اسس تسجيل الادوية البيولوجية المشابهة لسنة ٢٠١٥ صادرة عن

مجلس ادارة المؤسسة العامة للغذاء والدواء في جلسته رقم (٣٧) تاريخ (٢٠١٥/٥/٧)

استناداً للمادة (٥) من قانون الدواء والصيدلة رقم ١٢ لسنة ٢٠١٣ والمادة (٧) من قانون المؤسسة العامة للغذاء والدواء رقم ٤١ لسنة ٢٠٠٨

المادة (١) : تسمى هذه الاسس " اسس تسجيل الادوية البيولوجية المشابهة لسنة ٢٠١٥ " ويعمل بها من تاريخ نشرها في الجريدة الرسمية .

المادة (٢) : يكون للكلمات والعبارات التالية حيثما وردت في هذه الاسس المعاني المخصصة لها أدناه أو كما وردت في المادة الثانية من قانون الدواء والصيدلة الساري المفعول او التي وردت في الملحق رقم (٣) من هذه الاسس ما لم تدل القرينة على غير ذلك :

المؤسسة : المؤسسة العامة للغذاء والدواء .

الدواء البيولوجي : الدواء الذي يحتوي على مادة فعالة أو أكثر مصنعه من أو مشتقة من مصدر بيولوجي و التي تعتمد في تكوينها على البروتينات المستمدة من خلايا الكائنات الحية.

الدواء البيولوجي المرجعي : اول دواء بيولوجي مسجل عالميا من حيث التركيب للمادة البيولوجية واثبت فعاليته ومأمونيته بدراسات قبل السريرية (السمية) والدراسات السريرية ، على ان يكون مسجلاً في الاتحاد الأوروبي (عبر إجراءات التسجيل المركزية) او الولايات المتحدة الأمريكية أو اليابان او كندا أو استراليا و\ أو الأردن.

الدواء البيولوجي المشابه (Biosimilars): الدواء البيولوجي الذي يشابه الدواء البيولوجي المرجعي في فعاليته ومأمونيته وفي قدرته على احداث الاستجابة المناعية، وتشابه المادة الفعالة فيه المادة الفعالة في الدواء البيولوجي المرجعي من الناحية الجزيئية والبيولوجية، ويماثل الدواء البيولوجي المرجعي من حيث طريقة الاستعمال بينما يتطلب اي اختلاف من ناحية التركيز و الشكل الصيدلاني و التركيبة و المواد غير الفعالة وشكل العبوة تقديم التفسيرات العلمية على ان لا توثر هذه الاختلافات على سلامة الدواء .

اللجنة : لجنة تسجيل الادوية الجديدة .

موقع التصنيع : ينطبق موقع التصنيع على كل من :

أ. أي موقع مسؤول عن أي خطوة في تصنيع المادة/المواد الفاعلة(ابتداء من تخزين واستخدام (Working cell Bank) .

ب. أي موقع مسؤول عن أي خطوة في تصنيع المستحضر بشكله النهائي.

ج. موقع اجازة التشغيلات.

المادة (٣) : اهداف الاسس :
تهدف هذه الاسس الى إدخال مفهوم الدواء البيولوجي المشابه ، و توضيح الأساس العلمي لمتطلبات المقارنة مع الدواء البيولوجي المرجعي في ما يخص الجودة والسلامة و الفعالية والمبني على استخدام أحدث التقنيات الفنية والإجراءات التحليلية ، بالإضافة للتركيز على المتابعة ما بعد التسويق وتحديد التفاصيل لضمان التتبع من أجل رصد أي اختلافات محتملة في السلامة والفعاليه لها.

المادة (٤) : نطاق تطبيق الاسس :

تطبق هذه الاسس على الأدوية البيولوجية المشابهه التي تحتوي على المواد الفعالة (البروتينات المستمدة من خلال وسائل التكنولوجيا الحديثة مثل طرق تحوير الحمض النووي(well characterized proteins) و لا تطبق على المنتجات المشتقة من الدم واللقاحات والمناعية /المواد المسببة للحساسية ، و الأنسجة، و الجينات و منتجات العلاج بالخلايا الجذعية.

المادة (٥) : يحظر تسجيل الادوية البيولوجية المشابهة إلا بعد اعتماد مواقع تصنيعها (حسب التعريف الوارد في المادة ٢ من هذه الاسس).

المادة (٦) : يحظر تداول الادوية البيولوجية المشابهة إلا بعد تسجيلها وتسعيرها وصدور رقم تسجيل لها.

المادة (٧) : للمؤسسة ان تطلب اي معلومات او دراسات لم ترد ضمن هذه الاسس من أجل ضمان سلامة وفعالية وجودة هذه المنتجات على ان يكون هذا الطلب مبررا".

المادة (٨): يجب تسجيل المخفف او المذيب الخاص بالادوية البيولوجية المشابهه حسب اسس تسجيل الادوية.

المادة (٩) : إن تسجيل دواء بيولوجي ما لا يعني قبول تسجيله بكافة أشكاله الصيدلانية وجميع تراكيزه، وإنما يجب تقديم طلب تسجيل لكل منها.

المادة (١٠): بالنسبة للادوية البيولوجية المشابهة المسجلة قبل صدور هذه الاسس ، تطبق هذه الاسس عند تجديد التسجيل.

