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Review

A Practical Guidance for Biosimilars Approval--Strategy for the ROW

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Abstract: Biological drugs are inaccessible to more than 80% of the world population due mainly to their high costs; this is a significant concern of the World Health Organization. Biosimilars are supposed to reduce the cost burden, but their approval process is complex, including expensive and irrelevant studies. While the Stringent Regulatory Authorities (SRAs) have adopted the guidance of the FDA or EMA, such adoptions are neither necessary nor practical for the rest of the world (ROW). We present a science-driven, rational approach to formulate regulatory guidelines that will enable faster biosimilars' entry into the ROW without compromising their safety and efficacy. The key recommendations include removing animal and safety efficacy testing, making analytical assessment more robust, and cGMP compliance assured through third-party audits. The ROW countries are also recommended to initiate a rapporteur system available in the EU, to overcome the biases and assure state-of-the-science evaluation as the common understanding of the critical quality attributes evolves. It is anticipated that stronger region agencies like those in the MENA region, with the leadership of the Kingdom of Saudi Arabia will help propel the idea faster across the globe.

Keywords: biosimilars; regulatory process; animal studies; clinical efficacy testing; interchangeability; FDA; EMA; MHRA; MENA; cGMP

1. Introduction

Biosimilars are biological products with "no clinical differences from the original reference product," as declared by all regulatory agencies[1]. Still, the FDA differs from all other agencies in allowing interchangeability or substitution unless the biosimilar product that is "clinically equivalent" is switched and alternated repeatedly to allow the status as an interchangeable biosimilar. Such is not the case with the rest of the world; the EMA has recently reasserted this position allowing switching with the reference product and other biosimilars.[2] Most other countries in the rest of the world have already begun this practice that remains in the US due to legislative matters.[3] Countries that follow the US practice would unnecessarily restrict the entry of biosimilars. This is one such example of misconceptions that need removing. The ROW countries should have only one class of biosimilars that are interchangeable with the reference product and other biosimilars.

Other areas of misconceptions include the use of animal testing[4] and clinical efficacy testing.[5] The MHRA recently announced that animal and clinical efficacy testing might be unnecessary.[6] Removing these studies, as justified in this paper, will change the development cycle of biosimilars and reduce the current cost of development from USD 100-300 million dollars,[7] which is the main barrier to entry of biosimilars, wherein more than 70% of the development cost goes to pay for the clinical efficacy testing. We will demonstrate that these studies are unnecessary and, if used to justify the variability of biosimilars in more stringent quality attributes, lead to the safety risk of biosimilars.

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The emerging country agencies generally lack the expertise to evaluate biosimilar registration applications; this deficiency can be readily removed by adopting the EMA system of using rapporteurs for registration filing. The same holds for the first audit to confirm cGMP compliance, which is better conducted by qualified auditors and not by the agencies for various reasons ranging from expertise to conflict of interest. These suggestions have not been welcomed by the agencies, perhaps due to the perception that these may be construed as weaknesses of the agency. However, this is a standard practice in the EU; the FDA also accepts third-party audits.[8] Another reason to adopt the suggestions presented above is to curtail graft in the registration practice as routinely caught in practice,[9] almost globally.[10]

While the suggestions made in this paper should apply to all emerging market regulatory agencies, it would be helpful if a group of regional agencies like those in the MENA region, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Yemen, Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, and Yemen decides to create a cooperative association because of the language homogeneity, except Iran. The lead country should be the Kingdom of Saudi Arabia, which holds the financial and intellectual power and abilities to create and implement these guidelines.

