وزارة الصحة العراقية

دائرة الامور الفنية

قسم التسجيل

ضوابط و إرشادات تسجيل أدوية المشابهات الحيوية في العراق

Basis and Guidelines for the Registration of Biosimilars in Iraq

Version	Author	Date	comment
1.0	Biological/ Biosimilar Products Registration Committee	28/3/2019	Final Guidelines

المقدمة

إن الغرض من توجه بلدان العالم الى إعتماد مبدأ المشابهات الحيوية (Biosimilar Products) في الاونة الاخيرة هو لتقليل نفقات الانظمة الصحية و إتاحة العلاج لأكبر عدد ممكن من المرضى وذلك من خلال توفير علاج شبيه للعلاج الاصيل (Innovator Biological Product) إعتمادا على مبدأ المنافسة بين هذه المستحضرات ، بتعبير اخر (تخليق مستحضرات مشابهه للمستحضر الاصلي لاستخدامها لمعالجة نفس الامراض).

يكون إثبات التشابه بين (Biosimilar Product) و (Innovator Product) من نواحي النوعية ، الفعالية البايولوجية ، المأمونية و الفائدة السريرية من خلال تنفيذ دراسات المقارنة الشاملة بين المستحضرين و هو أمر يجب توفره و إثباته ليكتسب المستحضر محض الدراسة صفة المشابه الحيوي (Biosimilar Product).

من الجدير بالذكر هنا أن مبدأ المستحضر الجنيس (Generic Product) الذي تم إعتماده أواخر القرن المنصرم و المبني على مبدأ التكافؤ الحيوي مع المستحضر المرجعي و الذي مجال تطبيقه هو (small molecule drugs) لا يمكن إعتماده لاثبات التشابه بين المستحضرات البايولوجية (Biological Product) و ذلك لكون جزيئات هذه المستحضرات أكثر تعقيدا بكثير ، لذلك من هنا جائت الحاجة لاعتماد مبدأ ال (Biosimilar Products).

تماشيا مع بلدان العالم والمحيط الاقليمي و لغرض الاستفادة من مبدا ال (Biosimilar Product) كان لابد من وضع "ضوابط وارشادات تسجيل ادوية المشابهات الحيوية في العراق" لكي تتوفر المعايير اللازمة لتسجيل هذه الأدوية في العراق ، ولكون مؤسسة الدواء الاوربية (EMA) قد إضطلعت بريادة مبدأ ال (Biosimilars) منذ أكثر من عشر سنوات فعلية ، فقد تم إعتماد إرشاداتها بشكل كبير في كتابة الوثيقة الحالية كما أن التحديثات التي تطرأ من (EMA) أو إرشادات مؤسسات أخرى في هذا الصدد كمؤسسة (US FDA) و (WHO) ممكن ايضا الإستعانة بها لتغطية بعض الجوانب عند الحاجة.

ان الضوابط والارشادات المنصوص عليها في هذه الوثيقة هي لأغراض تسجيل مستحضرات المشابهات الحيوية والكثير منها موجود ضمنا ولايتعارض مع "الضوابط الوطنية العراقية لتقييم المشابهات الحيوية " الموضوعة من قبل اللجنة الوطنية لإنتقاء الادوية لأغراض إقرار هذه المستحضرات.

تعاريف

اللجنة المختصة: المقصود باللجنة او اللجنة المختصة اينما وردت هي لجنة تسجيل الادوية البايولوجية والبايوسملر المشكلة بموجب الامر الوزاري المرقم ١٦٤٦ في ٢٠١٩/٢/١٢

المستحضرات الحيوية (Biological Products) : تمثل المستحضرات الحيوية صنف واسع من المستحضرات التي تستخدم في تشخيص ، منع ، علاج و شفاء الامراض و الحالات الطبية. هذه المستحضرات غالبا ما تحتوي على مادة فعالة واحدة أو اكثر مصنعة بواسطة التقنيات الحيوية و بإستخدام الأنظمة الحية كالأحياء المجهرية أو الخلايا النباتية أو الخلايا الحيوانية و تتميز هذه المستحضرات بكبر و تعقيد مادتها الفعالة.

المستحضر الحيوي المرجعي (Innovator/Reference Biological Product) : هو أول مستحضر بايولوجي مسجل عالميا من حيث المادة الفعالة ، و أثبت فعاليته و مأمونيته في الدراسات قبل السريرية و السريرية ومابعد طرحه في الاسواق ، إذ تم تسجيله في المؤسسة الأوروبية أو منظمة الغذاء و الدواء الأميركية أو كندا أو أستراليا و / أو العراق

مستحضر المشابه الحيوي (Biosimilar product) : هو المستحضر البايولوجي الذي يشابه المستحضر الحيوي المرجعي في فعاليته ومأمونيته، وتشابه المادة الفعالة فيه المادة الفعالة في المستحضر الحيوي المرجعي من الناحية الجزيئية والبايولوجية، ويماثله في طريقة الاستخدام، وان اي اختلاف من ناحية التركيز أو الشكل الصيدلاني أو تركيبة المواد غير الفعالة أو التعبئة يتطلب تقديم التبريرات العلمية على ان لاتؤثر اي من هذه الاختلافات على فعالية ومأمونية المستحضر.