المادة (١١) :عند إجراء اي تغيير على الادوية البيولوجية المشابهة بعد التسجيل يجب تقديم معاملة اصولية بخصوص التغيير و تقديم المرجعية لهذا التغيير .

المادة (١٢) : تتبع هذه الاسس تعليمات الاتحاد الاوروبي EMA بخصوص الادوية البيولوجية وحسب ما ورد في الملاحق من هذه الاسس و ينطبق عليها اي تحديث على هذه التعليمات تباعا".

المادة (١٣) : تنطبق اسس تسجيل الادوية سارية المفعول على الادوية البيولوجية المشابهة.

مجلس ادارة

المؤسسة العامة للغذاء والدواء

(ملحق رقم ١)
قائمة محتويات اسس تسجيل الادوية البيولوجية المشابهة

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ملحق (رقم ٢)

المقدمة و المتطلبات

Introduction

Policy statement:

While the launch of similar biological products (Biosimilar) would provide patients with potential access to affordable medicines, it is also prudent to ensure that the quality, safety and efficacy of such products are not compromised.

It is therefore important to ensure that control measures are in place to ensure the quality of the manufacturing process and of its products and to safeguard patients against possible adverse events.

So far, the European Union (EU) through the European Medicines Agency (EMA) has the most well developed regulatory framework for biosimilars and which is supported by specific guidelines, the information in this guidance is adopted from the EMA guidelines so in implementing this guideline, all the relevant Guidelines on biological products containing biotechnology-derived proteins as active substance and the Guidelines on similar biological medicinal products (also known as biosimilars) will be used as the basis for defining the registration requirements for biosimilars .

Jordan Food and Drug Administration (JFDA) reserves the right to request information or material, or define conditions not specifically described in this document, in order to ensure the safety, efficacy & quality of a therapeutic biologic product, JFDA is committed to ensure that such requests are justifiable on a science based issues & that decisions are clearly documented, as the experience and knowledge will be generated while applying these guidelines.

Also we recommend Applicants to seek advice before submitting their Biosimilar product application.

And finally, our experience demonstrates that transparent and open dialogue with all relevant stakeholders is key to put in place a robust and adapted regulatory framework in this emerging field.

Purpose:

This guideline is meant to:

- **Provide assistance to applicants (industry) on how to comply with the regulations.**
- **Introduce the concept of biosimilars.**
- **Require a baseline scientific comparison of the Biosimilar with the Reference drug (the comparability requirements) with regards to quality, safety and efficacy.**
- **Identify the level of clinical data that will be needed to evaluate and approve the Biosimilar.**
- **Focus on the Quality assessment, with head-to-head comparison to the Reference drug with full characterization of quality parameters using state of the art techniques and analytical methods or procedures.**
- **Focus on-marketing safety studies in order to monitor any potential differences in safety, including immunogenicity between the Biosimilar and Reference drug that become apparent once a Biosimilar enters the market.**
- **Specify details to ensure traceability with regards to Pharmacovigilance for biosimilars.**

Concept of biosimilars

Biosimilars are not generic biologics/biogenerics, thus the classic generic approach is scientifically not applicable (i.e demonstration of bioequivalence of the generic drug with the reference product is usually appropriate to infer therapeutic equivalence) and many characteristics associated with approval process used for generic drugs do not apply to biosimilars because of their ,biological origin , large & complex molecular structures and additional non-clinical and clinical data are usually required.
The aim of the biosimilar approach is to demonstrate close similarity of the biosimilar product in terms of quality, safety and efficacy to the reference medicinal product.

Scope and application

The demonstration of similarity depends mainly upon detailed and comprehensive product characterization, therefore, information requirements outlined within this document apply to biologic drugs that

contain, as the active substances, well characterized proteins derived through modern biotechnological methods such as recombinant DNA, into microbial or eukaryotic cell culture.
Conversely, the biosimilar approach is more difficult to apply to other types of biologics which by their nature are more complex, more difficult to characterize or to those for which little clinical regulatory experience has been gained so far. Therefore, it does not cover complex biologics such as blood-derived products, vaccines, immunologicals/allergens ,and tissue , gene and cell therapy products.

The manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy, Only one reference product is allowed throughout this exercise.

Eligibility for a biosimilar pathway hinges on the ability to demonstrate similarity to a reference product. Product employing clearly different approaches to manufacture than the reference product (for example use of transgenic organisms versus cell culture) will only be eligible for the regulatory pathway for biosimilars in justified cases.

Approval of a product through the biosimilar pathway is not an indication that the biosimilar may be automatically substituted with its reference product.
A biosimilar product cannot be used as a reference product by another manufacturer because a reference product has to be approved on the basis of a complete/full quality , non-clinical and clinical data package.

Non-clinical and clinical requirements outlined for biosimilar submission in this guidance document are applicable to biosimilars that have demonstrated to be similar to the reference product, based on results of the comparability exercises from chemistry, manufacturing and control (CMC) perspectives. When similarity of a potential biosimilar cannot be adequately established, the submission of such a product should be as a stand-alone biotechnological product with complete non-clinical and clinical data.

Non-clinical and clinical issues of specific products are further elaborated in product- class specific guidelines Based on the comparability approach and when supported by state-of-the-art analytical systems, the

comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. This in turn, depends on the clinical experience with the substance class and will be a case by case approach, also the extrapolation from one indication to another is principally possible but needs to be scientifically justified.