2. Regional Perspectives

The adoption of biosimilars in the ROW countries is difficult to estimate as the healthcare systems evolve, changes in country-specificities, and often, inconsistent regulations, clinical and treatment pathways, and low awareness among stakeholders; all making it difficult for biosimilar products to realize their full potential. For example, except for Iran, all other countries in the MENA region require clinical efficacy testing.[11] In addition, all MENA region regulatory authorities either follow FDA or EMA, and Egypt also includes the WHO.[12]

In recent years, the MENA market has seen a noticeable increase in the value share of biologics, in line with general industry trends. Biologics' value share in the MENA region was predicted to rise at a 30 percent annual pace reaching close to 10 billion USD. With over $2B in sales, the Kingdom of Saudi Arabia (KSA) dominates the market. The following three countries are Algeria, Egypt, and the United Arab Emirates (UAE), with about 450 million dollars in sales.[13]. This anticipated market expansion is triggered by healthcare costs, the GDP, and the demand for affordable therapies.[14] (Figure 1)

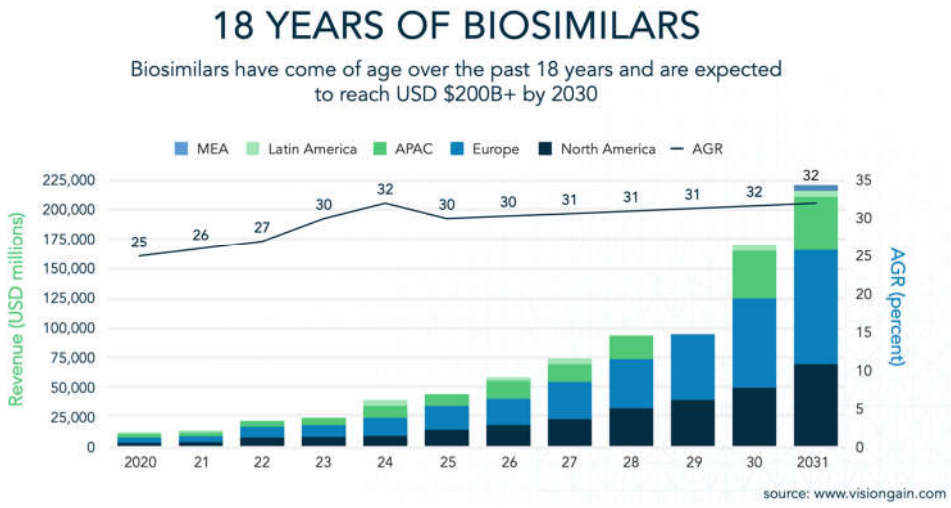

Figure 1. The growth potential of biosimilars.

However, most healthcare systems in the ROW are cost-conscious, and clinical outcomes and drug prices influence payment decisions. Healthcare systems are under additional pressure from the region's economic unrest, linked to rising oil prices, raising

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concerns about their ability to spend compared to industrialized markets. The economies of the nations in this region differ; some are strong enough to reduce their healthcare costs, while others are in financial difficulty. The complexity of the manufacturing process, high price, accessibility to competing for generic medications with lower pricing, increased frequency of specific disorders like diabetes, and rising rates of cancer-related mortality are additional difficulties in the region. Nevertheless, government assistance, initiatives, and simple rules should result in significant market openings.[15] Most of the ROW countries also suffer from being unable to manufacture these products. If the ROWs wish to opt for economic growth and make the high-cost drugs affordable to its citizens, this possibility must be considered.

3. Biosimilars Development Pathway

In 2006, the EMA released the first biosimilar guidance and gave the first product its approval.[16] The FDA brought its guidelines in 2009.[17] The WHO is not a licensing authority, so it only guides its 194 member countries.[18] Countries basing their guidelines on WHO advice often misconstrue these guidelines as they create their guidelines.[19] For example, the Indian guidelines[20] continue to require extensive animal toxicology testing and redundant and meaningless efficacy studies.[21],[22]

The first tranche of biosimilar approval guidelines treated biosimilars like new biological drugs for an abundance of caution, including extensive analytical comparisons, animal pharmacology and toxicology, clinical pharmacology, and clinical safety and efficacy studies. The only concession allowed is the extrapolation of indications. A comparative clinical efficacy testing in one indication would be sufficient to qualify for all indications allowed for the reference product. To further assure safety and efficacy, biosimilars must have the same dose, strength, route of administration, and mechanism of action; the formulations may differ. Also, the prescribing information must be the same, and guidelines are available on writing the prescribing information for biosimilars.[23]