الضوابط

١. يتم اعتماد قائمة التدقيق Checklist الخاصة بالمستحضرات البايولوجية والمشابهات الحيوية والخاصة بقسم التسجيل في دائرة الامور الفنية عند تقديم ملف اي مستحضر Biosimilar لاغراض التسجيل (مرفق نسخة).
٢. تقوم لجنة تسجيل المستحضرات البايولوجية والبايوسملر بدراسة ملفات مستحضرات المشابهات الحيوية لاغراض تسجيلها وابداء الاستشارة للجنة الوطنية لانتقاء الادوية لاغراض الاقرار.
٣. تقوم هذه اللجنة بدراسة الملفات المقدمة وفق الضوابط والارشادات الحالية والمستقاة بشكل كبير من ارشادات منظمة الاتحاد الاوربي (EMA).
٤. نظرا لاهمية الموضوع ولكون الادوية البايولوجية الاكثر تعقيدا ،ستأخذ اللجنة المختصة بنظر الاعتبار بعض الحالات التي يكون فيها المستحضر غير متوائم مع الضوابط الفنية الحالية التي (هي مستقاة من ضوابط منظمة الاتحاد الاوربي) ان كان غير التوائم مقبول في ضوابط وارشادات المنظمات الاخرى وخصوصا ال U.S. FDA والـ WHO فيما يتعلق بهذه المستحضرات بعد تقديم الشركة او من يمثلها لتقرير عن ذلك مبني على اسس فنية وعلمية رصينة.
٥. فيما يخص مستحضرات المصانع الوطنية من الـBiosimilar مستقبلا فيجب تقديم مشروع انتاج هذه المستحضرات الى دائرة الامور الفنية والتواصل مع لجنة تسجيل المستحضرات البايولوجية والبايوسملر منذ البدء لضمان انسيابية تسجيل هذه المستحضرات لاحقا.
٦. ان من شروط تسجيل مستحضر الـ Biosimilar هو تداول المستحضر في بلد المنشأ لفترة لاتقل عن ثلاث سنوات مع تقديم تقارير السلامة الدورية PBRER الخاصة بهذه الفترة. اما المستحضرات المرخصة من قبل الـ EMA والـ FDA فأنه يستلزم تداولها سنة واحدة على الاقل في بلد المنشأ. تستثنى المستحضرات الوطنية من شرط التداول في بلد المنشأ.
٧. دراسات الـ(biosimilar comparability studies) تكون بالمقارنة مع المستحضر المرجعي الاصيل (Innovator Biological Product) حصرا وخلاف ذلك يتطلب تقديم الاسباب والدراسات للبت بها من قبل اللجنة المختصة.
٨. تعتمد اللجنة في التقييم على مبدأ التدرج (stepwise approach) ومجموع الادلة (totality of evidence) للوصول الى القناعة الكاملة بكون المستحضر هو Biosimilar وعلى الشركة او من يمثلها مسؤولية الاقناع التام للجنة المختصة وأطفاء اي عدم يقينية متبقية (residual uncertainty) في تشابه المستحضر المقدم مع

المستحضر المرجعي(Innovator) من خلال اجراء مزيد من دراسات النوعية والدراسات السريرية وغير السريرية وفق الضوابط العالمية.

٩. هناك بعض المستحضرات رغم كونها مستحضرات غير بايولوجية الا ان درجة تعقيدها وعدم تجانس مادتها الفعالة (heterogeneous products) يجعلها ايضا خاضعة لـ(biosimilar comparability studies) كما هو معمول به من قبل منظمة الدواء الاوربية. مثال على ذلك هو مستحضر الenoxaparin sodium

١٠. تقوم اللجنة المختصة بزيارة مواقع المصانع التي تنتج مستحضرات الـ Biosimilars غير الحاصلة على شهادة الـ EMA or US FDA سواء اكانت هذه المواقع مسجلة او غير مسجلة في وزارة الصحة العراقية لاغراض اعتماد هذه المواقع لانتاج مستحضرات الـ Biosimilars

١١. سيكون جزءا من الزيارة المطلوبة في النقطة اعلاه خاصا بمستحضر او مستحضرات الشركة المزمع تسجيلها ويفضل ان يكون هذا المستحضر او هذه المستحضرات في مرحلة الانتاج (in production process) وقت الزيارة لكي يتسنى للجنة جمع ادلة اكثر عن مشابهة هذه المستحضرات للمستحضرات المرجعية الاصيلة لاحقا.

١٢. اي تغيير جوهري في مراحل تصنيع المستحضر كتغيير مصدر الخلايا او مواد وسط النمو او ظروف نمو الخلايا يستلزم اشعار قسم التسجيل في وزارة الصحة وتقديم دراسات ال comparability exercise التي تثبت عدم تأثير هذه التغييرات على نوعية، فعالية، ومأمونية الدواء لتدرس من قبل اللجنة المختصة لادامة حالة تسجيل المستحضر لدينا، وخلاف الاشعار يتم تعليق تسجيل المستحضر وطلب الغائه ان لزم الامر اذا تأكد للجنة حدوث هكذا تغييرات دون اعلامها.

١٣. يمكن للجنة المختصة طلب تنفيذ زيارة لموقع تصنيع المستحضر عند حدوث تغييرات في المستحضر (النقطة اعلاه) او عند اعادة تسجيل المستحضر وتنفيذ بعض الاجراءات كسحب عينات تحتوي المادة البروتينية الفعالة من وسط النمو في مرحلة افراز المادة الفعالة مباشرة من المفاعل الحيوي) (bioreactor or roller bottle) او السحب من المادة الفعالة غير المعبأة (bulk) واجراء الفحوصات اللازمة عليها بعد تنقيتها في مختبرات المصنع لضمان نوعية المادة الفعالة وغيرها من المتطلبات التي تحدد في حينها وحسب المستحضر المقدم.

١٤. ان تسجيل اي مستحضر Biosimilar ذو تركيز وشكل صيدلاني معين لايعني قبول تسجيل التراكيز (القوى) والاشكال الصيدلانية الاخرى لنفس مادته الفعالة وانما يجب تقديم ملف منفصل لكل منهما وتقديم وصف كامل لاوجه التشابه والاختلاف.

١٥. نظرا لكون الافضلية الوحيدة لمستحضرات المشابهات الحيوية (Biosimilars)هو امكانية كون سعرها ارخص من المستحضرات المرجعية (Innovators) لذلك يجب ان يكون سعر المشابه الحيوي اقل "بنسبة مقبولة" من سعر المستحضر الاصيل عند طرحه للسوق وعند التعاقد والشراء من قبل مؤسسات وزارة الصحة العراقية.

١٦. يمكن للجنة تسجيل الادوية البايولوجية والبايوسملر طلب رأي قسم اللجان الاستشارية فيما يخص قسم من الدراسات السريرية لادوية المشابهات الحيوية وحسب التخصص لكل منها.

الوثائق المطلوبة في ملف تسجيل المشابه الحيوي

١. طلب خطي لتسجيل المستحضر يقدم من قبل المكتب العلمي الذي يمثل الشركة المنتجة.
٢. نسخة من كتاب تخويل الشركة المنتجة للمكتب العلمي المخول في العراق.
٣. جدول محتويات ملف تسجيل المستحضر المقدم للتسجيل.

