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Reflection Paper

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The Role of Product-specific Monographs for Biotherapeutic Products in Pharmacopoeias

This reflection paper describes a scientific and regulatory rationale for a new format and scope for monographs of biotherapeutic products (BTPs) replacing the traditional product-specific format and focusing on the establishment of methods relevant for product-class specific testing strategies, thereby adding value and facilitating the development of new BTPs including similar biotherapeutic products (SBPs).

Abstract

Pharmacopoeias' mission is to ensure access to quality medicines in the market place by the provision of public standards (written norms as well as physical reference standards) that define the quality attributes and related ranges relevant for the established safety and efficacy of these drugs.[1,2,3] Product-specific monographs of active (small molecule) pharmaceutical ingredients (APIs) and, in certain regions also of finished products, are used as one means for ensuring quality of small molecule drugs. These standards are also recognized for ensuring the quality of generic drugs and facilitating their development.

However, the current format and scope of product-specific monographs are unlikely to fulfill a role of similar importance for BTPs. Instead, they could inadvertently interfere with health authority approvals of manufacturing changes to originator drugs and similar therapeutic products. If the similar therapeutic candidate is deemed acceptable just because it meets this standard, with omission of other relevant evidence (including a full similarity assessment performed by a competent drug regulatory agency demonstrating comparable quality, safety and efficacy with an approved reference product) application of these monographs could increase the risk that patients get exposed to medicines that lack assurance of quality. Hence, alternative approaches are to be considered to ensure the value and benefits of pharmacopoeia standards. One avenue to achieve this could be the development of performance based monographs for product-classes of BTPs, that focus on analytical tools (methods) and their physical standards to control for their performance rather than methods, limits and reference standards specific for a single product with limited relevance.

[1] US Pharmacopeial Convention (undated) *Our Vision.* http://www.usp.org/about-usp/our-vision/
[2] Council of Europe (undated) *Background & Mission of the European Pharmacopoeia.* https://www.edqm.eu/en/european-pharmacopoeia-background-50.html/
[3] Pharmaceutical and Medical Devices Agency (PMDA), Japan (undated) *About PMDA.* http://www.pmda.go.jp/english/about/index.html/

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Key messages

1. Product-specific monographs are useful for the development and the control of APIs and their generic copies which can be fully characterized. For these products, identity can be confirmed by analytical means and therefore predefined quality standards are applicable ensuring product quality, safety and efficacy.[4]
2. Due to their inherent complexity and interdependence with their manufacturing processes, the quality and consistency of BTPs can only be defined and ensured through individual and comprehensive process and product-specific control strategies. End-product testing alone does not ensure quality, safety, and efficacy.
3. Established global regulatory pathways for approving SBPs do not follow the generics approach but base decision making of similarity on the totality of the evidence specific for each SBP candidate and including quality, pre-clinical and clinical assessments with the commercially available and approved Reference Biotherapeutic Product (RBP).[5,6,7,8]
4. BTPs and SBPs that would not meet an established product-specific pharmacopoeia standard might be classified as of inferior quality, without consideration of attribute criticality as well as the pre-clinical and clinical evidence available to support their quality and/or similarity to the RBP. Conversely, copies of a RBP that meet an established product-specific pharmacopoeia standard - recognizing that the extent of characterization could differ between simple non-glycosylated proteins and complex, glycosylated proteins - might be deemed of acceptable quality, without consideration of other required evidence indicating a lack of similarity to the RBP (e.g. with regards to safety and immunogenicity). Both of these conclusions are inappropriate.
5. Pharmacopoeias could play a supporting role in the area of biotherapeutics by focusing activities on the development of more generally applicable recommendations for the control and characterization of BTP-classes including relevant analytical methods and physical standards to control performance. Following this concept, abandoning the development of new product-specific monographs and abolishing available monographs for specific BTPs, pharmacopoeias would establish a defined, agreed-upon, shared analytical language for the biotech industry and regulators worldwide. This approach would facilitate the meaningful analytical assessment of the properties of these BTP-classes and thus the development of both new BTPs and SBPs.

