

Commentary

A pragmatic regulatory approach for complex generics through the U.S. FDA 505(j) or 505(b)(2) approval pathways

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The diverse nature of complex drug products poses challenges for the development of regulatory guidelines for generic versions. While complexity is not new in medicines, the technical capacity to measure and analyze data has increased. This requires a determination of which measurements and studies are relevant to demonstrate therapeutic equivalence. This paper describes the views of the NBCD Working Group and provides pragmatic solutions for approving complex generics by making best use of existing U.S. Food and Drug Administration's abbreviated approval pathways 505(j) and 505(b)(2). We argue that decisions on the appropriateness of submitting a 505(j) or 505(b)(2) application can build on the FDA's complex drug product classification as well as the FDA's much applauded guidance document for determining whether to submit an ANDA or a 505(b)(2) application. We hope that this paper contributes to the discussions to increase the clarity of regulatory approaches for complex generics, as well as the predictability for complex generic drug developers, to facilitate access to much-needed complex generics and to promote the sustainability of the healthcare system.

Keywords: complex drugs; complex generic drug products; nonbiological complex drugs; generics; follow-on products; FDA

General introduction

The application of innovative technology in the development of new advanced therapeutics is currently transforming the scientific and medical landscape. An increasing number of sophisticated treatment options become available for patients and include products with a complex active ingredient, formulation, route of delivery, or dosage form. We now see rapid advances, for example, in the application of nanotechnology for the development of new complex drug products.^{1,2} Being mostly of particulate form, these products generally show a high variability in terms of size, shape, materials used, and complexity of their structures.^{3,4} While the advances are yielding very promising new drug applications, they are often at relatively

high costs, as seen in the field of oligonucleotide drug delivery.⁵ After innovative products have been granted approval, they may also bring new opportunities to generic drug developers and at the same time, regulatory systems may be facing the challenge to assess complex generic versions of these complex products.

Other than generic medicines of low-molecular-weight active pharmaceutical ingredients (APIs), the development of complex generics requires a more sophisticated planning and development process. Transparency and clarity of the regulatory process is, therefore, crucial to bring high-quality generic product to patients. The lack of well-defined regulatory approaches to address the unique characteristics of current and future complex generics

could increase the regulatory uncertainty for generic drug developers. This could jeopardize timely patient access to safe and effective complex generics and encumbers the objectives of U.S. government proposed drug competition strategies for lowering drug prices.⁶ Streamlining the regulatory process for complex generic drug products is, therefore, crucial to maintain a balanced and sustainable healthcare system, in which we can afford innovative treatment approaches that often come at high costs, such as the oligonucleotide drug products.

The need for transparent and harmonized regulatory approaches for complex generics

In recent years, the global scientific and regulatory community has started to recognize the significant scientific challenges that exist for complex generic drug products, regarding their assessment of therapeutic equivalence. However, efforts to align regulatory processes are still ongoing. In the United States, the amount of evidence required for the approval of a complex generic still appears to often rely on a case-by-case approach by the FDA. Nonetheless, in the past years, the FDA has done tremendous work to increase harmonization and clarity on how to regulate complex generic drug products, for example, by publishing product-specific guidance documents (PSGs) on a regular basis or offering preabbreviated new drug application (pre-ANDA) meetings and leading several international initiatives.^{7–10} Despite these important efforts, the appropriateness of current regulatory approaches for approving therapeutically equivalent complex generics remains a hot topic in current scientific and regulatory discussions.^{11–13}

In 2018, the U.S. Government Accountability Office (GAO) assessed FDA's processes for reviewing complex generics and indicated that the unclarity and inconsistency of the regulatory approach for complex generics may create setbacks for generic drug developers in the United States.¹⁴ In the GAO report, in which it refers to a subgroup of complex drug products called nonbiological complex drugs (NBCDs),^a the GAO recommends the FDA

to increase transparency for issuing new PSGs for complex drugs, as well as to publicly announce planned significant revisions to existing PSGs for complex drugs. However, current FDA guidance lacks any reference to which abbreviated approval pathways should be followed.