٤. نسخة من قرار اقرار المستحضر من قبل اللجنة الوطنية لانتقاء الادوية.
٥. إستمارة تسجيل (الملحق ٥) موقعة و مختومة في كل صفحة.
٦. شهادة تسجيل المستحضر ، أصلية و مصدقة.
٧. شهادات تسجيل أو تسويق المستحضر في البلدان الأخرى (مصدقة)
٨. طريقة تحليل المستحضر (مختومة من الشركة المصنعة).
٩. مواصفات التعبئة و التغليف (الأولي و الثانوي) للمستحضر تشمل الابعاد مع المصور الملون و كذلك الرقعة المصرحة الداخلية ، تكون جميعها مختومة.
١٠. شهادة تحليل المستحضر ، موقعة و مختومة من الشركة المصنعة .
١١. صلاحية طريقة التحليل (Analytical Method Validation)
١٢. مواصفات المواد الأولية (الفعالة و غير الفعالة) المستحضر موقعة و مختومة من الشركة المصنعة.
١٣. خطوات طريقة تصنيع المستحضر ، موقعة و مختومة من الشركة المصنعة.
١٤. دراسة الثباتية لثلاث وجبات من المستحضر ، تجرى وفقا لخصائص ذلك المستحضر.
١٥. مواصفات المستحضر أثناء الإنتاج ، موقعة و مختومة من الشركة المصنعة.
١٦. شهادة خلو تركيبة المستحضر من العوامل المسببة لجنون البقر و المواد المستخلصة من الخنازير.
١٧. تركيبة المستحضر ، موقعة و مختومة من الشركة المصنعة.
١٨. قائمة الدول التي تم تسجيل المستحضر فيها مع دول التداول وحجم التداول.
١٩. بحوث و نشرات علمية عن المادة الفعالة للمستحضر (في حال كون هذه المادة مستحدثة لأول مرة).
٢٠. نسبة الكحول في المستحضر (إن وجدت).
٢١. نسخة من النشرة الطبية المرفقة للمستحضر (باللغتين العربية و الإنكليزية).
٢٢. عينتان من المستحضر.
٢٣. شهادة سعر المستحضر (بالدولار أو اليورو) في البلدان المجاورة ، مع السعر المفترض في العراق.
٢٤. شهادة ملائمة المادة الفعالة للمستحضر ، مع شهادة ممارسة التصنيع الجيد الصادرة من سلطة البلد المصنع ، موقعة و مختومة من الشركة المصنعة.
٢٥. شهادات تحليل المواد الأولية (الفعالة و غير الفعالة) للمستحضر ، موقعة و مختومة من الشركة المصنعة.
٢٦. مواصفات المستحضر موقعة و مختومة من الشركة المصنعة.
٢٧. قرص مدمج يتضمن كافة الوثائق المطلوبة للتسجيل.
٢٨. دراسات المقارنة مع المستحضر الأصيل من كافة نواحي الجودة (في قرص مدمج منفصل).
٢٩. الدراسات قبل السريرية (في الحيوانات) و السريرية مقارنة مع المستحضر الأصيل (في قرص مدمج منفصل).
٣٠. ملخص ملف نظام اليقظة الدوائية (PSMF) و تقرير السلامة الدوري (PBRER) و خطة إدارة المخاطر للمستحضر (RMP) (في قرص مدمج منفصل).
٣١. احدث نسخة من الملف التقني المعتاد لتسجيل المستحضر CTD (للاجزاء ٢، ٣، ٤، ٥) مرفق في قرص مدمج (ان كان متوفرا).

ملاحظة: ادناه قائمة بهذه الوثائق مكتوبة باللغة الانكليزية

جمهوريــة العـــراق
وزارة الصحـــــــــــــة
والبيئة
دائرة الأمور الفنية
قسم التسجيل

كۆماری عیراق
وه زارهتي ته ندروستي
فهرمانگەی کاروباری هونەری

Biosimilar product registration checklist

No.: …….. Date: / /2019 **مكتب ..... العلمي**

Product name, Conc., dosage form……..…..

INN name (active ing.):……../ Package:……...

MAH: ……/ Origin:…….……..……....

Manufacturer(s)	Date & No. of registration

	1	Original letter requesting product registration		17	Certificate of gelatin (BSE free & not of pork origin) legalized from health authority, *if applicable*
	2	Copy of authorization letter (stamped)		18	Product formula signed & stamped (2 copies)
	3	Table of contents		19	Literature scientific studies, if a new drug
	4	Copy of product approval letter by NBSD		20	Alcohol percentage, if present
	5	Registration form (appendix 5) signed & stamped by company for every page		21	Package leaflet (Arabic and English) & SmPC
	6	Original product certificates (CPP) legalized		22	2 finished product samples (unexpired)
	7	Marketing or reg. certificates of other countries (legalized) depending on reg. status		23	Price certificate is dollar or in euro (EX factory, CIF in Iraq, CIF in 3 neighboring countries, CIF in European countries) legalized
	8	List of countries where product has been registered and marketed (issued by the company)		24	Certificate of analysis for active and inactive ingredients
	9	Specification of packaging materials primary & secondary with dimensions and colored artwork of outer package and inner label stamped by manuf. company (2 copies)		25	Certificate of suitability (COS) for active ing. or copy of GMP from the authority of manuf. country of the active ingredients signed & stamped by the manuf. company, if applicable
	10	Method of analysis stamped by manuf. company (2 copies)		26	Specifications of finished product signed and stamped by manuf. company (2 copies)
	11	Certificate of analysis of finished product signed & stamped by manuf. company		27	CD containing the reg. dossier documents
	12	Validation of method of analysis (2 copies)		28	Biosimilar comparability studies ensuring the product quality aspects (on separate CD)
	13	Specifications of raw materials (active & inactive) signed and stamped by manuf. company		29	comparative pre-clinical & clinical studies with the reference product (on separate CD)
	14	Method of manufacturing signed & stamped by manuf. company		30	Pharmacovigilance requirements: PMSF, RMP, & PBRER (on separate CD)
	15	Stability study for three batches (product-dependent)		31	Copy of product latest CTD (modules 2, 3, 4, and 5) on CD. (if available)
	16	In process specifications stamped by manuf. company			