Over time, the agencies became more convinced of the safety of biosimilars in response to challenges made to the guidelines.[24] It became well accepted that the animal testing of biosimilars is redundant[25] since now even the new biological products may not be required to conduct such testing because the mechanism of action of biological drugs involves receptor binding that is often unavailable in animal species.[26] The value of clinical efficacy testing has also come under criticism for scientific reasons since these studies cannot fail[27] and, if used to overcome a lack of similarity in analytical or clinical pharmacology, create a higher safety risk possibility if these studies are taken into account for approval. An excellent example of progressive changes to guidelines comes from the MHRA. Last year, as the Brexit transition period came to a close, the MHRA published its first comprehensive guideline on 14 May 2022[28] that breaks from all other guidelines by providing clear judgment for not requiring animal and clinical efficacy studies.

Clinical pharmacology studies, including pharmacokinetic and pharmacodynamic comparisons, are part of the analytical methodologies, where we establish similarities in how the body sees the drug and vice versa. These should be enhanced and recommended to adopt newer technologies and approaches to establish structural equivalence.

Several ICH guidelines provide scientific support to developing biosimilars, and these should be made part of every guideline.[29] There is a dire need for harmonizing the regulatory guidelines,[30] but it is not likely to happen, as evidenced by historical events; for example, the guideline for the approval of generic chemical drugs remains diversified for more than fifty years since chemical generics were introduced.[31] Countries do not agree on which oral product should have a waiver of bioequivalence study; Japan denies all. So, when it comes to a class or products as complex as biologics, it is understandable why harmonization and global concurrence may not be possible. It has little to do with science but the legislative nature of these guidelines and the perspective held by the agencies that are often difficult to convince otherwise. We are pushing the idea of a standard that may be used globally and ensure biosimilars' safety and effectiveness.

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Now that we have 18 years of experience in using biosimilars and hundreds of published reports on their safety and efficacy, a strong opinion has emerged[32,33] that significant amendment to the approval guidelines for biosimilars must change, not only to reduce the development cost but also to enhance the safety of these products. Furthermore, lowering the development cost is essential to bring more biosimilars, as there are only nine out of more than 150 possible biosimilar molecule candidates approved in the US and 14 in the EU. There are over 200 molecules that could provide excellent accessibility to patients.

4. Amended Approval Elements

The determination of biosimilarity is based on a combination of testing, including analytical and biological assays, animal pharmacology or toxicology, clinical pharmacology comparisons, as well as clinical efficacy testing; in patients, both of which should be disallowed[34] to reduce the risk of approving unsafe biosimilars if the animal studies and efficacy studies are used to justify analytical and pharmacology differences between the reference product and the biosimilar candidate.

Animal Testing

Testing new drugs in animals has long been the norm to prevent human harm. Because the reactive chemical groups can interact with numerous tissues to induce a harmful response, it is effective for chemical medicines. The toxicity of biological medications extends the pharmacological reaction since biological substances may not always exhibit a pharmacologic response in animal species. The primary method by which biological medicines work is through receptor binding. Therefore, a pharmacological or toxicological response is not expected if an animal species does not carry these receptors.[35]

The method used for testing also contributes to the lack of relevance of animal toxicological findings. For example, animal testing methods typically require administering a more significant dose to elicit a hazardous reaction; however, within this dose range, the responses are not anticipated to be linear, making it impossible to distinguish between similar items being tested. However, the developers continued this practice, even when the FDA or EMA had rejected considering these studies in evaluating the regulatory submission. In addition, animal toxicology studies may be deceptive if animal models are used to explain differences in impurity, post-translational modifications, or antibody reactions. For instance, applications for biosimilars included animal data[36] to substantiate such variability, but the FDA refused to accept the animal data.[37]

More than 130 products have received FDA and EMA approval, and none of the animal studies failed because they cannot fail. Now FDA recommends not conducting animal studies for new biological drugs.[38]

