REGULATORY FOCUS

Biosimilars Breaching Borders:

How FDA and EMA Find Common Ground

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Human clinical pharmacology pharmacokinetic (PK) and pharmacodynamic (PD) studies are vital for many reasons, and uniquely useful in extrapolating the efficacy and safety of biosimilars.

PK and PD studies are the most objective clinical trials, and are sensitive to changes in a drug product. But the workings and concepts behind such studies are not well understood by many in industry, and even physicians, in comparison with clinical efficacy.

This article presents a European perspective of biosimilar development with a focus on PK/PD, which helps provide context to an interpretation of the three new draft guidances from the US Food and Drug Administration (FDA) published in February 2012: *Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, *Guidance for Industry Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* and *Guidance for Industry Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

Regulatory Framework of EU Biosimilars, US Prospects

The development journey for a biosimilar medicine in the EU can take six to 11 years and carry considerable risk as well as scientific, clinical and regulatory effort to achieve success.[1-4]

The burden of proof is substantial, presented by European Commission (EC) directives and regulations, and guidelines from the European Medicines Agency (EMA and its Committee for Medicinal Products for Human Use (CHMP), such as those overarching requirements for pharmaceutical, nonclinical and clinical development [5-10] and product- or class-specific guidelines.[11-19]

Although, there have been 13 EU biosimilar approvals, these involve only seven sponsored development programs (see **Table 1**). This is a groundbreaking development internationally, which is why many regions of the world have largely adopted the European biosimilars framework.

The World Health Organization's (WHO) comprehensive guidance also largely reflects the EU position. In fact, it provides additional clarity, as well as covering all the disciplines: quality, nonclinical, clinical and regulatory in a single document.[20]

In the US, another highly regulated environment, the new law began evolving in stages in 2009 and 2010, and with the passage of the *Biologics Price Competition and Innovation Act* (*BPCI Act*), regulations and guidelines are now in development. The first step of the process was recently realized by the publication of the three draft guidances on 9 February 2012.[21-23]

They represent the overarching guidances for biosimilar development. Although they focus on the 351K abbreviated Biologic License Application (aBLA) biosimilars pathway of original biologics approved under the *Public Health Service Act* (*PHS Act*), FDA advises that the same principles apply to the 505b2 pathway used for approval of some biologics, such as the hormonal products insulin, somatropin, calcitonin, glucagon, hyaluronidase, etc., that were approved under the *Federal Food, Drug, and Cosmetic Act* (*FD&C Act*).

It is clear from the first reading of these guidances that FDA has taken into account both the EU experience and the WHO guidance and, more importantly, its own rich history of originator biologics approval and postapproval comparability criterion of biologics, to arrive at its own pathway for case-by-case approval. FDA officials had previously suggested that they would expand on principles adopted during the approval of enoxaparin sodium, a low molecular weight (LMW) heparin, a structurally complex, 4,500 Dalton[Da] polysaccharide, in their decision-making process.[24]

A fee structure for future biosimilar aBLA submissions are expected to be adopted in the first half of 2012 and will cover four planned FDA meetings and an Investigational New Drug (IND).[25]

The biosimilar approval process should be speeded by an EMA/FDA discussion and exchange "cluster"established in 2011, fostering collaboration between the world's two leading regulatory authorities.

Table 1: EU biosimilar landscape of approvals (marketing authorisations MAs)

(INN) of substance	MA holder	Date of EC approval	Brand name	Reference Product
Somatropin	Sandoz GmbH	12 April 2006	Omnitrope®	Genotropin®
	BioPartners GmbH	24 April 2006	Valtropin®	Humatrope®
Epoetin alfa	Sandoz GmbH	28 August 2007	Binocrit®	Erypo® /Eprex®
	Hexal GmbH	28 August 2007	Epoetin alfa HEXAL®	Erypo® /Eprex®
	Medice Arzneimittel Putter GmbH & Co. KG	28 August 2007	Abseamed®	Erypo® /Eprex®
Epoetin zeta	STADA Arzneimittel GmbH	18 December 2007	Silapo®	Erypo® /Eprex®
	Hospira UK Ltd.	18 December 2007	Retacrit®	Erypo® /Eprex®
Filgrastim	Ratiopharm GmbH	15 September 2008	Ratiograstim®	Neopogen®
	Teva Generics GmbH	15 September 2008	TevaGrastim	Neopogen®
	CT Arzneimittel GmbH	15 September 2008	Biograstim®	Neopogen®
	Sandoz GmbH	6 February 2009	Zarzio	Neopogen®
	Hexal GmbH	6 February 2009	Filgrastim HEXAL®	Neopogen®
	Hospira UK Ltd.	8 June 2010	Nivestim	Neopogen®