Regulations for the Registration of Proposed Biosimilars

1. A special checklist for the registration of biologics and biosimilars, prepared by the Department of Drug Registration/ Directorate of Technical Affairs, will be followed for the purpose of registering any proposed biosimilar submitted for registration.
2. The Biologics and Biosimilars Registration Committee within the Department of Drug Registration will study the submitted proposed biosimilar dossier for the purpose of registering these products. The committee can be also consulted by the National Board for the Selection of Drugs (NBSD) for the purpose of pre-approval of these products by the NSBD.
3. The committee will assess the submitted dossiers according to the current basis and guidelines which are mostly derived from the European Medicines Agency (EMA) guidelines for biosimilars.
4. Taking into account the importance of biosimilars and because biologics are highly complex products, the committee will deal with situations that cannot be addressed properly based on the current basis and guidelines (which are mostly derived from EMA guidelines) by consulting other biosimilar guidelines from other stringent regulatory authorities, such as US FDA.
5. Regarding biosimilar products manufactured by national pharmaceutical companies (future situation), these national companies should submit their biosimilar products plans and projects to The Directorate of Technical Affairs in the Iraqi MOH and start early communication with The Biologics and Biosimilars Registration Committee to ensure registering any future products from these companies smoothly and properly.
6. Any biosimilar submitted for registration should have been used in the country of origin for a period of at least three years supported by periodic benefit-risk evaluation report (PBRER). While, biosimilars authorized by EMA and US FDA, this period can be only one year supported by PBRER. National biosimilar products are exempted from this condition.
7. Biosimilar comparability studies of the proposed biosimilar product should be done in comparison with the innovator biological product. Other than that, reasonable and solid justifications as well as science-based studies have to be submitted to the committee to decide accordingly.
8. The committee will rely on a step-wise approach and assess totality of evidence to conclude the biosimilarity of the submitted product to the innovator product. The biosimilar product company or its representative in Iraq will be responsible for justifying any residual uncertainty in the biosimilarity of the submitted product to the innovator product through performing any necessary quality, non-clinical, and/ or clinical studies according to the international consensus guidelines.
9. Some pharmaceutical products even though they are not biologics, the complexity and heterogeneity of their active ingredients make them follow the biosimilar comparability studies with the innovator product to be approved by stringent authorities, such as EMA. The same standards as EMA, will be followed in Iraq. An example on such products is enoxaparin sodium.
10. The Biologics and Biosimilars Registration Committee should visit the manufacturing sites that produce biosimilar products that are not approved by EMA or US FDA, whether these sites are registered or not by the Iraqi MoH, in order to approve these sites for the production of biosimilar products.

11. During the above mentioned visit, the specialized committee members may also evaluate the company's product(s) intended to be registered in Iraq and it is preferred that this product(s) is in production process during the visit time to help the committee in collecting as much evidences as possible in the process of comparing the biosimilarity of this product(s) with the innovator product later after submitting the product full registration dossier.
12. Any substantial change(s) in the biosimilar manufacturing stages such as changing the expression host, growth media, growth conditions, etc. the company and its representative has to inform the Department of Drug Registration in the Iraqi MOH and the committee about this change(s) and submit the necessary comparability exercise that prove the product retained its original quality, efficacy, safety, and stability profiles to be evaluated by the committee to sustain the registration status of the respective product. Otherwise, the committee can suspend the product registration status or cancel it if necessary, when it becomes clear to the committee that such changes had happened to the product without an early notification from the company or its representative.
13. The committee has the right to request a visit to the biosimilar product manufacturer when substantial changes happen (see the point above) or during product re-registration and carry out some tests such as withdrawing samples containing the active protein from the growth media during the secretion phase directly from the bioreactor or roller bottle or withdrawing the sample from the bulk of the active ingredient and do the necessary testing after the required purification of the sample using the manufacturer resources to check for the quality of the active ingredient. Also, the committee would check for other necessary requirement that would be determined before and during the visit.
14. Registering any biosimilar product having certain strength and dosage form does not mean accepting other strengths and dosage forms of the same product active ingredient automatically. Hence, there has to be a separate dossier for each strength with the necessary description of the main differences and similarities between these different strengths and dosage forms.
15. Since the only advantage of biosimilars is the possibility of their "reduced price" compared to the corresponding innovators, the biosimilar price has to be lower than the originator price by an acceptable percentage when the biosimilar is launched into the private sector and during contracting and purchasing by the Iraqi health institutes.
16. The Biologics and Biosimilars Registration Committee can ask the advisory committees within the Iraqi MOH to give their opinions in some of the clinical studies related to the proposed biosmilar products, to help with the product registration.

Guidelines for the Registration of Proposed Biosimilars

Declaration: *Since European Medicines Agency (EMA) pioneered the field of biosimilars, its guidelines served as the foundation for writing this document. However, guidelines from other agencies such as U.S. FDA and WHO might be consulted when some issues cannot be addressed based on this document.*

General principles

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

In principle, the concept of biosimilarity is applicable to any biological medicinal product. However, in practice, the success of developing a biosimilar will depend on the ability to produce a medicinal product which is similar to the reference medicinal product, and to convincingly demonstrate the similar nature of the concerned products. This includes comprehensive physicochemical and biological characterization and comparison and requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product.

Therefore:

- The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is in principle not sufficient to demonstrate similarity of biological/biotechnology-derived products due to their complexity. The biosimilar approach, based on a comprehensive comparability exercise, will then have to be followed.
- The active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, for an active substance that is a protein, the amino acid sequence is expected to be the same.
- 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.
- Intended changes to improve efficacy (e.g. glycooptimization) are not compatible with the biosimilarity approach. However, differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be addressed, but may not preclude biosimilarity.
- If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.

Quality issues

➢ Manufacturing process of a similar biological medicinal product

- The development and documentation for biosimilars should cover two distinct aspects:
    1) Molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product
    2) Performance and consistency of the manufacturing process of the biosimilar on its own.
- The quality target product profile (QTPP) of a biosimilar should be based on data collected on the chosen reference medicinal product, including publicly available information and data obtained from extensive characterization of the reference medicinal product.
- The QTPP should form the basis for the development of the biosimilar product and its manufacturing process.
- A biosimilar is manufactured and controlled according to its own development, taking into account state-of–the-art information on manufacturing processes and consequences on product characteristics.
- As for any biological medicinal product, the biosimilar medicinal product is defined by the molecular composition of the active substance resulting from its manufacturing process, which

may introduce its own molecular variants, isoforms or other product-related substances as well as process-related impurities.

- As a consequence, the manufacturing process should be appropriately designed to achieve the QTPP.
- The expression system should be carefully selected, taking into account expression system differences that may result in undesired consequences, such as atypical glycosylation pattern, higher variability or a different impurity profile, as compared to the reference medicinal product.
- The formulation of the biosimilar should be selected taking into account state-of-the-art technology and *does not need to be identical to that of the reference medicinal product*.
- Regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance *should be demonstrated.*
- If a different formulation and/or container/closure system to the reference medicinal product is selected (including any material that is in contact with the medicinal product), its potential impact on the efficacy and safety of the biosimilar should be appropriately justified.
- The stability of the biosimilar product should be determined according to ICH Q5C. Any claims with regard to stability and compatibility must be supported by data and cannot be extrapolated from the reference medicinal product.
- It is acknowledged that the biosimilar will have its own lifecycle. When changes to the manufacturing process (active substance and/or finished product) are introduced during development, a comparability assessment (as described in ICH Q5E) should be performed.
- For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified in the dossier and addressed separately from the comparability exercise performed to demonstrate biosimilarity versus the reference medicinal product.
- Process changes may occur during the development of the biosimilar product, however, it is strongly recommended to generate the required quality, safety and efficacy data for the demonstration of biosimilarity against the reference medicinal product using product manufactured with the commercial manufacturing process and *therefore representing the quality profile of the batches to be commercialized.*

➢ Comparability exercise versus reference medicinal product; quality aspects

❖ Reference medicinal product

- The reference medicinal product used in the biosimilar comparability exercise at the quality level must be clearly identified (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, number of batches, lot number, age of batches, use).
- *Multiple different batches of the reference medicinal product should be used* to provide robust comparability data in order to generate a representative quality profile. Where several strengths or presentations are available, their selection should be appropriately justified. The age of the different batches of reference medicinal product (relative to the expiry dates) should also be considered when establishing the target quality profile.