[4] Inglis S (2013) *Global Challenges in Biological Standardization*. ECBS.
[5] WHO (2009) *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*. October 19-23.
[6] Health Canada (2010) *Guidance for Sponsors: Information and Submission for Subsequent Entry Biologics (SEBS)*. March 5.
[7] FDA (CDER and CBER) (2012) *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.
[8] European Medicines Agency (2013) *Guideline on Similar Biological Medicinal Products*. October 31.

Background

Monographs for specific drug products or drug substances are well established for small molecule pharmaceuticals. They provide common analytical methodology and acceptance criteria, as well as information on production, labeling, and storage used by producers and regulators to ensure the consistent quality of these products produced by multiple manufacturers. They also facilitate the development of generic alternatives to originators' small molecule products by defining minimum quality standards that a copy of the innovator's small molecule API must meet to be considered equally safe and efficacious. Recently, Pharmacopoeias, health authorities, biotech industry, and others have been discussing the applicability of product-specific monographs to BTPs, including recombinant monoclonal antibodies. Several of those monographs were already put in place in the late 1990s (e.g. Insulin, Somatropin, Erythropoietin, Filgrastim). These earlier biotherapeutic monographs followed essentially the same format originally designed for small molecule APIs and failed to recognize the important distinction in molecular size and complexity between BTPs and small synthetic drugs. It is important to note that they were authored prior to the establishment of the biosimilar concept when many believed that product-specific monographs for BTPs could be treated like generics. This assumption is still currently shared by some stakeholders despite the general understanding and acceptance that biosimilarity determination requires a tailored approach as new product-specific monographs are still being published in pharmacopoeia using the original format (e.g. Human Coagulation Factor VIIa).[9] Generally these product-specific monographs may give the false and risky impression that quality can be tested into a biotherapeutic instead of being designed into the product and its process, to ensure similarity to the RBP, as international guidance documents demand.[10,11,12,13]

It is the basic hypothesis of this reflection paper that there is a fundamental contradiction between the concept of "*biological similarity*", which is applicable to biotechnological pharmaceuticals and "*molecular identity*" which is applicable to small molecule pharmaceuticals (APIs).

1. Fundamental differences between small synthetic molecules and biomolecules

The fundamental difference between small molecules and large biomolecules is that the former can be *fully* characterized whereas the latter can be considered to be *well* characterized. Small molecules have low molecular weights and simpler molecular structures compared to biomolecules (e.g. recombinant monoclonal antibodies) and therefore are compatible with analytical techniques capable of structural characterization at the atomic scale. They are sequentially assembled through discrete chemical reactions, which employ fully characterized starting materials of high purity and effective means of purification. This mode of manufacture is able to routinely produce the desired product (API)

[9] European Pharmacopeia. *Human Coagulation Factor VIIa (rDNA) Concentrated Solution*. 8.0., p. 2410 – 2414.
[10] WHO (2009) *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*. October 19-23.
[11] Health Canada (2010) *Guidance for Sponsors: Information and Submission for Subsequent Entry Biologics (SEBS)*. March 5.
[12] FDA (CDER and CBER) (2012) D*raft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.
[13] European Medicines Agency (2013) *Guideline on Similar Biological Medicinal Products*. October 31.

at a purity close to one hundred percent (in the form of a single molecular entity). Their physical and chemical properties can be totally analytically characterized and controlled. Hence, copies of small molecule APIs can be deemed identical.

Conversely, many biomolecules have very high molecular weights, complex molecular structures including post-translational modifications, and their purity/impurity profiles comprise a large number of product-related variants and process-related impurities like host-cell proteins or host-cell DNA. Biomolecules are manufactured by use of living organisms such as bacterial or mammalian cells, and typically grown in complex media containing heterogeneous biological raw materials (e.g. animal and/or plant derived growth media), which may have limits in their state of characterization. These materials might also introduce a risk of contamination by adventitious agents (e.g. viruses, prions, etc.). Even seemingly negligible variations in any step of this lengthy and complex manufacturing process may bring about significant clinical differences to a product (e.g. efficacy, safety, and immunogenicity) due to the high sensitivity of biologic systems to environmental changes.