Definitions:

Reference product:
Innovator biological medicinal product either already approved/registered in the reference countries in the EU (via the centralized procedure) , USA, Australia, Canada and/or Jordan, this product should be registered on the basis of a complete dossier (full quality, safety & efficacy).
The reference product is used in demonstrating the comparability of a biosimilar product through quality, non-clinical and clinical studies.

Biosimilar product (or similar biological medicinal product) :
A biosimilar is a biological medicinal product that is similar to the reference product in terms of quality, safety & efficacy, contains a version of the active substance that is similar, in molecular and biological terms, to the active substance of the reference product. The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product.
Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed, additional data should be provided. Any difference should not compromise safety.

2.0 IMPLEMENTATION OF GUIDANCE:

2.1 Comparability exercise considerations:

- Biosimilars can be approved based on an exercise to demonstrate proof of similarity in terms of quality, safety and efficacy of an already approved reference product.
- The same reference product should be used throughout the comparability program in order to generate coherent data and conclusions.
- Comparative quality, non-clinical and clinical studies are needed to substantiate the similarity of structure/composition, quality, efficacy and

safety ; immunogenicity between the biosimilar and the reference product.

- The pharmaceutical form, strength , dosage and route of administration should be the same as that of the reference product. Any differences between the biosimilar and the reference product should be justified by appropriate studies on a case-by-case basis.

- Comparability with the chosen reference product should be addressed for both the active substance and drug product.

- It is not expected that the quality attributes in the biosimilar and the reference product will be identical. For example, minor structural differences in the active substance such as variability in post-translational modifications may be acceptable, however, should be justified, supportive information demonstrating that such differences will not affect the clinical safety , efficacy and immunogenicity should be provided.

- Quality differences may impact the amount of non-clinical and clinical data needed, and will handled on a case by case approach.

- The aim of the biosimilar comparability exercise is to demonstrate that the biosimilar product and the reference medicinal product chosen by the applicant are similar at the level of the finished medicinal product

- For some analytical techniques, a direct or side-by-side analysis of the biosimilar and reference medicinal product may not be feasible or give limited information (e.g. due to the low concentration of active substance and/or the presence of interfering excipients such as albumin). Thus samples could be prepared from the finished product (e.g. extraction, concentration, and/or other suitable techniques). In such cases, the techniques used to prepare the samples should be outlined, and their impact on the samples should be appropriately documented and discussed (e.g. comparison of active substances before and after formulation/deformulation preparation).

-Representative number of batches produced according to a manufacturing process with proven consistency intended for commercial use should be used to cover all comparability studies.

2.2 QUALITY GUIDELINES

A biosimilar product is derived from a separate and independent master cell bank, using independent manufacturing and control method, and should meet the same quality standards as required for innovator products. A full quality dossier is always required.

In addition the biosimilar manufacturer is required to submit extensive data focused on the similarity, including comprehensive side by-side physicochemical and biological characterisation of the biosimilar and the reference product.

The base requirement for a biosimilar is that it is demonstrated to be highly similar to the reference product, due to the heterogenous nature of therapeutic proteins, the limitations of analytical techniques and the unpredictable nature of clinical consequences to structure/biophysical differences, it is not possible to define the exact degree of biophysical similarity that would be considered sufficiently similar to be regarded as biosimilar, and Therefore Comparative non-clinical and clinical data has to be submitted; the latter has to be judged for each product independently.

Applicants should note that the comparability exercise for a biosimilar versus the reference product is an additional element to the requirements of the quality dossier and should be dealt with separately when presenting the data.
Information on the development studies conducted to establish the dosage form, the formulation, manufacturing process, stability studies and container closure system including integrity to prevent microbial contamination and usage instructions should be documented.

2.2.1 Manufacturing process considerations:

The biosimilar product is defined by its own specific manufacturing process for both active substance and finished product.
The process should be developed and optimized taking into account state-of-the-art science and technology on manufacturing process & consequences on product characteristics.
A well defined manufacturing process with its associated process controls assures that an acceptable product is produced on a consistent basis.
ICH Q5D & ICH Q5A (R1) shall be followed for cell line qualification (MCB and WCB), cells at the limit of in vitro cell age used for production, recommended viral detection and identification assays, virus testing in unprocessed bulk, virus clearance and virus testing on purified bulk, evaluation and characterization of virus clearance procedures, and all other issues in this guidance.
ICH Q5B guidelines are essential for the evaluation of the biosimilar manufacturing process & should be followed for analysis of expression products, characterisation of the expression and all other issues mentioned in this guidelines regarding the manufacture of biotechnological products.
A separate comparability exercise, as described in ICH Q5E, should be conducted whenever change is introduced into the manufacturing process

during development (include improvement of process, increasing scale, improving product stability, and complying with changes in regulatory requirements),the manufacturer generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product, such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate, as the comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and post-change product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

The manufacturer(s) for biosimilar should be approved by JFDA starting from the drug substance to the final finished product according to the drug manufacturer accreditation criteria.

2.2.2 Reference product considerations:

- The same reference product should be used for all three parts of the dossier (i.e Quality, Safety and Efficacy).
- The brand name, pharmaceutical form, formulation and strength of the reference product used in the comparability exercise should be clearly identified.
- The shelf life of the reference product and its effect on the quality profile adequately addressed, where appropriate.
- Comparisons of the active substance in the biosimilar product made against public domain information e.g. pharmacopoeial monographs are not sufficient to demonstrate similarity, reference standards are not appropriate for use as a reference product.