- Publicly available reference standards (e.g. Ph. Eur.) *cannot* be used as the reference medicinal product for demonstration of biosimilarity. However the use of these standards plays an important role in method qualification and standardization.

❖ Biosimilar comparability exercise

- An extensive comparability exercise will be required to demonstrate that the biosimilar has a highly similar quality profile when compared to the reference medicinal product.
- This should include comprehensive analyses of the proposed biosimilar and reference medicinal product using *sensitive and orthogonal methods* to determine not only similarities but also potential differences in quality attributes. These analyses should include side-by-side comparative studies unless otherwise justified.
- Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy.
- If relevant quality differences are confirmed (for which the absence of a clinically relevant impact will be difficult to justify) it may be challenging to claim similarity to the reference medicinal product, and thus, a *full* Marketing Authorization Application may be more appropriate.
- Alternatively, the applicant *could consider adequate revision* of the manufacturing process to minimize or avoid these differences.
- 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. It is not expected that all quality attributes of the biosimilar product will be identical to the reference medicinal product. However, where qualitative and/or quantitative differences are detected, such differences should be justified and, where relevant, demonstrated to have no impact on the clinical performance of the product. This may include additional non-clinical and/or clinical data, as outlined in the Guideline on similar biological medicinal products, as well as in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Particular attention should be given to quality attributes that might have an impact on immunogenicity or potency, or that have not been identified in the reference medicinal product.
- The applicant *should demonstrate* that the desired product (including product-related substances) present in the finished product of the biosimilar is similar to that of the reference medicinal product.
- It is preferable to rely on purification processes to remove impurities rather than to establish a non-clinical testing program for their qualification.
- Quantitative ranges should be established for the biosimilar comparability exercise, where possible. 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.
- A descriptive statistical approach to establish ranges for quality attributes could be used, if appropriately justified. It should be noted that acceptable ranges used for the biosimilar

comparability exercise versus the reference medicinal product should be handled *separately from release specifications*.

- Quality attribute values which are outside or between the range(s) determined for a quality attribute of the reference medicinal product should be appropriately justified with regard to their potential impact on safety and efficacy.

❖ Analytical considerations

- Extensive state-of-the-art characterization studies should be applied to the biosimilar and reference medicinal products *in parallel*, to demonstrate with a high level of assurance that the quality of the biosimilar is comparable to the reference medicinal product.
- *It is the responsibility of the applicant to demonstrate* that the selected methods used in the biosimilar comparability exercise would be able to detect *slight differences* in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity).
- Methods used in the characterization studies form an integral part of the *quality data package* and should be appropriately qualified for the purpose of comparability.
- If applicable, standards and reference materials (e.g. from Ph. Eur., WHO) should be used for method qualification and standardization.
- 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 the previous 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).

❖ Physicochemical properties

- The physicochemical comparison comprises the evaluation of physicochemical parameters and the structural identification of product-related substances and impurities.
- A physicochemical characterization program should include a determination of:
  - the composition,
  - physical properties,
  - primary structure, and
  - higher order structures of the biosimilar,

  using appropriate methodologies.
- The target amino acid sequence of the biosimilar should be confirmed and is expected to be the *same* as for the reference medicinal product.
- The N- and C-terminal amino acid sequences, free SH groups and disulfide bridges should be compared, as appropriate.
- Any modifications/truncations should be quantified and any intrinsic or expression system-related variability should be described.

- Any detected differences between the biosimilar and the reference medicinal product should be justified with respect to the micro-heterogeneous pattern of the reference medicinal product (e.g. C-terminal lysine variability).
- The presence and extent of *post-translational modifications* (e.g. glycosylation, oxidation, deamidation, and truncation) should be appropriately characterized.
- If present, carbohydrate structures should be *thoroughly compared*; including:
    - the overall glycan profile,
    - site-specific glycosylation patterns
    - as well as site occupancy.
- The presence of glycosylation structures or variants not observed in the reference medicinal product may raise concerns and would require appropriate justification, with particular attention to non-human structures (non-human linkages, sequences or sugars).

❖ Biological activity

- The biosimilar comparability exercise should include an assessment of the biological properties of the biosimilar and the reference medicinal product as an essential step in establishing a complete characterization profile.
- Biological assays using *different and complementary* approaches to measure the biological activity should be considered, as appropriate.
- Depending on the biological properties of the product, different assay formats can be used (e.g. ligand or receptor binding assays, enzymatic assays, cell-based assays, functional assays), taking into account their limitations.
- Complementary or orthogonal approaches should be followed to accommodate limitations regarding validation characteristics of single bioassays.
- If relevant, separate assays should be employed to evaluate binding and activation of receptors.
- Where appropriate, cross-reference to non-clinical and/or clinical section(s) of the dossier may be made. It should be demonstrated that the biological assays are sensitive, specific and sufficiently discriminatory.
- The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate.
- These assays should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable.

❖ Immunochemical properties

- As detailed in the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, the immunological functions of monoclonal antibodies and related substances (e.g. fusion proteins based on IgG Fc) *should be fully compared*.
- This would normally include a comparison of affinity of the products to the intended target. In addition binding affinity of the Fc to relevant receptors *(e.g. FcγR, C1q, FcRn) should be compared*, unless justified.
- Appropriate methodologies *should* also be employed to compare the ability to induce Fab- and Fc-associated *effector functions*.