Chemistry, Manufacturing and Control (CMC)

A well-executed series of systematic chemistry, manufacturing and control (CMC) studies is fundamental to biosimilars development and approval in the EU, and is expected to play an important and fundamental part in future aBLA submissions in the US, as proven by FDA's emphasis in the recently published dedicated scientific considerations guidance[27] and quality guidance.[28]

Current advances in chemistry, biochemical and biophysics structural and analytical methods, as well as biological *in vitro* and *in vivo* testing, allow head-to-head comparisons to be made to the reference medicinal product (RMP) biologics both at the drug product (DP) level upon release and during stability testing (accelerated or stress release testing is recommended).

Since the process leading to the biosimilar drug substance (DS) is unique, and the DS of the RMP is unavailable, the two are not required to match perfectly in areas like process impurities. But, the RMP's DS usually can be extracted from the DP through a work-up and studied against the biosimilar DS to demonstrate comparability at the DS level.

Caution needs to be taken to ensure the Biosimilar DS is comparable batch-to-batch during DP manufacturing and other pharmaceutical development. Otherwise, the pivotal studies will not be relevant.

Comparing the EU experience with the FDA guidance,[29] it is notable that they are consistent and in agreement. Therefore, the robust and extensive EU CMC and biological testing—FDA calls the latter "functional" assays—for a biosimilar head-to-head program against the RMP should suffice for FDA, although it is advisable to verify details through FDA consultations. The "functional" assays may "include, but are not limited to, bioassays, biological assays, binding assays, and enzyme kinetics."[30]

Comparative primary, secondary, tertiary and quaternary structures (including aggregation); enzymatic post-translational modifications, such as glycosylation and phosphorylation; potential variants, such as protein deamidation and oxidation (including upon degradation); protein folding; process impurities; heterogeneity; and intentional chemical modifications, such as PEGylation sites,[31] among other characteristics, have to be thoroughly investigated in a comparability exercise for both EMA and FDA. There is no difference in the requirements.

If the biosimilar shows high "similarity," FDA should agree that the sponsor may have an appropriate scientific basis for a selective and targeted approach to subsequent animal and/or clinical studies.[32] FDA finds it desirable to identify a "meaningful fingerprint-like analysis algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods."

Preclinical Development Comparative Proof of Principle, Safety

Careful nonclinical development planning, beginning with a robust *in vitro* testing program proving comparability with head-to-head studies, is key to successful, compact preclinical development. This is emphasized by new EU monoclonal antibody guidance in 2010 minimizing testing and surprisingly attempting to avoid primate testing.[33]

There is EMA and CHMP consideration of a further new EU guidance for a reduced burden of animal testing for all proteins. FDA strongly emphasizes the "functional testing"[34, 35] that uses the same *in vitro* methods.

FDA maintains that animal toxicity data are useful when safety uncertainties remain after the extensive structural and functional characterization. Also, in general, nonclinical safety pharmacology, reproductive and developmental toxicity and carcinogenicity studies are not required.

"Under certain circumstances," FDA advises that a single-dose study in animals comparing the proposed product and RMP using PK and PD measures would be warranted, although no details are given. In addition, animal immunogenicity testing is required.

While both these aspects also have to be covered in an EU program, the PK part would normally be toxicokinetics as part of toxicology. In addition, repeat dose toxicity has been a standard requirement in the EU to date.

Clinical Pharmacokinetic, Pharmacodynamic Bioequivalence

In contrast to chemically-synthesized, small-molecule drugs (SMD), biologicals or biopharmaceuticals are a much more heterogenous class of biotechnology-derived proteins, which cannot be simply copied to obtain a "bioidentical" drug to be registered by just one PK bioequivalence (BE) study for a "generic."