All of these factors make it impossible to fully capture the properties of BTPs using a limited set of analytical methods and specifications described in a product-specific compendial monograph. Instead a total control strategy is needed for BTPs that significantly extends beyond end-product testing and includes comprehensive understanding and control of the manufacturing process.[14]

2. Fundamental differences between regulatory guidance for generics and SBPs

The aforementioned significant and fundamental differences between small molecule and large biomolecule drug products are mirrored in regulatory guidance documents that are specific to SBPs, and have led to the conclusion that the approach for approving generic drugs is not applicable for BTPs.[15] The molecular structure of a small molecule generic API must be identical to the reference product whereas for the drug substance of SBPs, some molecular differences are expected and might be acceptable, if justified by adequate pre-clinical and clinical studies.

Hence, the approach for demonstrating biosimilarity demands a comprehensive step-wise comparative assessment of the SBP candidate product against an individual RBP, which is already approved as a medicinal product on the basis of a full dossier. Importantly, extensive analytical comparisons between the SBP candidate (drug substance and drug product) and different batches of the commercially available RBP have to be performed and some differences between the SBP and the RBP drug substance are expected. Therefore, the step-wise similarity assessment generally includes, in addition to an analytical and *in vitro* functional demonstration of similarity, head-to-head non-clinical and clinical studies, to bridge the known and (potentially) not yet identified structural and functional differences between the RBP and the SBP.

[14] ICH (1999) *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products*. March 10.
[15] Ridgway A, Ritter N, Schiestl M and Schreitmueller T (2013) *Biosimilar Products. Scientific Principles, Challenges, and Opportunities*. BioProcess International 11(10).

In contrast, generics are generally not required to perform comparative pre-clinical and clinical studies with the originator product since the API can be compellingly analytically demonstrated to be structurally identical.[16,17] Consequently, demonstration of bioequivalence at the finished drug product level typically suffices to establish a generic (e.g. having bioavailability equivalent within certain established margins to that of the small molecule originator product).[18]

Furthermore, all SBP guidance indicate that specifications for SBPs should be established based on the applicant's unique experience with its own product (quality, safety, and efficacy) as well as the proper process experience rather than reliance on general specifications contained in a product-specific monograph's standardized tests and acceptance criteria or specifications from the RBP (if publicly available). In particular, it is expected that SBPs adhere to ICH Q6B, the key guidance document for specification setting for biotechnological products, and thus their quality control strategy should be linked to the manufacturing capabilities, product stability, pre-clinical and clinical studies as well as analytical performance.[19] This is also consistent with WHO's guidance document for SBPs where adherence to product-specific monographs is not listed as one of the six key principles for licensing of SBPs.[20]

The final decision on biosimilarity is based on the totality of the evidence provided, which comprises the results of comparative analytical, preclinical and clinical studies, and is specific to the unique SBP and its individual relationship to the selected RBP.

3. Product-specific monographs – differences in applicability for small synthetic molecules and BTPs

Pharmacopoeias worldwide, building on the aforementioned characteristics of small molecules, established monographs for APIs (and to a lesser extent for finished product), which define minimal common standards for identity, content, impurity, and general quality of these chemical pharmaceuticals.

These standards are essentially *analytical* standards, comprising: description of test methods to be used; respective acceptance criteria of critical quality attributes the chemical copy has to meet; and, when appropriate, additional physical national/international reference standards to be employed for assay system suitability (e.g. resolution) and/or test method sample read-outs (e.g. identity, content). Their exclusive reliance on analytics is considered acceptable since quality can generally be controlled by these specifications. Typically, the three dimensional molecular structures, molecular formulas, and molecular weights of the desired product and impurities are part of the product-specific monograph.

