regulatory process.

2 Regulatory harmonization will ease the way for Indian biosimilars in global market and will lead to potential cost and time saving for global launch.

3 At present, India has only one overarching biosimilar guideline which covers the requirements for all range of biosimilar products such as simple biologics – Peptides, Insulins; and complex biologics – mAbs. Moving forward, considering the product complexities, a product specific accommodative biosimilar guidelines shall be developed based on nature of molecule and worldwide experience of product.

2 MULTIPLE AGENCIES INVOLVED IN REVIEW OF BIOLOGICAL APPLICATIONS

4 At present there are multiple agencies involved in review of biological applications and grant for test and analysis and import permission purpose. Companies need to get an NOC from CDSCO and then apply to FDA for test license. This is a redundant process without any value addition. Currently there is requirement of Form CT-11/14/15, and Form-29 to manufacture drugs for examination, test, analysis or CT or BE purpose at R&D and plant separately. The purpose of such requirement of Form CT-11/14/15 and Form 29, etc. needs more clarity and simplification for manufacturing of batches for CT/ BE/ Test and Analysis. Once a CT11/14/15 form is issued to the manufacturer, it should be good for developmental batches, clinical batches, etc.

5 RCGM representative may be part of the group constituted at CDSCO to regulate proposals involving rDNA derived drugs. This would save the time, reduce the involvement of multiple agencies. This would help to streamline the process of

regulatory approval of drug formulations in a time bound and coordinated manner.

6 For rDNA derived products, Pre-Clinical Toxicity (PCT) protocol as well as report is evaluated by RCGM and gives recommendation to CDSCO for initiation of clinical trial.

- For all standard protocol studies of 1x, 2x, 5x of human equivalent dose in one or two animal species should not be reviewed by RCGM. If anyone wants to run a modified protocol, then a review could be helpful.
- For conducting animal Toxicity studies, Certificate of Analysis (COA) or releasing testing data is needed. Requirement of a detailed biosimilarity data at that stage is a huge set back/burden for the developers. Since DCGI also reviews the same data again so an additional review by RCGM appears redundant.

7 For this, CMC requirement of RCGM is also extensive. The CMC requirements for biosimilar should be phase appropriate and critical quality attributes (CQA) of the product may be evaluated in detail and relied upon by the committee. CMC or Clinical regulatory requirements shall be simplified based on nature of the product and guideline shall specify the minimum expected lots to be used in CMC analytical similarity studies. This will help the industry to understand the requirements in advance and all regulatory requirements can be mapped in to the biosimilar development plan accordingly.

8 CDSCO reviews CT proposal through the Subject Expert Committee (SEC). The import of any new product/ strain/ biological material/ rDNA material for test and analysis purpose require permission from different agencies. There should be single online portal/agency to grant permission of import of new product/ GMO/ HMO/ rDNA material for test and analysis purpose. The following division of labour is recommended:

- RCGM should handle Genetically Modified Organisms (GMO) and safety related approvals, review and approval of Toxicity study report. There should be no protocol review.
- FDA to handle the Drug related approvals.
- CDSCO to handle product approvals, including CT and MAA

3 INVOLVING NIB DURING BIOSIMILAR APPROVAL REVIEW CYCLE

9 Currently National Institute of Biologicals (NIB) is part of joint inspection for a product approval, before CT22/23 approval. In some cases, NIB suggests industry to add additional release tests to the specification during joint inspection. This is a welcome step that gives opportunity to review the developmental data and highlight the gaps to be addressed. If NIB is requested to release/test first 3 batches then that becomes a bottle neck because NIB have a lead time of 3 months after MA approval. On top of that they are not having drug specific qualified methods and reagents in place so that adds to the time beyond 3 months.

- This may remain as an audit deficiency, in turn delaying the approval timeline and in addition to the regular review cycle time of DCGI.

4 CONSERVATIVE DECISION MAKING FOR EARLY CLINICAL DEVELOPMENT OF NCES/BIOLOGICS/ BIOSIMILARS BY INVESTIGATIONAL NEW DRUG (IND) COMMITTEE

10 IND Committee expert panel should consist of full-time experts with a right mix of Academic and Industry expertise capable of evaluating the Risk-benefit of every project, with complete accountability, so that the decision making is improved.

11 There is inadequate review of non-clinical data by IND committee experts and as a result, the Risk-benefit profile is not properly assessed by Committee.