2.2.3 Analytical procedure considerations:

- Extensive sensitive state-of-the-art analytical methods should be applied to maximize the potential for detecting small differences in all relevant quality attributes.
- If available, standards and international reference materials [e.g from

European Pharmacopeia (Ph.Eur), WHO etc.] should be used for method qualification and validation.

2.2.4 Characterisations considerations:

Characterisations of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the following key points:

1- Physicochemical properties:

Determination of composition, physical properties also should consider the concept of the desired product (and its variants) as defined in ICH Q6B. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered and properly identified.

2-Biological activity:

Include an assessment of the biological properties towards confirmation of product quality attributes that are useful for characterisation and batch analysis, and in some cases, serve as a link to clinical activity. Limitations of biological assays could prevent detection of difference that occur as a result of a manufacturing process change.

3-Immunochemical properties:

When immunochemical properties are part of characterisation, the manufacturer should confirm that the biosimilar product is comparable to the reference product in terms of specific properties.

4-Purity, impurities and contaminants:

Should be assessed both qualitatively and quantitatively using state-of-the-art technologies and firm conclusion on the purity and impurity profiles be made.

Accelerated stability studies of the reference and of the biosimilar product shall be used to further define & compare the degradation pathways/stability profiles.

Process-related impurities are expected, but their impact should be confirmed by appropriate studies (including non-clinical and/or clinical studies).

complete side by-side characterisation is generally warranted to directly compare the biosimilar and the reference product.

The manufacturer should also assess impurities which may be present. Impurities may be either process or product-related. They can be of known structure, partially characterized, or unidentified. When

adequate quantities of impurities can be generated, these materials should be characterized to the extent possible and, where possible, their biological activities should be evaluated and individual and/or collective acceptance criteria for either process or product-related substances should be set and justified, as appropriate.

Measurement of quality attributes in characterisation studies does not necessarily entail the use of validated assays, but the assay should be scientifically sound and adequately justified by the manufacturer providing results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

2.2.5 Setting specifications:

The analytical procedures chosen to define drug substance or drug product specifications alone are not considered adequate to assess product differences since they are chosen to confirm the routine quality of the product rather than to fully characterise it.

The manufacturer should confirm that the specifications and ranges are appropriate to ensure product quality (reference to the ICH Q6B guidelines).

These ranges should be based primarily on the measured quality attribute ranges of the reference medicinal product and should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified. The relevance of the ranges should be discussed, taking into account the number of reference medicinal product lots tested, the quality attribute investigated, the age of the batches at the time of testing and the test method used.

2.2.6 Stability considerations:

- Proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents.
- Accelerated and stress stability studies are useful tools to establish degradation profiles and can therefore contribute to a direct comparison of biosimilar and the reference product. Appropriate studies should be considered to confirm that storage conditions and controls are selected.
- ICH Q5C and Q 1A(R2) should be consulted to determine the conditions for stability studies .
- For a biosimilar approach, it would be worth comparing a biosimilar

with reference product by accelerated stability studies as these studies at elevated temperature may provide complementary supporting evidence for the comparable degradation profile

2.3 NON-CLINICAL AND CLINICAL GUIDELINES

2.3.1 General

The information in this section provides only general guidance on non-clinical and clinical data requirements for biosimilars, the non-clinical studies should normally be conducted prior to the initiation of any clinical studies.

These studies should be comparative and aim to detect differences between the biosimilar and the reference product.

The requirements may vary depending on the drug classes (for example: insulin, growth hormone) also for clinical parameters such as therapeutic index, the type and number of indications applied.

The final biosimilar product (using the final manufacturing process) intended for commercial use) should be used for non-clinical and clinical studies. Clinical comparability is done in stages, much like a traditional program.

Efficacy & safety (including immunogenicity) for each indication will either have to be demonstrated or a justified (through robust scientific rational) as extrapolation from one indication to another. proposed indications for biosimilar must be identical or within the scope of indications granted for to the reference product.

Each section will address the following:

- Non-Clinical: the pharmaco-toxicological assessment.
- Clinical: the requirements for PK/PD, efficacy studies .
- Clinical safety & Pharmacovigilance : clinical safety studies as well as the risk management plan with special emphasis on studying immunogenicity of the biosimilar as clinical trials and a robust post marketing Pharmacovigilance are essential to guarantee the products safety and efficacy over time.

2.3.2 Non-clinical requirements:

-Biosimilars should undergo appropriate non-clinical testing sufficient to justify the conduct of clinical studies. These studies should be comparative and aim to detect differences between the biosimilar and the reference product and not just response per se.