❖ Purity and impurities

- The purity and impurity profiles of the biosimilar and the reference medicinal product should be compared both *qualitatively* and *quantitatively* by a combination of analytical procedures.
- Appropriate orthogonal and *state-of-the-art methods* should be used to identify and compare the product-related substances and impurities.
- This comparison should take into account specific degradation pathways (e.g. oxidation, deamidation, aggregation) of the biosimilar product and potential post-translational modifications of the proteins.
- The age/shelf-life of the reference medicinal product at the time of testing should be mentioned, and its potential effect on the quality profile should be discussed, where appropriate.
- Comparison of relevant quality attributes, tested at selected time points and storage conditions (e.g. *accelerated or stress conditions*), could be used to further support the similarity of the *degradation pathways* of the reference medicinal product and of the biosimilar.
- Process-related impurities (e.g. host cell proteins, host cell DNA, reagents, downstream impurities, etc.) are expected to differ qualitatively from one process to another.
- State-of-the-art analytical technologies following existing guidelines and compendial requirements should be applied, and the potential risks related to these identified impurities (e.g. immunogenicity) will have to be appropriately documented and justified.

❖ Quantity

- Quantity should be determined using an appropriate assay and should be expressed in the same units as the reference medicinal product. A comparable strength should be confirmed for the biosimilar and reference medicinal product.

➢ Specifications

- As for any biotechnology-derived product, the selection of tests to be included in the specifications (or control strategy) for both drug substance and drug product is product specific and should be defined as described in ICH Q6B. The rationale used to establish the proposed range of acceptance criteria for routine testing should be described.
- The claimed shelf-life of the product should be justified with *full stability* data obtained with the biosimilar medicinal product. Comparative real-time, real-condition stability studies between the biosimilar and reference medicinal product are not required.

Non-clinical and clinical issues

- To support biosimilarity, relevant non-clinical studies should be performed before initiating clinical trials.
- A stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product. Analytical studies (see previous sections) and in vitro pharmaco-toxicological studies should be conducted first and a decision then made as to the extent of what, *if any*, in vivo work in animal studies will be required.

- It is important to note that, to design an appropriate non-clinical study program, a clear understanding of the reference product characteristics is required.
- Results from the physico-chemical and biological characterization studies (i.e. comparability of the biosimilar to the reference product) should be reviewed from the point-of-view of potential impact on efficacy and safety.
- The following approach may be considered and should be tailored to the product concerned on a case-by-case basis. The approach taken will need to be fully justified in the non-clinical overview.

❖ *In vitro* studies

- In order to assess any potential difference in biological activity between the biosimilar and the reference medicinal product, data from a number of comparative *in vitro* studies, some of which may already be available from quality-related assays, should normally be provided.

These studies should include relevant assays on:

1) Binding to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects and/or pharmacokinetics of the reference product.
2) Signal transduction and functional activity/viability of cells known to be of relevance for the pharmaco-toxicological effects of the reference product.

- The studies should be comparative in nature and should not just assess the response per se. To obtain unambiguous results, the methods used should be scientifically *valid and suitable* for their purpose.
- The studies should be sensitive, specific and sufficiently discriminatory to provide evidence that observed differences in quality attributes are clinically not relevant.
- The studies should compare the concentration–activity/binding relationship of the biosimilar and the reference medicinal product at the pharmacological target(s), covering a concentration range where potential differences are most sensitively detected.
- They should be performed with *an appropriate number of batches* of the reference product and of the biosimilar representative of the material intended for clinical use. Assay and batch-to-batch variability will affect the number needed.
- The number tested should be sufficient to draw meaningful conclusions on the variability of a given parameter for both the biosimilar and the reference product and on the similarity of both products.
- Together, these assays should cover the whole spectrum of pharmacological/toxicological aspects known to be of clinical relevance for the reference product and for the product class.
- The applicant should discuss to what degree the in vitro assays used are representative/predictive for the clinical situation according to current scientific knowledge.
- Since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, these assays can be considered as paramount for the non-clinical biosimilar comparability exercise.

Determination of the need for in vivo studies

- It is acknowledged that biotechnology-derived proteins may mediate in vivo effects that cannot be fully elucidated by in vitro studies. Therefore, non-clinical evaluation in in vivo studies may be

necessary to provide complementary information, provided that a relevant in vivo model with regard to species or design is available.

- Factors to be considered when the need for in vivo non-clinical studies is evaluated, include, but are not restricted to:
    - Presence of potentially relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).
    - Presence of potentially relevant quantitative differences in quality attributes between the biosimilar and the reference product.
    - Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins.

- Although each of the factors mentioned above do not necessarily warrant in vivo testing, these issues should be considered together to assess the level of concern and whether there is a need for in vivo testing.
- If the biosimilar comparability exercise for the physicochemical and biological characteristics and the non-clinical in vitro studies are considered satisfactory and no issues are identified which would block direct entrance into humans, an in vivo animal study *is usually not considered necessary*.
- If product-inherent factors that impact PK and/or biodistribution, like extensive glycosylation, cannot sufficiently be characterized on a quality and in vitro level, in vivo studies may be necessary. The Applicant should then carefully consider if these should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers.
- If there is a need for additional in vivo information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered.
- If a relevant in vivo animal model is not available, the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk.

❖ In vivo studies

- If an in vivo evaluation is deemed necessary, the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information.
- Animal studies should be designed to maximize the information obtained.
- Depending on the endpoints used, it may not be necessary to sacrifice the animals at the end of the study.
- The duration of the study (including observation period) should be justified, taking into consideration the PK behavior of the reference medicinal product and its clinical use.
- When the *model allows* and if not otherwise justified, the PK and PD of the biosimilar and the reference medicinal product should be quantitatively compared, including, if feasible, a dose concentration-response assessment including the intended exposure in humans.
- For safety studies a flexible approach should be considered, in particular if non-human primates are the only relevant species.
- The conduct of standard repeated dose toxicity studies in non-human primates is usually not recommended.
- If appropriately justified, a repeated dose toxicity study with refined design (e.g. using just one dose level of biosimilar and reference product and/or just one gender and/or no recovery animals)

or an in-life evaluation of safety parameters (such as clinical signs, body weight and vital functions) may be considered.

- For repeated dose toxicity studies where only one dose is evaluated, this would usually be selected at the *high end of the dosing range* and should be justified on the basis of expected toxicity of the reference medicinal product.
- The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended.
- Due to the different production processes used by the biosimilar and reference product manufacturers, qualitative differences of process related impurities can occur (e.g. host cell proteins). The level of such impurities should be kept to a minimum, which is the best strategy to minimize any associated risk.
- Qualitative or quantitative difference(s) of product-related variants (e.g. glycosylation patterns, charge variants) may affect biological functions of the biotechnology-derived protein and are expected to be evaluated by appropriate in vitro assays.
- These differences and impurities may have an effect on immunogenic potential and the potential to cause hypersensitivity.
- It is acknowledged that these effects are difficult to predict from animal studies and should be further assessed in clinical studies.
- Although immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for interpretation of in vivo studies in animals. Therefore, blood samples should be taken and stored *for future evaluations* of pharmacokinetic/toxicokinetic data if then needed.
- Studies regarding safety pharmacology, reproduction toxicology, and *carcinogenicity are not required* for non-clinical testing of biosimilars.
- Studies on local tolerance are usually not required. However, if excipients are introduced for which there is no or little experience with the intended clinical route of administration, local tolerance may need to be evaluated.
- If other in vivo studies are performed, evaluation of local tolerance may be part of the design of that study instead of the performance of separate local tolerance studies.