[16] WHO (2009) *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*. October 19-23.
[17] The Drug Price Competition and Patent Restoration Act of 1984, also known as the "Hatch-Waxman Act"
[18] FDA (CDER) (2010) *Guidance for Industry. Bioequivalence Recommendations for Specific Products*.
[19] ICH (1999) *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products*. March 10.
[20] WHO (2009) *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*. October 19-23, pp 8-9.

These monographs are recognized as minimal quality standards for generics. Typically, generic manufacturers are not requested to go beyond what is mandated by the relevant product-specific monograph for APIs. However, given an applicant's own manufacturing process, the regulatory agency might identify and mandate additional tests to maintain product quality based on their specific filing. Manufacturers can use their own methods (different from the methods mentioned in the pharmacopoeia) but they must be cross-validated to exclude any deviation compared to the pharmacopoeial method.

Product-specific monographs are legally binding in many countries. In the Unites States, for example, not adhering to the identity standard in a product-specific monograph means that the product is considered adulterated and subject to seizure and removal from the market.[21,22,23]

In contrast, it is expected that SBPs may show some differences to a RBP, given their complex and highly sensitive biosynthetic route of manufacture, but that the differences between drug substances as regards quality attributes can be deemed acceptable by health authorities, if the totality of data demonstrates that any observed difference on a molecular level does not lead to any clinically relevant differences in efficacy and safety.[24]

Hence minimal quality standards have no utility since they are expected to be overruled by the unique relationship each SBP candidate has with the RBP and the SBP-specific total evidence provided. A product-specific monograph, once established for a specific BTP, might therefore inadvertently delay the licensure of an otherwise suitable SBP (i.e. an SBP for which clinical biosimilarity has been demonstrated) or the SBP may be deemed of questionable quality, because the product does not meet a pre-defined analytical requirement as outlined in the respective monograph (e.g. acceptance criteria set for a product variant specific to the RBP's manufacturing process). The monograph could even interfere with the approval of the licensed RBP itself in another country, because the originator's product does not meet this country's product-specific monograph (e.g. potency relative to international reference standard that may be derived from other sources, and using a different biological assay), regardless of the extensive evidence available that the drug is safe and efficacious. Conversely, a product-specific monograph might account for the expected larger variability of BTPs by defining the minimal analytical requirements less stringently (e.g. broad acceptance criteria). However, this might create the alternate risk that a specific SBP might be deemed acceptable, possibly overriding contradicting evidence (e.g. in regard to safety and immunogenicity). A similar risk is the potential misuse of established product-specific monographs for SBPs in countries with less developed regulatory systems as the statement "compliance with existing monograph" may be the only regulatory requirement for registration.

[21] Federal Food, Drug, and Cosmetic Act. 501(b), 502(e) (3), 502(g).
[22] 21 CFR 299.5(c)
[23] Federal Food, Drug, and Cosmetic Act. Section 505(j) 21 U.S.C. 355(j) and Section 505(j)(2)(A)(vii)(IV)
[24] Differences in other elements of the comparability exercise, such as pre-clinical and/or clinical, are expected to be within acceptable statistical parameters showing both products to be deemed "comparable" rather than "equivalent" but not "different". The "tolerability" threshold for differences becomes much narrower as the comparability exercise moves stepwise.

Furthermore, product-specific monographs are mainly written for APIs. The API of small molecules is typically stored as dried powder in its pure form without compounding. There are currently only a limited number of finished product-specific monographs for small molecules available, given the impact of compounding on dissolution profile, bioequivalence and stability of the finished product. It is important to note that excipients are added to the drug substance solution at multiple points in the manufacturing process to lessen degradation and enhance stability. Therefore the analyses conducted on protein drug substance and protein final drug product are often different. For example, purity is best evaluated in the drug substance, while analyses of final drug product will include tests of excipients. Furthermore, the stability of protein drug substance and final drug product may differ significantly, depending on pH, concentration, excipients and whether the product being stored is a liquid at 2-8°C, if it is frozen, or if it is a lyophilized powder. Therefore, any comprehensive control scheme for a protein drug must address the critical analyses that must be conducted on the bulk drug substance as well as those that need to be conducted on the final drug product. Therefore, creating product-specific monographs on the drug substance itself without any consideration of its configuration - drug substance and drug product - may not address potential quality issues due to storage conditions and form.