The term "biosimilar" was chosen in Europe for these large-molecule drugs, comprising recombinant proteins, monoclonal antibodies (mAbs), blood and plasma-derived products or vaccines that are obtained from cells of mammals, bacteria, insects, plants or yeasts, as well as of genetically modified animals, bacteria or plants. To understand the challenging regulation, the impact of the following differences in PK and PD between biosimilars and generics need to be considered:

1. There is no guarantee that manufacturing a biosimilar will lead to a product stable and comparable with the innovator RMP, even if the same genetic construct, technique, formulation and packaging are used,[36] even if this information about the innovator product is known.
2. Although the amino acid sequence (primary structure) of a protein can be mimicked, e.g., for a lower molecular weight (MW) biologic like filgastrim (18,800 Dalton [Da]) up to the high-MW Factor VIII (264,000 Da), both local folding (secondary structure) and global folding (tertiary structure) with its hydrogen or disulphide bonds, in some cases even a quaternary structure (stable association of two or more polypeptide chains), may differ depending on the cell lines used and lead to alterations in PK, PD, efficacy and safety.
3. The manufacturing process may also affect post-translational modifications such as the extent of glycosylation (e.g., erythropoetins) and/or sialic acid content (e.g., follicle stimulating hormone, FSH), which may alter PK, PD, efficacy and safety.
4. The 5,000- to 200,000-fold higher MW of biologicals and their sometimes more fragile nature compared to SMDs has important consequences on PK and duration of action.
5. Endogenous concentrations, e.g., for (tissue) hormones or blood products have to be taken into account, which may be pulsatile or be produced continuously, exhibit chronotropic variability or be released following specific signals.
6. In spite of substantial progress in assay methods, limitations beyond the primary structure, binding characteristics or interference with endogenous compounds or anti-drug antibodies (ADAs) still exist.
7. The higher binding specificity of biologicals to their target structures and, consequently, their much lower molar dose compared to SMDs in conjunction with the frequent inability to determine metabolites and/or degradation products need to be considered in many studies on biosimilars.
8. The formation of ADAs may affect PK, PD, efficacy and safety.

Much progress has been achieved in the EU in the last five years, particularly by EMA guidelines,[37] to thoroughly address biologicals' complex PK to support the applicant for a biosimilar development.

In contrast, much less written guidance exists regarding PD due to the lack of validated surrogate biomarkers for many targets. This situation prompted FDA to start the "Critical Path Initiative," EMA to launch the "Innovation Task Force" and the current collaboration of both authorities. Where such a biomarker has already been accepted, e.g., glucose for insulin, or even if it is not considered an adequate surrogate biomarker such as IGF-1 for growth hormone or leucocytes for G-CSF, this is reflected in drug-specific guidelines, as provided by EMA for erythropoetins , FSH, G-CSF, insulin and somatropin.[38-46]

Given the variety of pharmacological targets and their postulated biomarkers, an overarching set of guidelines cannot include all specific biomarkers because there are too many "unvalidated" biomarkers, which may be acceptable on a case-by-case basis in a bioequivalence study. But even if a specific guidance already exists, consulting the respective authority for PK and PD Scientific Advice (SA) prior to starting a biosimilar program is still recommended. This should also include the justification for the RMP selection.

The following sections cover therapeutic proteins, but do not include plasma-derived products and vaccines with their special requirements and existing guidelines.

It is not known whether FDA will write product-specific (hGH, FSH, GCSF) or product class-specific (mABs) guidances later on, but the current guidances raise aspects of development that essentially agree with the points above, and the need for seeking individual biosimilar product advice.

The EU has seen different development programs for the same target molecules under different sponsorship, each with a unique strategy. This proves there is no single path for such biologics.

Pharmacokinetics

Currently, there are two general guidelines with specific recommendations for PK studies: *Guideline on similar biological medicinal products containing monoclonal antibodies* (Draft),[47] which explicitly refers to the *Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins*,[48] which provides more details on PK for the development of both innovative biologicals and biosimilars.

Both guidelines acknowledge the variable nature of biologicals, including mAbs, and require the most appropriate method to show PK bioequivalence (BE). EMA and FDA explicitly offer SA meetings on biosimilars to agree case-by-case on study design and procedures, depending upon the PK properties of the compound under examination.

In its new guidances, FDA emphasises the importance of presenting the full package of pharmaceutical (including biological) data before arriving at any recommendation for a clinical program. Also, FDA reiterates throughout that, "Human PK and PD studies comparing a proposed product to the RMP generally are fundamental components in supporting a demonstration of biosimilarity."

FDA will decide the scope and magnitude of clinical studies depending upon the "extent of residual uncertainty about the biosimilarity of the two products."[49]

All product-specific EU guidelines[50] strongly recommend performing a PK study as a first step, not only to show BE, but also to support the pivotal Phase-3 study when useful in combination with PD assessment(s), whereby a Phase-2 study generally is not required. For biosimilars with a shorter half-life such as erythropoetins, FSH, G-CSF or somatropin, the standard BE approach as for SMDs, i.e., a single-dose (SD) crossover study is adequate.