- Ongoing consideration should be given to the use of emerging technologies (For e.g In vitro techniques such as real-time binding assays may prove useful. In vivo, the developing genomic/proteomic microarray sciences may, in the future, present opportunities to detect minor changes in biological response to pharmacologically active substances)

In vitro studies:

- **Receptor-binding studies or cell-based assay (e.g cell-proliferation assay) should be conducted when appropriate**

In vivo studies:

- **Animal pharmacodynamic study, using relevant PD markers to clinical use if pertinent.**
- **At least one repeat-dose toxicity study, including toxicokinetic measurements, should be conducted in relevant species.**
- **Relevant safety observations (for e.g local tolerance) can be made during the same toxicity study.**

The rationale for request of antibody measurements in the context of the repeat dose toxicity study :

- **Generally, the predictive value of animal models for immunogenicity in humans is considered low. Nevertheless, antibody measurements (e.g antibody titres, neutralising capacity, cross reactivity) as part of repeated dose toxicity studies is required to aid in the interpretation of the toxicokinetic data and to help assess, as part of the comparability exercise, if structural differences exist between the biosimilar and the reference product.**

Other toxicological studies, including safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar unless warranted by the results from repeated toxicological studies and /or the known properties of the reference product .

2.3.3 Clinical requirements

2.3.3.1 Pharmacokinetic (PK) studies

Comparative pharmacokinetic studies should be conducted to

demonstrate the similarities in pharmacokinetic (PK) characteristics between biosimilar and the reference product.

If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homologous model for such comparative PK studies. Sponsors should provide a scientific justification for the selection of patients versus healthy in PK, PD studies

The choice of designs must be justified and should consider factors such as clearance and terminal half-life, linearity of PK parameters, where applicable the endogenous level and diurnal variations of the protein under study, production of neutralizing antibody, conditions and diseases to be treated , route of administration.

Based on the product and on the half-life of the molecule an appropriate pharmacokinetic design should be set. For short half-life products, a crossover design is recommended while a parallel study will be used for long half-life products and those of high risk of immunogenecity

The acceptance range/equivalence margin to conclude clinical PK comparability should be defined prior to the initiation of the study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the reference product.

Other PK studies such as interaction studies or other special populations (e.g children, elderly, and patients with renal or hepatic insufficiency) are usually not required, unless indicated so by the nature of the reference product and the indication(s) approved thereof.

2.3.3.2 Pharmacodynamic (PD) studies

PD studies should be comparative in nature, the Parameters should be clinically relevant or a surrogate marker which is clinically validated. The PD study may be combined with a PK study and the PK/PD relationship should be characterised..

2.3.3.3 Confirmatory Pharmacokinetic/ Pharmacodynamic (PK/PD)

Comparative PK/PD studies may be sufficient to demonstrate comparable clinical efficacy, provided all the followings are met: (however, cases when approval on the basis of PK/PD data might be acceptable are highly

limited):

- PK & PD properties of the reference product are well characterized.
- Sufficient knowledge of PD parameters is available.
- At least one PD marker is accepted as surrogate marker for efficacy.
- Dose response is sufficiently characterised (ICH E10).
- Equivalence margin is pre-defined and appropriately justified.
- The most sensitive population, dose(s), and route of administration have been used .

2.3.3.4 Clinical efficacy trials.

Comparative clinical trials (head-to-head adequately powered, randomized, preferably double blind, parallel group clinical trials, so-called equivalence trials) are required to demonstrate the similarity in efficacy and safety profiles between biosimilar and the reference product.
The study population should be representative of approved therapeutic indication for the reference which is sensitive to detect potential differences between biosimilar and reference products

Equivalent rather than non-inferior efficacy should be shown in order for the biosimilar to adopt the posology of the reference product and to open the possibility of extrapolation to other indications, which may include different dosages
Clinical comparability margins should be prespecified and justified in both statistical and clinical grounds by using the data of the reference product. As for all clinical comparability trial design, assay sensitivity has to be assured (ICH E10).

Demonstration of similarity may also allow extrapolation of efficacy and safety data to other indications of the reference product under a well defined set of conditions.

2.3.3.5 Clinical safety and Immunogenicity

- The safety of biosimilar should be demonstrated to be similar to the reference product in terms of nature, seriousness and frequency of adverse events. Thus data from sufficient number of patients and sufficient study duration with sufficient statistical power to detect major

safety differences are needed.

- For products intended for administration for longer than 6 months, the size of the safety database should typically conform with the recommendations of ICH E1 on the extent of population exposure to assess clinical safety.

Data from pre-approval studies are insufficient to identify all differences in safety. Therefore, safety monitoring on an ongoing basis after approval including continued benefit-risk assessment is mandatory.

Immunogenicity which is the ability of a substance to trigger an immune response in a particular organism , also the capability of a specific substance to induce the production of antibodies in the human body. Potential immunogenicity is a key issue for biosimilars and may have serious clinical consequences. In fact, all biopharmaceuticals, in contrast to conventional drugs, demonstrate a greater capacity to induce antibodies and to elicit immune reactions.

Immunogenicity may be influenced by factors related to the biopharmaceutical itself, such as manufacturing process, formulation, aggregates, contaminants and impurities, and also by factors related to the patient, such as the type of disease, dose and length of treatment, the route of administration or depressed immune response in cancer patients, comorbidities and co-medications.

A written rationale on the strategy for testing immunogenicity should be provided. State-of-the-art methods should be used, validated to characterize antibody content (concentration or titre), neutralizing antibody & cross- reactivity.

Special attention should be paid to the possibility that the immune response seriously affects the endogenous protein and its unique biological function.

2.3.3.6 Pharmacovigilance Plan/Risk Management Plan (RMP)

Any post-market Risk Management Plan (RMP) should include detailed information of a systematic testing plan for monitoring immunogenicity of the biosimilar post-market.