Recent ICH guidance documents Q8, Q9, Q10, and Q11 emphasize the use of knowledge gained from product development studies and manufacturing for specification setting of BTPs for commercialization.[25,26,27,28] They also highlight effective management of risk to product quality, active management of product knowledge, and continuous improvement overall throughout the product life-cycle to maintain and enhance the quality of the product. The current format of product-specific monographs, which is in use essentially unchanged for decades now, with its generic and static frame of specifications and exclusive focus on analytical testing is contradicting the principles and dynamic approach set forth by this new paradigm for pharmaceuticals. This is corroborated by ICH Q6B, which states "*New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate*".[29] Product-specific monographs may imply that quality can be tested into the product instead of designed into the product and its processes, to ensure similarity to the RBP, as guidance documents demand. In all these cases, the purpose and mandate of product-specific monographs to facilitate access for patients to medicines of assured standard quality may not be realized.

The aforementioned found acknowledgement in the decision of the European Directorate for the Quality of Medicines & Health Care (EDQM) in November 2009 to exclude biological products from the scope of Certificates of Suitability of Monographs of the European Pharmacopoeia (CEPs).[30] The

[25] ICH Q8 (R2) Pharmaceutical Development, August 2009.
[26] ICH Q9 Quality Risk Management, 9 November 2005.
[27] ICH Q10 Pharmaceutical Quality Systems, April 2009.
[28] ICH Q11 Development and Manufacture of Drug Substance, November 2012
[29] ICH (1999) *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products*. March 10, p 2.
[30] Public Health Committee (2007) *Resolution AP-CSP (07) 1 on the 'Certification of Suitability to the Monographs of the European Pharmacopoeia* (Revised Version). Adopted by the Public Health Committee (CD-P-SP) on February 21, 2007.

CEP is used to certify that a product-specific monograph in the European Pharmacopoeia is able to adequately control the quality of the manufacturer's pharmaceutical ingredient obtained by a given manufacturing route. The exclusion of biological products supports the idea that compliance to the monograph is not sufficient to ascertain the quality, safety and efficacy of these products.

Similar concerns related to BTPs and SBPs were expressed by Steven Kozlowski (United States Food and Drug Administration (US FDA)): "*Monographs may specify attributes and ranges that do not impact clinical performance*"; "*Material reference standards may have attributes and ranges that do not impact clinical performance*"; and "*Neither type of standard should delay or interfere with the marketing of a drug or post-approval changes deemed safe and effective by the National Regulatory Authority".*[31]

In another example, based on feedback from US FDA, the original United States Pharmacopeia (USP) Draft Chapter <129>, "Critical Quality Attributes of Recombinant Therapeutic Monoclonal Antibodies" which contained test methods and acceptance criteria for monoclonal antibody quality attributes, was revised to focus on validated compendial analytical procedures with established system suitability criteria and physical standards to control for their analytical performance at time of analysis. The chapter was renamed to "Analytical Procedures for Therapeutic Recombinant Monoclonal Antibodies" to reflect the change in scope and content of the document.[32]

4. Proposed complementary approach for BTPs – combining benefits of product-specific monographs with the concept of SBPs

Product-specific monographs for APIs define analytical tests and respective generic acceptance criteria to which specific products must adhere. For BTPs, generic acceptance criteria to which a BTP or SBP must comply are inadequate, given the complex nature of these BTPs and the concept of biosimilarity, as outlined above. In spite of these concerns, pharmacopoeias could play an important role in the area of biotherapeutics by focusing on developing recommendations more generally applicable for development and characterization of BTPs, and adapting their current format of product-specific monographs to provide performance-based monographs for product-classes that focus on sets of analytical tools (methods) and physical standards to control for performance. Pharmacopoeias would thereby establish a defined, agreed upon, shared analytical language for the biotech industry and regulators worldwide. This approach would facilitate the development of new BTPs and also SBPs.