However, referring to mAbs with their long half-life ($t_{1/2}$), only a parallel-group design is considered appropriate. As long as a biosimilar study includes primarily analytical methods with no results uncovered or otherwise compromised through bias during the study, an open design is justified.

If PD and/or safety are study objectives, it is preferable to perform a double-blinded study. In view of the variable nature of biologicals, any decision on study design should be adequately justified, particularly if deviating from recommendations.

The study population should be primarily homogeneous and sensitive in order to reduce variability, with the sample size chosen for a study with no therapeutic intention and to provide meaningful results. Elimination PK for some biologicals, in particular mAbs, may differ to a relevant extent between healthy subjects and patients due to a large dependency on receptor density and uptake; e.g., by over-expression of receptors in tumors or inflamed tissues in patients.

For new, innovative drugs, such PK differences may impair reliable extrapolations to patients if healthy subjects are used. In contrast, comparative, non-therapeutic biosimilar PK or PK-PD studies of healthy subjects are accepted, as long as possible endogenous substances can be reliably suppressed. The healthy subjects' population usually is the most homogenous, more rapid to recruit and does not introduce ethical issues, provided there is no safety concern.

If patients are used, e.g., to obtain more relevant PD results within a Phase 1 study, variability can be reduced by selection regarding age, body weight, identical target disease and concomitant diseases, number of previous and concomitant treatments or expression of antigens, if feasible. Even strong selection criteria may not secure a comparable receptor expression.

If a biological is licensed for more than one indication, a different patient population than the Phase 3 study may be used in a biosimilar PK study in order to assess the PK BE most sensitively. In this scenario, population PK (PPK) is recommended for the Phase

3 study to obtain further data to allow a claim of biosimilarity and to support extrapolation between indications.

FDA discusses this in its new scientific considerations biosimilars guidance,[51] stating that PPK is "an efficient way to quantitate the influence of covariates" (e.g., age or renal function).

For biosimilar studies, the EU position is that a single-dose study is most sensitive in both linear or non-linear and time-dependent PK, but also to avoid potential immunogenicity if there is a noteworthy risk. The use of multiple doses (MD) is wise if assessment of a concentration-response relationship appears to be necessary to provide stronger evidence of biosimilarity.

If only one dose is planned, the highest therapeutic dose should be used, in particular in the case of non-linear PK. If an MD PK study in patients is performed, PK should ideally be done after the first dose and at steady state, for instance for mAbs. In the case of results that seriously question PK BE, the relevant regulatory authority should be consulted as to how to proceed with the biosimilar development.

Within a clinical setting with different therapeutic MD regimens for a licensed RMP, the most sensitive key PK parameters should be selected. If the license spans more than one indication, the population with the most reliable PK characterization should be selected for a biosimilar PK BE study, without the need to cover all therapeutic regimens and/or indications in the biosimilar development.

Whenever possible, a monotherapy setting is preferable to limit variables. If therapeutic efficacy can be expected in a MD PK study, e.g., using cytotoxic mAbs in cancer, possible time-dependent PK changes will have to be considered in the study design.

If antibody formation or receptor shedding during a therapy including a mAb is to be expected, baseline concentrations and their levels during the study and at least until the study ends should be followed up to allow for a conclusive PK interpretation.

In accordance with the small molecule drugs (SMDs) guidelines,[52] the primary endpoints of testing PK for BE are area under the curve (AUC) and measured maximum concentration (C_{max}), if not considered secondary in a guideline (as is sometimes the case with C_{max}, e.g., with the insulin EU biosimilar guideline).

For MD comparisons, at least the concentration preceding the next dose (C_{trough}) at steady state must be added. As is the case with SMDs, BE may be assumed if the 90% confidence intervals of the biosimilar versus the RMP fall within the acceptance range (0.8; 1.25). Exceptions from this standard, as sometimes also apply to C_{max} for SMDs, should be thoroughly justified in advance.

Secondary endpoints explicitly should include $t_{1/2}$, clearance (CL) and volume of distribution at steady state (V_{SS}), where $t_{1/2}$ and CL are rather judged as also being of primary interest in the available EMA guidance for erythropoetins (EMEA, 2010) or FSH (EMA, 2011). It should be noted that V_{SS} can also be determined after a single dose, provided the respective PK is linear and independent from time. Additional PK parameters may be added, for example, least mean residence time (MRT) as a more reliable time parameter for drug availability may be of particular value.