The ineffectiveness of testing biosimilars on animals is widely known. Still, this issue will soon be rendered irrelevant because the US Senate is debating legislation to stop animal biosimilar research. In the BPCIA, section (bb) is amended from "(bb) animal studies (including the assessment of toxicity" to "an assessment of toxicity (which may rely on, or consist of, a study or studies described in item (aa) or (cc)); (aa) is analytical assessment and (cc) is clinical testing." This bill, sponsored by Senator Lujan of New Mexico, is now on the table in Senate and expected to be signed soon.[39]

Clinical Efficacy

The gold standard for evaluating the clinical efficacy of novel medications compared to placebo has come under fire recently. Dr. Janet Woodcock, a past acting commissioner of the FDA, has stated: 'Why should we put patients through all these different trials just to check a box.' The FDA has recently questioned this idea of real-time testing, claiming that clinical efficacy testing is "broken."[40] Following the 21st Century Cure Act, new digital technologies and real-world evidence (RWE) are necessary.[41] Recently, the FDA has

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announced policies and funding to encourage the development of novel clinical trials, and substitute trials with non-clinical methodologies.[42]

We can list several reasons why clinical efficacy trials are the least sensitive to detecting any clinically significant difference when evaluating two products expected to be highly similar. The reasons why these studies do not fail include the low study power, requiring a much larger number of subjects than used to approve the reference product, arbitrarily accepting a clinical difference, and inability to judge the clinical response that is not always linearly dose-dependent. According to Dr. Woodcock, "checking a box" is all that such testing amounts to because biosimilar candidates are only given one efficacy trial.[43] In contrast, the biosimilar product may have several indications.

The clinical effectiveness trials have not revealed any clinically significant differences between a biosimilar and its reference product, according to a review of the published literature. Therefore, they have not led to any product withdrawals or recalls from the market. These data are available in the 96 EPAR files from EMA[44] and 37 approval documents from the FDA.[45] These regulatory submissions all passed their clinical efficacy assessment. In addition, the research published on the clinicaltrials.gov website[46] substantiates that all 141 studies for which the findings are provided complied with the required standards. The PubMed database also provides 435 randomized control clinical trials conducted between 2002 and 2022 that failed to detect a clinically significant difference.[47]

The main reason to remove clinical efficacy testing is not just cost avoidance but also ethical and hazardous concerns. The ethical concerns arise from the universal belief that no unnecessary exposure to healthy subjects should be made as codified in the US 21 CFR 320.25(a)(13), the universal belief that "No unnecessary human testing should be performed."[48] The hazardous concerns arise from the possibility of justifying critical analytical and pharmacology profiles based on efficacy studies.

5. Proposed Guideline Concept Summaries

Scope

The guideline is expected to serve as an advisory to all jurisdictions to create approval guideline documents to comply with local legislative requirements.

Definition.

A biosimilar product has the same safety and efficacy, mode of action, dose, frequency, route, and concentration (strength) as the reference product. This guideline applies to the following products:

- Polypeptides, conjugates, and the products and derivatives that contain them. These proteins and polypeptides can be highly purified and characterized using appropriate analytical methods. They are created using recombinant or non-recombinant cell-culture expression systems.; an example of non-recombinant cell-culture expression systems may include the production of botox.
- Alpha-amino acid polymers composed of 40 or fewer amino acids are considered peptides, not proteins. Glucagon, liraglutide, nesiritide, teriparatide, and teduglutide are peptides. A peptide is regulated as a chemical drug and copied as a generic drug.
- Not applicable to other product types, including proteins and polypeptides extracted from tissues and bodily fluids.

Reference Product

It is a biological product first approved in one of the four ICH member countries with a complete regulatory dossier and sourced from the same country (US, EU, UK, and Japan). If the reference product has been registered in multiple member countries using the same dossier, then either product can be chosen without needing any bridging study. Only one source of reference can be used. The lowest strength product should be selected when several strengths or presentations are available for the reference product. To account for the production variability of the reference product, several batches of reference products should be purchased over time (months to years) straight from the relevant

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market. The reference product batches should be tested during the allotted shelf life and stored according to the label's suggested storage conditions. Testing batches that have been held for a long time (for example, frozen at -80°C) or beyond their designated shelf life may occasionally be possible if reliable data show that the storage conditions do not affect the relevant quality attributes. The age of the reference product batches (relative to expiry dates) at the testing time should be documented during the analysis.