12 Incentivizing the SEC members for devoting the necessary time to review the data generated in support of proposed clinical trial for an IND application. This will help in better understanding of the scientific rationale for study design, sample size, safety etc.

13 This results in conservative decisions by the IND committee. The committee tends to advise staggered clinical development i.e., to conduct study first in small number of subjects and then followed by larger number of subjects. This leads to considerable delay in Clinical development timelines.

14 Unlike other countries (e.g., US), simultaneous conduct of multiple trials is often discouraged despite favourable risk-benefit assessment. E.g., Phase I and Phase

III or Phase III and switch-study in case of biosimilars can be conducted in parallel.

15 Conservative decision making is a key reason for studies shifted to outside India. The automatic route of approval (30 days) should be applicable to biosimilars & bio-better applications as well since the extent of R&D efforts in such products is no less than NCEs.

5 PRE-CLINICAL ANIMAL STUDIES FOR SIMILAR BIOLOGICS (BIOSIMILARS)

16 As per the current CDSCO "Guidelines on Similar biologics" for all rDNA Biosimilars animal toxicity studies are mandatory.

17 Ideally, the PCT protocol should not be reviewed by agency, companies should be allowed to conduct the study as per regulatory requirement.

18 A step wise approach should be adopted for a need to conduct the preclinical toxicity studies. EMA and US FDA recommend a step wise approach:

- An animal toxicity is only needed if uncertainties are observed during the CMC studies.
- For Biosimilars, normally there are no requirements for these toxicity studies in presence of current state of art analytical tools, a very high level of similarity is established between the molecule being developed and the reference product.

19 The animal toxicity studies and immunogenicity studies in the non-relevant animal species should be discouraged.

20 Moreover, in India the toxicity studies are normally conducted on rats and rabbits, which in most cases e.g., MABs are non-relevant species. The data generated from these studies is just a check box activity and may at times be counterproductive.

21 RCGM also insist on conducting the animal immunogenicity studies. Since most of the Biosimilars are humanized proteins, they elicit immune response which cannot be extrapolated to the human immune response and therefore this data becomes irrelevant from the product development perspective. ADA/immune studies in animals do not add value and are onerous and time consuming. Also, this requirement was previously not there and added recently.

22 Pre-clinical study should be waved off from the current guideline. Pre-clinical studies for biosimilars in irrelevant species are not required for EU and USA submission. Strong analytical similarity data with 3-5 lots of Reference Medicinal Product (RMP) is sufficient as non-clinical package. to reduce the cost and time involved in the biosimilar development.

23 Reduce / remove the mandatory requirement of preclinical toxicology studies for biosimilars in line with global regulatory agencies (US/Europe). This will help to minimize the development timelines.

6 RCGM EXPECTATIONS AT PRECLINICAL STAGE- STRINGENT SCRUTINY AT EARLY STAGE

24 Bio-similarity is being reviewed by RCGM with high scrutiny even at the preclinical stage. The RCGM expects that during pre-clinical toxicity study the biosimilar molecule should demonstrate similarity with 3 batches of reference product to a high level.

25 Normally when the sponsor approaches the RCGM for, the product development is at an early stage. When the biosimilar development is an evolving process, there will be many scale ups and process improvements in the process moving from PCT and up to MA application.

26 Industry requests DBT for a stage appropriate scrutiny of Biosimilarity depending upon whether the molecule/product is suitable to progress to preclinical toxicity studies.

27 It is suggested that the review of detailed similarity assessment should be conducted jointly by RCGM and CDSCO at later stages viz., in Phase III clinical and Marketing Authorisation Application (MAA) submissions.

28 In the regulated markets like the USA and Europe, Biosimilarity is reviewed at MA stage only as the Biosimilarity is considered as a part of the “totality of evidence” and the onus lies with the manufacturer to generate evidence of Biosimilarity throughout the development cycle.

7 ADVISORY COMMITTEE IN RCGM/DCGI, COMPOSITION & PROCESS SIMPLIFICATION

29 It would be useful to introduce an advisory committee in RCGM/DCGI for the guidance and advisory to Indian industry. This can provide input on each company's status on biosimilar product portfolio and suggest for improvement in dossier before final submission.