Some PK peculiarities of biologicals also need to be considered in planning and interpretation of biosimilar PK studies (EMEA, 2007).[53] Although assay methods are not specifically addressed, it is necessary to emphasize the importance of validation. No matter which assay is used, it should include pre-study and within-study validation.

Pre-study validation has to address the compliance of the assay with respect to:

1. stability of the analyte in relevant matrix
2. specificity
3. accuracy
4. precision
5. lower and upper limits of quantification and limit of detection
6. concentration-response relationship
7. dilution linearity

The within-study validation should use samples from a bio-study and control samples (QC and calibration standards) to confirm the correct performance of each assay run.

Regarding PK peculiarities for proteins, the EMA guideline[54] provides some worthwhile hints. If the biological is not given intravenously (i.v.), absorption, in particular, from the favored (patient can self-administer), subcutaneous (s.c.) administration site, incomplete

bioavailability may result due to pre-systemic elimination that may occur in the lymphatic system and tissues. While passing the lymphatic system, the recovery in lymph is correlated to MW.

In addition, small proteins are subject to first-pass elimination due to proteolytic degradation in tissues. Thus, different skin and tissue morphology in diverse body parts not only explains different PK results dependent on the injection site, but also the dependence of absorption from drug concentration, injection volume or depth of injection and various patient-specific factors. Insulins exemplify this complexity.

The V_{SS} for large proteins or molecules corresponds with the plasma volume and is similar to the distribution of albumin (approximately 0.1 L/kg). The tissue distribution process of biologicals often occurs by (receptor-mediated) cellular uptake, and not by extensive diffusion as for SMDs, which require a much higher dose, resulting in much larger V_{SS}.

Due to the more-specific binding processes of biologicals, adequate concentrations are often achieved despite a much lower V_{SS}. As biological degradation frequently occurs at the target site, tissue distribution is often part of the elimination process. Therefore, both PK and PD have to be shown for a biosimilar in comparison to the original.

Capacity-limited binding to the target, proteins or barriers to distribution, and elimination may lead to non-linearity or time-dependent kinetics during multiple-dose PK until saturation occurs. Such processes may also coincide with down- or up-regulation of target receptors or the formation of antibodies, which may be difficult to control in a parallel-group biosimilar study.

In contrast to most small molecule drugs (SMDs), for which only the unbound fraction can reach the target receptor, the activity of a therapeutic protein may often be related to both an unbound and bound fraction and to its binding kinetics. For interpretation of PK and/or PK-PD results, it may be important to distinguish between the free and bound fraction if a less active or inactive metabolite has the same binding site.

Binding sites for therapeutic proteins may be unspecific, such as albumin and a-acid glycoprotein, or soluble receptors such as shed antigens or specific binding proteins directly related to drug action like growth hormone binding proteins (e.g. insulin IGF-BP) or other carrier proteins. Binding to soluble receptors may alter CL or V_{SS} of a therapeutic protein, resulting in time-dependent PK, necessitating determination of the protein's status before and during treatment to differentiate between free and bound receptors for a biosimilar in comparison to an innovator drug.

Only smaller proteins (<50,000 Da) can be eliminated via the kidney, while larger molecules may be subject to elimination in other tissues and/or in target cells through receptor-mediated endocytosis followed by catabolism. All proteins may undergo catabolism by ubiquitous proteases, and metabolites play a much less important role compared to SMDs.

Hepatic metabolism could also contribute to the elimination. Thus, any active metabolite has to be quantified in a biosimilar study or, if that is not possible, using a bioassay to determine total activity, as metabolites could also lead to time-dependent PK.

If this is known from the innovator, the EU guideline recommends studying several dose levels preferentially in an MD study and/or using population PK. In consequence, a biosimilar study has to avoid any bias by group differences related to the elimination pathways.

Pharmacodynamics

All available EU-specific guidelines recommend concomitantly assessing PD endpoints with PK whenever possible, even if PD does not refer to a validated surrogate biomarker, e.g., IGF-1 for somatropin or reticulocytes for erythropoetins. The background of this recommendation is the observation for proteins that not only PK, but also the concentration-response relationship may differ between two products.

EMA/CHMP (2010)[55] recommends the use of several doses of biologicals/mAbs "to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity." It is well recognized that it is easier to show equivalent clinical efficacy in Phase 3 studies than using PD biomarkers, if available at all, in a Phase 1 study.

Knowledge about any PD effect at least may indicate the presence of a biosimilar/mAb at the target site and, thus, may not only support biosimilarity but also provide useful information at least for the Phase 3 study. If more than one mechanism of action is related to the clinical indication(s), PD should cover all indications and seeking SA is recommended.