The RMP should include:

o Risk Identification and characterization (e.g case definitions, antibody assays);

o Risk Monitoring (e.g specific framework to associate risk with product);

o Risk Minimisation and Mitigation strategies (e.g plans to restrict to

intravenous use where necessary, actions proposed in response to detected risk etc.);
o Risk communication(e.g minimizing and mitigation messages for patients & physicians)
o Monitoring activities to ensure effectiveness of risk minimisation.
o Detailed information of a systematic evaluation of the immunogenicity potential of the biosimilar product .
o A discussion about methods to distinguish adverse event reports from those for other licensed products, including the reference product, should be included in the RMP.
o The RMP may be maintained and implemented throughout the life-cycle of the product.

- Risk minimization activities may differ from region to another so it's very important that the manufacturers should take the region specifications into consideration while setting the Risk Management plan.
addition to specifically assessing immunogenicity post-market, the risk management plan should take into account identified and potential risks associated with the use of the reference product and, if applicable, additional potential risks identified during the development program of the biosimilar and should detail how these issues will be addressed in post-marketing follow-up

- The Pharmacovigilance plan must be submitted in the registration file.
- The Pharmacovigilance plan should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety problems that may have resulted from the impurity profiles of a biosimilar, or may have been undetected in pre-market testing or otherwise not expected.

3.0 POST MARKET REQUIREMENTS

The Pharmacovigilance plan should be able to distinguish between the biosimilar and its reference product and tracking different products and manufacturers of products in the same class of medicinal products. Such capability is essential to help ensure adverse events are properly attributed to the relevant medicinal product (i.e traceability).
Traceability of the product should involve product identification defined in terms of non proprietary name, brand name, pharmaceutical form, formulation, strength, manufacturers name and batch number(s).

Periodic Safety Update Reports (PSURs) of biosimilars should be submitted and evaluation of benefit/risk of the biosimilar post-market should be discussed. Such systems should include provisions for passive Pharmacovigilance & active evaluations such as registries and post marketing clinical studies.
The compliance of the marketing authorization holder with their commitment and Pharmacovigilance obligations (implementation of RMP) will be closely monitored, reports should be continuously submitted to the authority (where appropriate) and SmPC should be updated whenever new findings .

4.0 ORGANISATION OF DATA / DOSSIER SUBMISSION .

The data for submission are organized according to the Common Technical Dossier (CTD), with full quality data (module 3) plus comparability exercise and abridged studies of the non-clinical (module 4) and clinical components (module 5).
Biosimilar should be submitted as new DRUGS and should take NDA number & evaluated by new drugs registration Committee.

Module 1: Regional Requirements, Certificates, Information & Administrative Documents.
Module 2: CTD file summaries.
Module 3: Quality part (drug substance & drug product)
Module 4: Non clinical studies
Module 5: Clinical studies, RMP & PSUR.
(Plasma master file should be submitted if product contains any material from plasma)
(Also to include batch record of three consecutive batches)

5.0 INTERCHANGEABILITY AND SUBSTITUTION.

Biosimilars are not generic products and cannot be identical, but similar to their reference products, further biosimilar do not necessarily have the same indications or clinical use as the reference product; thus, the decision to treat a new patient with either a reference product or its biosimilar medicine, or switch in an already treated patient, between a reference product and its biosimilar should only be taken following the opinion of a qualified health professional

Automatic substitution for biologicals (i.e the practice by which a

different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biologicals, including biosimilars.

6.0 NAME OF PRODUCTS

In order to facilitate effective Pharmacovigilance monitoring and tracing of adverse safety events and to prevent inappropriate substitution, the specific medicinal product (innovator or biosimilar) prescribed by the treating physician and dispensed to the patient should be clearly identified. Therefore, all biosimilars should be distinguishable by name i.e assign a brand name explicitly, using names that are not suggestive towards the originator nor towards other biosimilars, so every medicine will either have an invented (trade) name, or the name of the active substance (according to the current International Non-proprietary Name (INN) and WHO system) together with the company name/trademark.

The approved name, together with the batch number , the country of origin & manufacturer name are important for clear identification to support adverse drug reaction reporting and monitoring of the safe use of the medicine.

7.0 LABELING / PACKAGE INSERT

The labeling of biosimilars should provide transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product.
It is expected that the labeling of biosimilar meet the following criteria:

1. The package insert should be the same as the reference medicinal product, only for approved /extrapolated indications.
2. Identification via the trade name, name of the active substance together with the company name.

8.0 PRODUCT –SPECIFIC BIOSIMILAR GUIDLINES:

(Should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with other relevant CHMP guidelines)
In this section the most relevant parts of the following guidance can be found:

- Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins.

-Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues.