Characterization

The reference product is characterized by appropriate techniques, as described in ICH Q6B. These characterizations include determining physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity. Developers are encouraged to adopt newer technologies as available. Since the quality attributes of the reference product vary from batch to batch, it is essential to establish the ranges of these variations, to allow similar variability in the biosimilar candidate. The variations are either process-related or product-related (the expression system) (the manufacturing system). Generally, a variation in the product-related attributes cannot be resolved, requiring the developer to create a different expression system; the same can be the case for process-related attributes, but these are readily fixed. Both cases cannot submit safety studies to justify a significant difference.[49]

Impurity profiling is a prerequisite during biosimilar development, and specifications are set vis-à-vis the innovator for product-related variants. For example, a biosimilar may have fewer impurities in type and amount, but there shall be no unmatched impurity; this cannot be justified through any safety study unless this is already reported to be safe in the reference product.

Expression System

The expression system determines the product-related critical quality attributes (CQAs), which include primary structure, higher-order structures (HOS), glycosylation (only in eukaryotic hosts), product-related variations, and process-related variants. The primary structure is further broken down into the secondary structure, tertiary structure, and conformational stability; HOS into the oligosaccharide pattern, glycopeptide mapping, and monosaccharide/sialic acid content; size variants, charge variants, and related proteins resulting from the post-translational modification, as well as product-associated variants (HCD). The expression system should be the same class as the one used to express the reference product. The developers are also advised to select more steady expression systems; generally, high-yielding cell lines often produce more variants. Therefore, the cell lines should be qualified according to the ICH Q5D.

Post-translation Modifications

Since the primary sequence of a protein is fixed, it is expected to be precisely the same, except for justified post-translational modifications, such as terminal amino acids that are truncated in the body.

A few examples of heterogeneities produced during the creation, management, and storage of biological products a size-based heterogeneity (aggregates, fragments, and visible/subvisible particles),charge-based heterogeneities (acidic and basic variants), and other product modifications (reduced, oxidized, glycated, misfolded proteins, etc.).

When the environment changes during different stages of the production process, hydrophobic patches of the protein unfurl, causing accumulation or fragmentation. Immunogenic responses could occur. The aggregate size ranges from soluble aggregates to visible residues, depending on the duration of exposure to various stresses such as shear, thermal, chemical, freeze-thaw, etc. Protein loss due to interactions in the stationary phase and salt-induced aggregation or dissociation is a common issue during SEC analysis. To quantitatively evaluate the size distribution, sedimentation velocity-analytical ultracentrifugation (SV-AUC), a matrix-free substitute for SEC, is used.

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Charge variations are proteo-forms that arise in various colloidal matrices (such as culture media, in-process buffers, or formulation) at various phases of the manufacturing process and have changing charges. Therefore, several forms of cation exchange (CEX) chromatography are the preferable approach.

Non-enzymatic PTMs include oxidation, phosphorylation, sulfation, acetylation, methylation, and hydroxylation, which are formed during multiple stages of the manufacturing process. Therefore, liquid chromatography is preferred for characterizing PTMs and quantifying related molecular variants and impurities.

Cell substrates, such as HCPs, HCD, cell culture, and downstream processing residuals, are examples of process-related variations or residuals. The preferred methods for HCP and HCD detection and quantitation are enzyme-linked immunosorbent assays (ELISA) and real-time or quantitative PCR. Since they are a component of the release specification, these variants are not examined during the drug substance qualification phase.

Release Specification

Reference product characterization allows for establishing release specifications that are set before the analytical assessment. Characterization of the reference product will include determining its physicochemical properties, biological activity, immunochemical properties, purity, and impurities using suitable testing methods. The test lots can come from the lots used throughout the development process. However, at least one lot tested must be the one used for the first clinical trial, the PK/PD study. In addition, all test methods must be validated or verified if drawn from a pharmacopeia. Injectable products are allowed certain variations based on inevitable variabilities, such as ±3% for protein content, not more than 3% impurity, no single impurity of more than 1%, or ±15% for potency testing. Pharmacopeial specifications for the qualification of the dosage form, such as sterility, fill volume, delivered volume, and physical properties, are also not tested for comparison purposes. Other legacy attributes are independently established, like sterility, invisible particles (a controversial issue with biosimilars to consider as aggregates), protein content, potency, and physical properties specific to the biosimilar candidate. These standards can be used in defining the release specification of the biosimilar candidate.