<u>Clinical studies</u>

- It is acknowledged that the manufacturing process of the biosimilar product will be optimized during development. However, *it is recommended* to generate the clinical data required for the biosimilar comparability exercise with the biosimilar product derived from the commercial manufacturing process and therefore representing the quality profile of the batches to become commercialized. Any deviation from this recommendation should be justified and supported by adequate additional bridging data (as described in guideline ICH Q5E).
- The clinical biosimilar comparability exercise is normally a *stepwise* procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical biosimilar comparability.

  ❖ Pharmacokinetic studies

- Comparative pharmacokinetic (PK) studies designed to demonstrate similar PK profile of the biosimilar and the reference medicinal product with regard to key PK parameters are *an essential part* of the biosimilar development program.
- The design of a PK study depends on various factors, including clinical context, safety, PK characteristics of the reference product (target-mediated disposition, linear or non-linear PK, time-dependency, half-life, etc.).
- Furthermore, bioanalytical assays should be appropriate for their intended use and *adequately validated*.
- The biosimilar comparability limits for the main PK parameters should be defined and justified prior to conducting the study.
- The criteria used in *standard clinical bioequivalence studies*, initially developed for chemically derived, orally administered products, may be a reasonable basis for planning comparative pharmacokinetic trials for biologicals in the absence of specific criteria.
- Although the comparison of target-mediated clearance is of major importance in the biosimilarity exercise, it may not be feasible in patients due to major variability in target expression, including variability over time.
- A single dose cross-over study with full characterization of the PK profile, including the late elimination phase, is preferable.
- A parallel group design may be necessary with substances with a long half-life and/or a high risk of immunogenicity.
- The doses in the single dose PK biosimilar comparability study in healthy volunteers may be lower than the recommended therapeutic doses.
- PK studies are not always feasible in healthy volunteers. In this case, the PK needs to be studied in patients as part of a multiple dose study, if a single dose study is not feasible.
- A sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.
- If the reference product can be administered both intravenously and subcutaneously, *the evaluation of subcutaneous administration will usually be sufficient as it covers both absorption and elimination.* Thus, it is possible to waive the evaluation of intravenous administration if biosimilar comparability in both absorption and elimination has been demonstrated for the subcutaneous route. Omission of the
- PK study of intravenous administration needs to be justified, e.g., in cases when the molecule has an absorption constant which is much slower than the elimination constant (*flip flop kinetics*).
- In any PK study, anti-drug antibodies (ADA) should be measured in parallel to PK assessment using appropriate sampling time points.

❖ Pharmacodynamic studies

- It is recommended that pharmacodynamic (PD) *markers* are added to the pharmacokinetic studies *whenever feasible*. The PD markers should be selected on the basis of their relevance to the clinical outcome.
- In certain cases, comparative PK/PD studies *may be sufficient* to demonstrate clinical comparability of the biosimilar and the reference medicinal product, provided that the following conditions are met:

- The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, and euglycaemic clamp test to compare two insulins. Magnetic resonance imaging of disease lesions can be used to compare two β-interferons in multiple sclerosis.
- There may be PD-markers that are not established surrogates for efficacy but are relevant for the pharmacological action of the active substance and a clear dose-response or a concentration-response relationship has been demonstrated. In this case, a single or multiple dose-exposure-response study at two or more dose levels may be sufficient to waive a clinical efficacy study. This design would ensure that the biosimilar and the reference can be compared within the steep part of the dose response curve.
- In exceptional cases, the confirmatory clinical trial may be waived if physicochemical, structural and in vitro biological analyses and human PK studies together with a combination of PD markers that reflect the pharmacological action and concentration of the active substance can provide robust evidence for biosimilar comparability.

- When evidence to establish clinical biosimilar comparability will be derived from PK studies supported by studies with non-surrogate PD/biomarkers, it is recommended to *discuss such ("fingerprinting") approach with regulatory authorities*. The plan should include a proposal of the size of the equivalence margin(s) with its clinical justification as well as of the measures for demonstration of a comparable safety profile.

❖ Efficacy trials

- In the absence of surrogate markers for efficacy, it is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blind, by using *efficacy endpoints*.
- The study population should generally be representative of approved therapeutic indication(s) of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference.
- Occasionally, changes in clinical practice may require a deviation from the approved therapeutic indication, e.g. in terms of concomitant medication used in a combination treatment, line of therapy, or severity of the disease.
- Deviations need to be justified and discussed with regulatory authorities.

❖ Study designs

- In general, an equivalence design should be used. The use of a *non-inferiority design* may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration the

characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response relationship.

- A non-inferiority trial may only be accepted where the possibility of significant and clinically relevant increase in efficacy can be excluded on scientific and mechanistic grounds. However, as in equivalence trials, assay sensitivity has to be considered.

It is recommended to discuss the use of a non-inferiority design with regulatory authorities.

❖ Efficacy endpoints

- Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy per se, since this has already been established with the reference product. The purpose of the efficacy trials is to confirm comparable clinical performance of the biosimilar and the reference product.
- Committee for Medicinal Products for Human Use (CHMP) has issued disease-specific guidelines for development of innovative medicinal products. In the development of a biosimilar medicinal product, the choice of clinical endpoints and time points of analysis of endpoints may deviate from the guidance for new active substances. Therefore, CHMP has issued product-class-specific guidelines to guide the development of biosimilar medicinal products in certain areas.
- In the absence of such a guideline, comparability should be demonstrated in appropriately sensitive clinical models and study conditions.
- The applicant should justify that the chosen model is relevant and sensitive to detect potential differences with regard to efficacy and safety.
- Nevertheless, deviations from endpoints recommended in disease-specific guidelines need to be scientifically justified.
- Differences detected between the efficacy of the biosimilar and reference products should always be discussed as to whether they are clinically relevant. Generally, the aim of clinical data is to address slight differences observed at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product.
- *Clinical data cannot be used to justify substantial differences in quality attributes.*
- The correlation between the “hard” clinical endpoints recommended by the guidelines for new active substances and other clinical/pharmacodynamic endpoints that are more sensitive to detect clinically meaningful differences may have been demonstrated in previous clinical trials with the reference product.
- In this case, it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorization application of the reference product.
- However, it is advisable to include some common endpoints (e.g. as secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference product.
- Comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product.
- As for all comparative clinical trial designs, assay sensitivity has to be considered.