30 It is recommended to engage full time medical experts/clinicians in addition to external members in the committee who would understand the product development lifecycle and product specific requirements like NBEs, Biosimilars etc.

31 Experience/knowledge of drug development should be an eligibility criteria for the RCGM committee members.

32 Provision of an optional pre-submission meeting with RCGM office should be created to discuss the project in a comprehensive manner and to understand the desirable requirements so repeated deficiency/query can be minimized.

33 The administrative process from start of development till recommendations for clinical study can be simplified through single comprehensive application window.

34 This Process can be further simplified if there is a common interface between RCGM and DCGI office for biosimilar application to get timely permissions.

Note: Currently companies require multiple applications – for start of R&D, for producing small scale R&D batches, for clinical batches, for import of ref product etc. All these can be made part of a single online application. (Form C1/C3/C5 by RCGM & Form 29 from DCGI should all be unified on single portal and replaced with a single form which gives license to start R&D, import, test, and manufacture should be created in coordination with state and central agencies).

35 Assessment of product quality and evaluation of clinical protocol should be simultaneous activities - the combined assessment of specific subject matter experts should be provided in final assessment of protocol for study initiation. Post MAA review, a comprehensive query request should be raised, all

in one go. After the comprehensive queries are raised, only follow up queries should be asked. The multiple rounds of new queries are time consuming and unnecessarily delay the process. There strict timelines defined and there should be provision of deemed approval. No further queries should be raised after the deadline is over. E.g., for MAA time limit is 180 days, however, still the follow-up queries are raised. This is the standard process adopted by FDA and EMA for approval of biosimilars in their respective jurisdictions.

8 CLINICAL TRIALS WAIVER (PHASE I/III)

36 The analytical similarity assessment can be the basis of approval especially for providing recommendation to conduct clinical studies.

37 Clinical trials (Phase I/III) can be waived off for certain small biosimilars (i.e., Insulin, Insulin analogues, Growth factors-Non mAb molecules) and giving approval based on strong analytical/biological data as well as comparability studies/data.

38 New product categories where there are already elaborate development guidelines issued by CDSCO (e.g., Phase I studies of biosimilars) should not be routinely referred to SEC, unless there is a departure from guidelines in the proposed plan.

9 REDUCE NUMBER OF SUBJECTS FOR CLINICAL TRIALS (PHASE I/III)

39 Number of subjects for clinical trials (Phase I/III) can be reduced for well-established monoclonal antibodies (mAb) molecules (Rituximab, Infliximab, Adalimumab etc.).

40 However, more emphasis can be given on Immunogenicity and Pharmacovigilance studies.

41 Physicochemical parameters should be more stringent and highly comparable to reference biologics.

10 ALL PROTOCOLS NEED TO GO TO DCGI FOR APPROVAL. THERE IS NO AUTHORITY TO INSTITUTIONAL REVIEW BOARDS (IRB) FOR PROTOCOL APPROVAL

42 DCGI should empower IRBs to review and approve protocols for multiple Phase 1 and Phase 2 studies once the IND is open. Only Phase 3 registration study protocols should be reviewed by DCGI for approval.

43 Currently, there is requirement to submit Protocols at each stage of drug development to DCGI and get approval.

44 For NCEs/Biologics/Bio-similar Clinical programs, DCGI submission and approvals are required for each of the multiple Phase 1, Phase 2 and Phase 3 studies. This leads to significant delay in innovative drug development.

45 Internationally, in USA, there is requirement of one time IND submission during which USFDA reviews entire dossier. For further studies, IRBs are authorized to review Protocols and provide approval.

11 REPURPOSED DRUG

46 In case of follow on /conventional vaccines / biosimilars, a generic, already approved, protocol design for similar product for clinical trial (s) shall be followed.

47 Upon complete review of CMC, animal toxicity, Clinical and Safety data, once SEC/DCGI authorize a drug as a biosimilar, there should be no need to conduct additional studies for extrapolation of already approved indications for RMP. Currently these are being referred to SEC and at times denied without any valid grounds.

48 Where large, global clinical trials of biosimilar have been conducted with India as a participating country, the legacy requirement of ‘minimum 100 patients from India’ should be waived off.

12 PHASE-4 FOR APPROVED DRUG

49 Phase 4 clinical study expected for each approved indication of biosimilar will not add any additional value but enhance hurdles. PSUR and Post Marketing Surveillance data should be adequate.