Formulation

It is acceptable for biosimilars to have a formulation that differs from the formulation of the reference product. Despite any variations in the constituent composition, a formulation with the same number of inactive ingredients or fewer is recommended unless prohibited by intellectual property. Excipients utilized in creating biological products should not be included in another formulation. The integrity, activity, and potency of the active ingredient should be demonstrated, as well as the formulation's stability, compatibility (i.e., how it interacts with excipients, diluents, and packaging materials), and compatibility. Additional safety tests are needed to ensure there is no unexpected leaching of packaging components into the product if the principal packaging in contact with the product is different. Developers are advised to choose a primary packaging material that is similar instead because these studies would typically be challenging to defend. No unique excipients that have ever been used in a comparable product may be included in the formulation, and all excipients must be free of animal products.

Comparative Analytics

Test Methods

Critical product and process-related variants are compared with the reference product to enable suitably, not necessarily validated methods since some of the test methods used cannot be fully validated. Analytical methods must be sensitive, qualified, and sufficiently discriminatory to detect possible differences. The methods used to assess quality attributes for the batch release can also be used for analytical assessment, as detailed in

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the ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), where appropriate. In addition, robust data require the application of suitable orthogonal methods.

The number of batches

Three reference product batches would be adequate to confirm a higher-order structure, but the number of batches necessary depends on the expected variability. The regulatory file will need a bridge study with at least three PPQ lots; analytical assessment can include development lots. However, it must contain at least one at-scale cGMP lot used for clinical testing. More batches are needed for others where statistical analysis is done.

Data Evaluation

A visual comparison is adequate for test findings supplied as printed output, such as spectra. The application of quantitative statistics requires data from about ten batches each, and the most effective inference is obtained from the 3Sigma range that is calculated for the reference sample as (μref-3σref, μref + 3σref). The 3Sigma test is accepted if the MinMax range of the test sample is within the 3Sigma range. The 3Sigma approach provides a more practical compromise of error rates, further improving with a larger sample size.

Reference Standards

For biological assay and physicochemical testing of succeeding lots, in-house primary reference material is a suitably described sample created by the manufacturer from a representative lot or lots and against which in-house working reference material is calibrated. It is the only reference material allowed for reference purposes and its working reference materials. Publicly available reference standards (e. g., Ph. Eur.) cannot be used as the reference product for the demonstration of biosimilarity. However, using these standards can be used for method qualification and standardization. No specification in any monograph for drug substance or drug product can be used to establish a specification of reference product or biosimilar candidate. Test methods can be used after verification.

Functional Assays

Analytical and in vitro functional levels should be used to identify critical quality characteristics (CQA). Functional assays, such as those that look at apoptosis, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cellular cytotoxicity, should be relevant to the potential MOA in all therapeutic indications. A biological occurrence should be considered applicable to the MOA unless sufficient evidence to the contrary is presented. Functional tests (ADCC, ADCP, and CDC) are not required for a reference product that mainly targets a soluble antigen.

Stability

According to ICH Q5C, the biosimilar candidate's stability needs to be assessed. Analytical evaluation is extended through stress stability testing to show that the degradation products are comparable to the reference product. Tests for sterility, endotoxins, microbiological limits, volume in the container, uniformity of dosage units, and allowable particle matter are included in the pharmacopeia's general monographs; The pharmacopeial standards can be used for these tests because they are release specification tests. Accelerated and stress stability investigations are required to create deterioration profiles and enable a further direct assessment of structural similarity. To decide the requirements for stability studies that give pertinent data to be compared, ICH Q5C and Q1A(R) should be consulted.