The EMA (2007)[56] guideline requires measuring efficacy and safety biomarkers for originator biologicals as well as the PK evaluation in the same study. This general statement appears to be more important for those products with a very complex PK as outlined above, but less important for a product with linear PK that corresponds with linear efficacy.

The requirements for study design and biomarkers may depend on available information for an innovator product, if any. If new knowledge evolves on either PK-PD or the concentration-response relationship for a certain mechanism of action or an indication of the originator's biologic, it is likely that authorities will require including these RMP findings into a biosimilar study. It is also evident that for some therapeutic areas with several pathomechanisms and a large variety of possible biomarkers, the choice of an appropriate biomarker related to one of several mechanisms of action requires careful selection and justification.

Generally, statistical proof of PD biosimilarity has to be at a 95% level of confidence. Guidances also allow the justification of other confidence levels based on scientific grounds and/or available data on the originator.

FDA states in its scientific considerations guidance[57] that, "A human PD study that demonstrates a similar effect on a clinically relevant PD measure or measures related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) can also provide strong support for a biosimilarity determination." FDA guidance devotes a lot of space to PD and PK, much less to Phase 3 efficacy studies, and is consistent with European implemented experience.

Conclusion

Once the pharmaceutical basis of a new biosimilar drug substance is established, proof of principle from nonclinical testing will bridge to a most essential stage in its development, that of clinical pharmacology studies with PK and PD independently, or combined PK/PD where the correlation is known. These studies will allow an extrapolation to efficacy and safety, including immunogenicity of the RMP, permitting claims as to all the indications.

FDA fingerprinted the low molecular weight heparin (LMWH) enoxaprin sodium based on the agency's five criteria, each of which captures different aspects of its "sameness" to the Lovenox reference (*Orange Book*) listed product. The proof of "sameness" is more precise than that of "(bio)similarity" which is how LMWH is defined in European guidance, and allowed FDA to approve all label claims of Lovenox for the new generic, and also be assured of immunogenicity without any clinical Phase 3 studies.

This surprising FDA decision challenged EMA's authority to reevaluate its LMWH biosimilarity 2009 guideline. In late 2011, it released a concept paper to update the earlier guidance providing an opening for discussion "about including the possibility of a modification in clinical data requirements, providing similarity of physicochemical characteristics of the biosimilar and the reference LMWH has been convincingly shown, and similar efficacy and safety can be ensured by other means."

In the EU, immunogenicity has to be proven in a long, involved clinical safety study that often lasts 12 months or more and has not been extrapolated from PK as with FDA's decision on enoxaprin sodium. However, it is noteworthy that FDA points out cases where there would be a need for immunogenicity to be proven in a clinical setting (as for Europe).[58]

One note of caution: if EU immunogenicity data are submitted, sponsors should ensure that the testing methods themselves are thoroughly validated according to FDA guidance.[59,60]

While proof of benefit is not needed in the EU, proof of clinical equivalence might be required above and beyond PK and PD studies, for example as basis of the approval of growth hormones (somatropins Valtropin and Omnitrope) or Epoetin alfa (Binocrit) or future plans for mAbs, FSH or even LMWHs.

The unacceptability of "differences" in properties of the biosimilar medicine is an intricate part of EMA CHMP thinking, and is incorporated in the EMA/CHMP EU mAb guideline. This same concept is repeatedly addressed by the FDA guidance as well.

EMA, CHMP and FDA are aligned in requiring proof of biosimilarity with equivalence from quality, nonclinical and clinical standpoints, without the need to provide evidence of clinical benefit by the biosimilar. There should also be no significant differences in efficacy or safety, but this evaluation can lead to different agency interpretations and final outcomes. This has already been illustrated by the enoxaprin sodium case.

The pivotal role that clinical pharmacology plays is common to both US and EU systems. Many of the FDA/EMA principles, and even detailed requirements in the FDA guidances, also appear to be mostly in common or at least aligned, including the concept of considering what FDA calls the "totality" of the evidence in its estimation of biosimilarity.

FDA has taken bold and far-reaching action in allowing the use of a non-US reference product, for example the RMP sourced from the EU, supported by scientific bridging data (and manufacturing site) as described in the questions and answers guidance.[61] This is a major stride toward international development of biosimilars.

FDA has not decided yet on the type of information sufficient to enable it to determine that a biosimilar product is also interchangeable with the reference product.[62,63] The prerequisites for approval are likely to unfold as experience is gained with submissions.

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