- Guideline on non-clinical and clinical development of similar biological medicinal
products containing recombinant human follicle stimulating hormone (r-hFSH)
EMA/597110/2012

- Guideline on non-clinical and clinical development of similar biological medicinal
products containing recombinant Granulocyte Colony-stimulating Factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005)

- Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins . (EMA/134870/2012)

- Guideline on similar biological medicinal products containing biotechnology-
derived proteins as active substance: non-clinical and clinical issues the non-clinical and clinical requirements for Somatropin- (EMEA/CHMP/BMWP/94528/2005)

- Guidelines on non-clinical and clinical development of of similar biological medicinal products containing recombinant Interferon alfa-containing medicinal products (EMEA/CHMP/BMWP/102046/2006)

- **Guidelines on non-clinical and clinical development of of similar biological medicinal products containing recombinant Interferon beta-containing medicinal products (EMA/CHMP/BMWP/652000/2010)**

- **Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)**

الملحق (رقم ٤) الاختصارات و التعاريف و المراجع

8.0 APPENDICES

9.1 Appendix I (Abbreviations and Acronyms)

9.4 Appendix II (Glossary of terms)

9.3 Appendix III (references)

APPENDIX I:

Abbreviations and Acronyms

BWP	**Biologics Working Party**
CMC	**Chemistry, Manufacturing and Controls**
CHMP	**Committee for Medicinal Products for Human Use**
CDCR	**Control of Drugs and Cosmetic Regulations**
DNA	**Deoxyribonucleic Acid**
EU	**European Union**
EMA	**European Medicines Agency**
GMP	**Good Manufacturing Practice**
ICH	**International Conference of Harmonisation**
INN	**International Non-proprietary Names**
NCE	**New Chemical Entity**
NPCB	**National Pharmaceutical Control Bureau**
PK/PD	**Pharmacokinetic/Pharmacodynamic**
Ph Eur	**European Pharmacopeia**
PSUR	**Periodic Safety Update Reports**
QWP	**Quality Working Party**
RMP	**Risk Management Plan**
WHO	**World Health Organisation**

APPENDIX II:

GLOSSARY OF TERMS

Antibody
A spectrum of proteins of the immunoglobulin family that is produced, in the human (or animal) body, in response to an antigen (e.g., a virus or bacterium, or a foreign protein unknown to the bodyís immune system). Antibodies are able to combine with and neutralize the antigen, as well as to stimulate the immune system for defense reactions.
Retrieved from "http://www.biology-online.org/dictionary/Antibody" :This page was last modified at 21:16, October 3, 2005.

Antigen
An antigen is any substance that causes the immune system to produce antibodies against it. An antigen may be a foreign substance from the environment, such as such as chemicals, bacteria, viruses, or pollen. An antigen may also be formed within the body, as with bacterial toxins or tissue cells.

Biologic (Biological medicinal product)
Biological products include a wide range of products either synthezised or extracted from a biologic system, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. They often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available.
(Taken from: http://www.fda.gov/Cber/faq.htm#3).

Biotechnology
A set of tools that employ living organism (or part of organism) to make or modify products, to improve plants and animals, or to develop microorganisms for specific uses.
or A collection of technologies that use living cells and/or biological molecules to solve problems or make useful products *(http://www.ncbiotech.org/biotech101/glossary.cfm)*
Accordingly, modern technology includes the use of the new genetic tools of recombinant DNA to make a new genetically modified organism.

Biotherapeutics
Therapeutic biological products, some of which are produced by recombinant DNA technology

CMC (Chemistry, Manufacturing, and Control)
The section of a submission dealing with the substance properties, manufacturing and quality control, intended for evaluating the provided information in the context of the current standards in chemical science and technology, and the current regulations.

Comparability
A conclusion that a given product has highly similar quality attributes before and after manufacturing process changes, and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. And additional non-clinical and clinical data are usually necessary for the demonstration of comparable efficacy and safety to the reference medicinal product.
ICH Q5E, http://www.ich.org/LOB/media/MEDIA1196.pdf)

Comparability Excercise
The activities including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.
(ICH Q5E, http://www.ich.org/LOB/media/MEDIA1196.pdf)

Drug substance
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. Also termed active pharmaceutical ingredient (API). (http://www.fda.gov/CDER/guidance/4286fnl.htm).

Drug product
The dosage form of a medicinal product in the final immediate packaging intended for marketing. (ICH Q1A, http://www.ich.org/LOB/media/MEDIA419.pdf).

Equivalent
Equal or virtually identical in the parameter of interest. Small non-relevant differences may exist. Equivalent efficacy of two medicinal products means they have similar (no better or no worse) efficacy ,s a f e t y a n d / o r i m m u n o g e n i c i t y and any observed differences are of no clinical relevance.

Follow-on Biologic
Term sometimes used to describe similar biological medicinal products (biosimilars) in the U.S.

Glycoform
A glycoform is defined as an isoform of a glycosylated protein with identical polypeptide sequence, but with different sugar (saccharide) structures attached to the sites of glycosylation by either post-translational or co-translational modification. Such differences in glycosylation may affect properties of the glycoprotein such as biological activity, half-life, receptor binding, etc.

Glycosylation
Glycosylation is the process or result of enzyme-catalyzed addition of sugar residues (saccharides) to proteins and lipids. The process is one of the principal co-translational and post-translational modification steps in the synthesis of membrane and secreted proteins.

ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.
For more information, see http://www.ich.org/.

Immunogen
Any substance that is recognized as foreign by the immune system in a (particular) higher organism and induces an immune response which may include the formation of antibodies and developing immunity, hypersensitivity to the antigen, and tolerance.

Impurity
In drug substance : Any component of the new drug substance that is not the chemical entity defined as the new drug substance.
(ICH Q3A, http://www. ich.org/LOB/media/MEDIA422.pdf)
In drug product : Any component of the new drug product that is not the drug substance or an excipient in the drug product.
(ICH Q3B, http://www.ich.org/LOB/media/MEDIA421.pdf)

In-process control (or: Process control)
Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.
(Taken from: ICH Q7A, http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843)

Interchangeability
"Interchangeability is the medical practice of changing one medicine for another for same indication that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber"

Isoform
Any of two or more functionally similar proteins that have a similar but not identical amino acid sequence and are either encoded by different genes or by RNA transcripts from the same gene which have had different exons removed.