❖ Clinical safety

- Clinical safety is important throughout the clinical development program and is captured during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study.

- Comparative safety data should normally be collected pre-authorization, their amount depending on the type and severity of safety issues known for the reference product.
- The duration of safety follow-up pre-authorization should be justified. Care should be given to compare the type, severity and frequency of the adverse reactions between the biosimilar and the reference product, particularly those described in the SmPC of the reference product.
- The applicant should provide in the application dossier an evaluation of the specific risks anticipated for the biosimilar. This includes in particular a description of possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion-related reactions and immunogenicity.
- The principles for the assessment of immunogenicity of therapeutic proteins and monoclonal antibodies have been described in two CHMP guidelines (EMEA/CHMP/BMWP/14327/2006; EMA/CHMP/BMWP/86289/2010).
- The potential for immunogenicity of a biosimilar should be investigated in a comparative manner to the reference product and should follow the principles as laid down in the aforementioned CHMP guidelines unless it can be justified that there is a need for deviation from this approach.
- The type and amount of immunogenicity data will depend on the experience gained with the reference product and the product class.
- Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule which must meet all current standards.
- Analytical assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient.
- The analytical assays should preferably be capable of detecting antibodies against both the biosimilar and the reference molecule but should at least be able to detect all antibodies developed against the biosimilar molecule.
- Usually, the incidence and nature (e.g. cross-reactivity, target epitopes and neutralizing activity) of antibodies and antibody titers should be measured and presented and should be assessed and interpreted in relation to their potential effect on clinical efficacy and safety parameters.
- Duration of the immunogenicity study should be justified on a case-by-case basis depending on the duration of the treatment course, disappearance of the product from the circulation (to avoid antigen interference in the assays) and the time for emergence of humoral immune response (at least four weeks when an immunosuppressive agent is used).
- Duration of follow-up should be justified based on the time course and characteristics of unwanted immune responses described for the reference medicinal product, e.g. a low risk of clinically significant immunogenicity or no significant trend for increased immunogenicity over time.
- In case of chronic administration, one-year follow up data will normally be required *pre-authorization*. Shorter follow-up data pre-authorization (e.g. 6 months) might be justified based on the immunogenicity profile of the reference product. If needed, immunogenicity data for an additional period, up to one-year, could then be submitted post-authorization.
- Increased immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and *would question biosimilarity*. However, also a lower immunogenicity for the biosimilar is a *possible scenario, which would not preclude approval as a biosimilar*.

- In case of reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population *could erroneously suggest* that the biosimilar is more efficacious than the reference product.
- It is therefore recommended to pre-specify *an additional* exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial. This subgroup analysis could be helpful to establish that the efficacy of the biosimilar and the reference product are in principle similar if not impacted by an immune response.

Extrapolation of efficacy and safety from one therapeutic indication to another

- The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified.
- In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required.
- Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data.
- It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication.
- Additional data are required in certain situations, such as

1. The active substance of the reference product interacts with *several receptors* that may have a different impact in the tested and non-tested therapeutic indications

2. The active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications

3. The studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

- Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.

Pharmacovigilance plans/ Risk management plan (RMP)

- A continuous, life-cycle pharmacovigilance and risk management are essential for biological and biosimilar to rapidly detect any important changes in product safety and efficacy over time, because these products are evolving through their life-cycle and consequently their safety profile may change.

- Manufacturers should ensure that, at the time of the marketing authorization, they have in place an appropriate pharmacovigilance system including the services of a qualified person

responsible for monitoring pharmacovigilance and the necessary means for the notification of adverse reactions that occur in any of the countries where the product is marketed.

- The manufacturer should submit a risk management plan (RMP) at the time of submission of the marketing authorization application as part of the registration dossier.
- All parts of a RMP are required for a biosimilars, with the exception of RMP part II, module SI "Epidemiology of the target population". Updates to the RMP should address the safety specification, pharmacovigilance plan and risk minimization measures.
- The submission of a RMP, or an update thereof, is also normally required if a significant change in the marketing authorization, including a new safety update or a new manufacturing process of a
- biotechnology-derived medicinal product is emerged. Therefore RMP may be maintained and implemented throughout the life-cycle of the product.
- Any post-authorization update to the RMP or any risk minimization activities in place for a biosimilar should be similarly applied to the relevant reference product, and vice-versa, unless justified, e.g. where available information suggests that the clinical concern prompting the update was product- specific (i.e. not related to the active substance or other common excipients).
- Any post market RMP should contain detailed information of a systemic testing plan for monitoring immunogenicity of the bisimilar post marketing.
- The RMP should include a discussion about methods used to distinguish adverse event reports from those for other licensed products, including the reference product.
- The compliance of the marketing authorization holder with their commitment and pharmacovigilance obligation (implementation of RMP) will be closely monitored, reports will be continuously submitted to the authority (where appropriate) and SmPC should be updated whenever new findings.
- Periodic safety update reports (PSURs/ PBRER) of biosimilars should be submitted at the time of application as part of the registration dossier and evaluation of benefit-risk of biosimilar post-marketed should be discussed. Such systems should include provisions for passive pharmacovigilance and active evaluation such as registries and post marketing clinical studies.
- Regarding the stability and cold chain; beyond the point of manufacture and release, overall product stability is maintained by adherence to appropriate storage and handling conditions and cold chain and good distribution practices. Non-adherence to these processes and standards may affect the stability and quality of biosimilars, which in turn may introduce or alter immunogenicity or contamination. This may affect certain batches, therefore; life-cycle pharmacovigilance at the levels of products and batches is crucial.
- Regarding traceability, the pharmacovigilance plan should be able to distinguish between the reference product and biosimilar and tracking different products and manufacturers of the same class of products, this is important for the proper attribution of adverse event.

- Traceability of the product should include product identification, defined in terms of brand name, pharmaceutical form, formulation, strength, manufactures name and batch number, country of origin. The Iraqi pharmacovigilance center will provide the proper system for the collection, assessment, understanding and communication of any safety concern.

لجنة تسجيل المستحضرات البايولوجية والبايوسملر المشكلة بموجب الامر الوزاري ١٦٤٦ في ٢٠١٩/٢/١٢