This said, pharmacopoeial recommendations of sets of analytical tools to be considered appropriate for analytical characterization, analytical comparability, and/ or quality control testing of BTPs and SBP candidate drug substances could add value to the biotech industry and regulators. Such model sets could facilitate and speed-up the development of both originator BTPs and SBPs by the provision

[31] Kozlowski S (2011) *Science & Standards Symposium on Biologics & Biotechnology: Advancing Quality Standards through Analytics and Assays*. Seattle, Washington, October 3.
[32] Informal Discussion with USP Biologics Staff, October 2012.

of analytical tools whose performance parameters, characteristics, controls, and data output are well understood and well interpretable. These sets would ensure that assays used by the biotech industry are state-of-the-art and capable of addressing critical parameters and what regulatory authorities can expect with respect to assay performance. For example, they would ensure that analytical strategies (methods) employed are sensitive to detect differences between the SBP and RBP of specific product-classes (e.g. mass spectrometry techniques to identify and characterize quality attributes of BTPs such as amino acid sequence analysis, carbohydrate structures, sulfhydryl groups and disulfide bridges; powerful innovative analytical platforms for charge analysis, such as quantitative image capillary isoelectric focusing). The sets of recommended analytical methods could be tailored for the specific needs of these product-classes (recombinant monoclonal antibodies, antibody drug conjugates; enzymes, etc.). They could also provide reliable state-of-the-art means for counterfeit and adulteration assessments.

The sets of analytical tools could be complemented by sets of respective standards that ensure that these assays are performing as intended when established in a laboratory and applied to a BTP of a given product class at time of usage.

When developing these performance-based monographs for BTP-classes it is critical that the pharmacopeia ensure industry, health authority and academic experts are consulted and included in the development of those recommendations. This effort may lead to a universal and agreed upon analytical language across the industry for BTPs, specific to the product-class investigated.

Conclusions

With the introduction of the biosimilarity concept, it became clear that copies of BTPs cannot be considered as analogous with generics. Hence, pharmacopoeias should redefine the current scope and format of product-specific monographs for BTPs, which were originally put in place decades ago for small molecule products and subsequently directly applied to biotherapeutics. This procedure is inconsistent with the currently agreed practice focusing on the continuous accumulation of product knowledge, understanding of critical quality attributes and a risk-based approached to quality assurance. The scope and format specific for BTPs should focus on recommendations of well-defined and globally harmonized analytical testing strategies, which are tailored to the needs of particular BTP-classes. These strategies may comprise both written (test descriptions) and physical standards (assay control materials) that facilitate the meaningful analytical assessment of the properties of these classes.

Consequently, pharmacopoeias may consider reassessing the suitability and purpose of existing monographs for BTPs with a view to the arguments displayed in this paper and refrain from elaborating new product-specific monographs on BTPs but instead consider the development of a set of testing recommendations applicable to different BTP-classes. Pharmacopoeias may thereby continue to fulfill their mission to ensure access to medicines of standardized quality in the form of originator BTPs, their SBPs as well as educating all stakeholders engaged with these products.

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IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships initiative studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries and the IFPMA Code of Practice sets standards for ethical promotion of medicines.

About EGA

The European Generic medicines Association represents the European generic and biosimilar pharmaceutical industries, which provide high-quality cost-competitive medicines to millions of Europeans. Companies represented within the EGA provide over 150,000 jobs in Europe. Generic medicines save EU patients and healthcare systems over €35 billion each year and account for 54% of all dispensed medicines but for only 21% of the pharmaceutical expenditure in Europe.