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Process Qualification

Upstream and downstream processes must be validated before conducting any analytical assessment for similarity. Bridging studies are required to validate if the production size changes; however, once the clinical pharmacology studies are completed, no batch size change is allowed; the developer may do this under ICHQ5E, which applies only post-approval.

Clinical Pharmacology

Pharmacokinetic and pharmacodynamic studies are an extension of analytical assessment reflecting how the body sees the molecule and vice versa. Even though a product is administered intravenously, PK studies are required to assess the extent and strength of receptor binding that might change pharmacokinetic parameters like the distribution volume and clearance. This applies to all biosimilars even if they are not administered by the parenteral route, like the biological drugs injected into the eye. It is noteworthy that the purpose of PK/PD studies is to compare the profile, not characterize the profile of the reference product and the biosimilar candidate; the testing can be conducted in a local population to reduce the inter- and intra-subject variability, thus reducing the study size. All studies must conform to the standards associated with bioequivalence testing. The PK experiment should be planned and powered to demonstrate equivalence to the reference product, ideally in healthy volunteers. Crossover or parallel designs should be supported by a robust design. Although a crossover strategy is superior at identifying changes, it may not be suitable for reference products with solid immune responses or lengthy half-lives. If suitable population PK or PK-PD models for the reference product are available in the literature, modeling and simulation should be considered for optimizing the study design, such as choosing the most sensitive dose(s), study population, and sample size to discover PK differences. Consideration should be given to linear (nonspecific) clearance and nonlinear (target-mediated) clearance, for instance, through dosage selection and evaluation of partial areas under the curve (AUCs). Body weight adjustments or other factors (such as subject sex) to be employed in the statistical analysis of a parallel group experiment should be predefined in the statistical analysis strategy. The equivalence margins must be pre-specified, with an interval of 80. 00 - 125. 00% is generally acceptable. The PK trial should demonstrate equivalence of the primary PK parameters, usually AUC0-∞ and Cmax. If the extrapolated portion of AUC0-∞ makes up >20% of the total AUC0-∞ in >20% of observations, this requires a discussion of the study's validity. A root cause analysis should be carried out, and the results should be appropriately taken into account in the planning and execution of a new PK study if a PK study is unsuccessful (i.e., the 90% confidence intervals for the main PK parameters do not completely fall within the pre-specified acceptance limits).In most cases, the cause of failure is the subject variability that can be reduced by choosing narrow criteria for qualification in terms of gender and age. The PK trial can be used to test PD parameters, and descriptive results should be provided to support a finding of biosimilarity.

Immunogenicity

When B cells are activated, they produce T cells that express antibodies, giving biological products their immunogenicity. If the immunogenicity profile differs but cannot impact the disposition profile, the differences will be meaningless and not necessary to compare, as in the case of insulins. During the PK trial, data on immunogenicity and safety should be gathered. Anti-drug antibody (ADA) production rate, kinetics, and assessment of their impact on PK (and PD) using a predetermined group study of ADA-negative and ADA-positive participants are some of these options. Although they wouldn't be a replacement for the immunogenicity assessment in the PK trial, in vitro immunogenicity assays might enhance the functional, analytical assessment. Results of short-term immunogenicity analyses may not reflect real-world experience with biologics, including biosimilars. In particular, rare ADA-related adverse events may not be detected in the

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premarketing phase due to the limited size of the population exposed and the greater scrutiny of patient care in the clinical trial setting. Therefore, it is recommended to monitor immunogenicity in pharmacovigilance and risk management plans that also monitor other adverse drug reactions.

Naming

Biosimilars should have a brand name and share the same International Nonproprietary Name (INN) as the reference product and any additional designations required in the local jurisdiction. Biosimilars should also have a different brand name.

Label

The label must state all risks associated with the reference product, have the same indications, and be formatted and detailed as described in this guidance without exception. Once a biosimilar candidate is proven highly similar to the reference product, all indications granted to the reference product are allowed, provided they are not protected by market exclusivity or patents. The developer may not request fewer or additional indications.