Originator product(reference product):
An originator product is defined as the product for which a marketing authorization is granted to a given marketing authorization holder (MAH) for a given active substance based upon a complete dossier.
(Taken from: http://medagencies.org/mrfg/docs/rec/rec annexII.pdf)

Pegylation
Pegylation is the covalent (chemical) attachment of polyethylene glycol

(abbreviated PEG), a chemically inert and non-toxic polymer, to another substance or material, e.g. to a protein. In drug development, pegylation is an established method to improve on the pharmacokinetic profile of therapeutic compounds. Pegylation has been very successfully applied to the development of second-generation biotherapeutics, such as pegylated interferon-alpha.

Pharmacovigilance
According to the WHO definition, pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post- marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.
(For details, see http://www.emea.eu.int/pdfs/human/ich/571603en.pdf)

Pre-clinical (non-clinical)
During preclinical drug development (which precedes the clinical trials in patients), a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Generally, genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. (Taken from: http://www.fda.gov/cder/handbook/preclin.htm)

Similarity
If a company chooses to develop a new biological medicinal product claimed to be similar to a reference medicinal product, comparative studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product.
(eg. http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf)

Specification
A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.

Conformance to specification means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.
(ICH Q6B, http://www.ich.org/LOB/media/MEDIA432.pdf)

Structure (primary, secondary, tertiary, quaternary)
Terms used to describe the two- and three-dimensional arrangement of the polypeptide chain in a protein. Primary structure is a synonym for the sequence of amino acid residues; the secondary structure is formally defined by hydrogen bonds between backbone amide groups (forming structure elements such as the a-helix and the b-pleated sheet), whereas tertiary structure describes the proteins overall shape, also known as its fold. The arrangement of multiple folded protein subunits which are assembled in a multi-subunit complex is called quaternary structure.

Substitution, generic
Generic substitution is the dispensing of a different brand or an unbranded drug product for the drug product prescribed; i.e., the exact same chemical entity in the same dosage form but distributed by a different company.
(Taken from: World Medical Association Statement on Generic Drug Substitution, 1989/2005, see http://www.wma.net/e/policy/d9.htm)

Substitutability
"Substitution refers to the pharmaceutical practice of dispensing one medicine for another equivalent and interchangeable medicine for the same indication at the pharmacy level, often without informing the treating physician".

Validation
The process of demonstrating that the system (or process) under consideration meets in all respects the specification of that system or

process. Also, the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements. In the manufacturing of medicinal products, production processes, cleaning procedures, analytical methods, in-process control test procedures, and computerized systems all have to be validated according to the ICH guidelines for Good Manufacturing Practice.
(ses http://www.ich.org/LOB/media/MEDIA433.pdf)

Well-characterized biologic
A well-characterized biologic is a chemical entity whose identity, purity, impurities, potency and quantity can be determined and controlled. Most of these products are recombinant DNA-derived proteins or monoclonal antibodies. For DNA-derived proteins, determining identity requires establishing the primary and secondary structures, including amino acid sequence, disulfide linkages (if possible), and post-translational modifications such as glycosylation (the attachment of carbohydrate side chains to the protein). Monoclonal antibodies can be identified with rigorous physicochemical and immunochemical assays. Purity and impurities must be quantifiable, with impurities being identified if possible; the biological activity and the quantity must be measurable.
(see http://pubs.acs.org/hotartcl/ac/96/nov/fda.html)

Appendix III References:

- **EMA guidelines:**

  It should be noted that the Committee for Medicinal Product for Human Use (CHMP) has or may develop additional guidance documents addressing both (the quality, non-clinical and clinical aspects, also for product-class specific documents).

- **EMA -Overarching biosimilar guidelines**
- **EMA- Product-specific biosimilar guidelines**
- **EMA- Other guidelines relevant for biosimilars**
- **EMA- Scientific Guidelines on Biological Drug substances**
- **EMA- Scientific Guidelines on Biological Dug Products**
- **FDA- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product**

- **FDA- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**

- **ICH guidelines:**

- ICH S6- Pre-clinical safety Evaluation of Biotechnology-derived pharmaceuticals.

- ICH E8- General consideration for clinical trials.

- ICH E9- Statistical principles for clinical trials.

- ICH Q5C - Quality of Biotechnological products: Stability testing.

- ICH Q5D - Derivation and characterization of cell substrates used for production of Biotechnological /Biological products.

- ICH Topic Q5E, Step 4 Note for Guidance on Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

- ICH Q5A - Viral safety evaluation of Biotechnology products derived from cell lines of human and Animal origin.

- ICH Q5B Quality of biotechnological products: analysis of the expression construct in cells used for production of r-dna derived protein products.

- ICH Q6B, Step 4 Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

- ICH Q11- Development and manufacture of drug substances (chemical entities and biotechnological/biological entities.

- WHO- GUIDELINES ON EVALUATION OF SIMILARBIOTHERAPEUTIC PRODUCTS.

• The proposed WHO document on Regulatory Expectations and Risk Assessment for Biotherapeutic Products(for biosimilar)