Substitution

Biosimilars can be substituted or interchanged with the reference product or other biosimilars approved using the same reference product.[50] The EMA has recently confirmed it

Pediatrics

No pediatric compliance studies are required for biosimilars.[51]

Human Factor Studies

These studies are required to ensure that the correct dose is administered when a patient administers a product. However, if the device used is highly similar to the device used by the reference product, these studies are waived. In addition, no such studies are required when the product is administered by a healthcare professional.

Risk Management Plan

The risk management plan (RMP) for a biosimilar product is the same as for the reference product. Furthermore, brand name and batch number must ensure precise biosimilar traceability.

6. Regulatory Procedures

There is an urgent need to simplify the submission procedures and expedite approvals. To do this, the following administrative procedures are recommended.

If a product is approved in one of the ICH countries,[52] its approval should be automatic and subject to submission of a copy of the dossier that had resulted in the approval; this applies to both new and biosimilar biologics. The prescribing information should be identical to what is required in the country of origin. There is no efficacy testing in the local population because these studies can never fail and are simply a waste of resources.

- Establish a stringent post-market adverse event reporting system such as those offered in the EU and the US.
- Biosimilars should be declared interchangeable with reference products and other biosimilars.

For the products approved in non-ICH countries, the agency should adopt the EMA evaluation system using external rapporteurs and adopt the EMA policy of requiring a rapporteur evaluation. This is not an admission of the agency's lack of qualification to evaluate but a means of harmonizing the quality of the dossier and giving a fair chance to

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the developers to assure safety and efficacy. The rapporteur submits the report to the agency and the sponsor; the agency then decides whether to accept a submission. The EMA offers a list of rapporteurs, but these can be any experienced reviewers; the developer gets a chance to rebut the evaluation and challenge the findings to make it a fair and transparent exercise

- A third party must conduct the analytical assessment study that the agency has qualified for. The developer can conduct all other studies.
- No animal studies are required.
- No efficacy testing is required if the analytical assessment and clinical pharmacology match the reference product.
- The reference product must be the first biological approved in one of the SRA countries.
- Since no additional clinical testing is anticipated, the batches tested must be at scale and GMP compliant for clinical pharmacology testing.
- There should be no provision for biological APIs, as some suppliers are pushing this to the emerging markets. The drug substance is the product, and the entire manufacturing process determines the safety and efficacy.

GMP Compliance

Any GMP-compliance or ISO-compliance certification held by the developer and manufacturer is of little value. GMP compliance is established based on the product and indirectly on the rest of the infrastructure. A GMP audit should be conducted immediately after the agency's formal submission and acceptance for review. An auditor will be approved by the agency from a list submitted by the manufacturer. While agencies like the FDA and EMA conduct their audits, they also allow third-party audits where possible or necessary. This suggestion is most significant and helps assure the safety and efficacy of products. However, agencies in emerging markets often consider this an admission of their weakness. If a qualified third-party auditor can approve a facility and the product, this will have more robustness. The cost of this audit is borne by the manufacturer. We strongly urge the MENA agencies to adopt this policy and not spend resources on developing internal teams; hundreds of qualified auditors are available at a reasonable cost.

7. Conclusion

Biosimilars have proven to be one of the safest categories of products, yet it is a newer class of biological drugs approved; the regulatory guidelines have created a complex and expensive pathway that is now proven unnecessary. While the EMA and MHRA, as well as the FDA, have relaxed many testing requirements, the regulatory agencies, where the expertise to evaluate the registration submission is lacking, have insisted on continuing stricter compliance with the EU or FDA guidelines. This practice has blocked the development of indigenous biosimilars because of the high cost and longer time required. The guidance presented in this paper allows faster biosimilar approval without compromising their safety or efficacy.

Once adopted, this guideline may become the global acceptance guideline; we suggest starting it with the MENA region for various reasons, including the language and mutual acceptance of regulations. In addition, the MENA population is 500 million, the EU 750 million, and the US 350 million, requiring the MENA region to consolidate its regulatory pathway, as has been done in the EU and the US.

It is anticipated that the success of the approach presented will allow other regional agencies to combine their efforts in harmonizing their guidelines to remove the issue of affordability of biological drugs.

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