To reflect on current regulatory practice and to provide pragmatic suggestions for addressing challenges within existing regulatory frameworks, this paper describes the views of the NBCD Working Group on how to make best use of existing abbreviated approval pathways of 505(j) and 505(b)(2) for approving complex generics.¹⁷

Current regulatory practice for complex generics

For a generic drug product to be approved and evaluated as therapeutically equivalence (TE), it needs to be pharmaceutically equivalent (PE) as well as bioequivalent (BE) to the reference listed drug (RLD).^{18,19} This approach is suitable for "simple" small molecule generics but comes with challenges for PE and/or BE with complex generics. To address the challenges of complex generics, the FDA suggests additional comparative physicochemical characterization of test and reference product to demonstrate PE in terms of formulation and microstructure arrangement sameness. This equivalence demonstration involves a step-wise comparison to the RLD with respect to analytical characterization, and, in some cases, clinical studies.

From a regulatory perspective, there are two abbreviated routes^b that can be approached for the approval of a generic drug product with a potential therapeutic equivalence rating: the "traditional" generic application via 505(j), sometimes referred to as the abbreviated new drug application (ANDA), and, in theory, the 505(b)(2) application. The latter is less common for this purpose but has been used in the past for granting marketing authorization for

quantified. These properties may also be substantially altered by the manufacturing process, and together consequently impact product performance.^{15,16}

^bThe regulatory pathway for biosimilars via 351(k) is left aside in the context of the discussion as 351(k) only permits approval of biological products and is, therefore, by definition out of scope for synthetically derived complex drug products.

^aNBCDs can be defined as medicinal products with synthetic and often nanoparticulate structures whose physicochemical properties cannot be fully characterized or

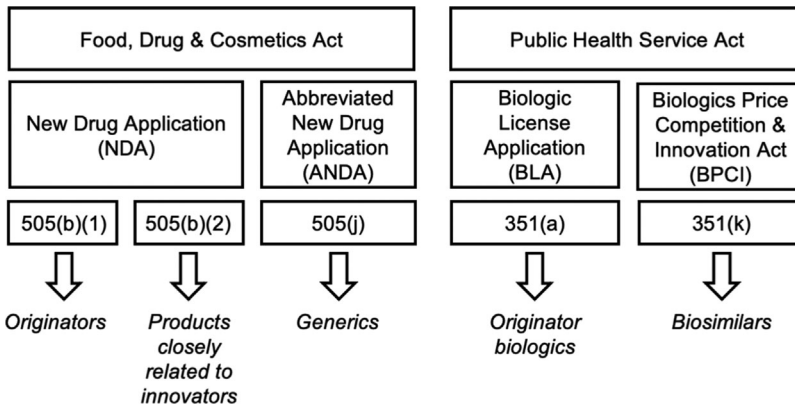


Figure 1. Schematic representation of the FDA approval pathways (adapted from Husaarts *et al.*).²¹

generic drug products relying in part on data from the RLD, as in the case of some recombinant products (Fig. 1 and Box 1).^{20,21} The FDA has shown that the 505(b)(2) option could, therefore, provide an interesting alternative for the approval of a complex generic, especially when the clinical studies that are needed to demonstrate TE fall outside the remit of the 505(j) pathway. It is important to note that while 505(j) applications by default lead to a therapeutic equivalence rating, this is not necessarily the case for 505(b)(2) applications. Nonetheless, it is possible to obtain a therapeutic equivalence rating with a 505(b)(2) application, as demonstrated with several extended-release products and topical products that were granted a therapeutic equivalence rating by the FDA.^{22,23}

Intrinsic to the ANDA and NDA label of the two pathways, applications to 505(j) are handled by the Office of Generic Drugs (OGD), while 505(b)(2) applications fall under the responsibility of the Office of New Drugs (OND). In addition, 505(b)(2) provides greater flexibility in the choice of types of studies, as well as data and information to be included in the application.¹⁷ 505(j) only allows a certain degree of flexibility regarding additional physicochemical characterization and/or *in vivo* BE studies. The 505(b)(2) application on the contrary may call for additional clinical studies, for example, to assess and compare the safety and efficacy profiles of generic versus RLD (Box 1). The 505(b)(2) application may, therefore, provide a scientifically more robust alternative for approving complex generics within the existing regulatory framework.

A pragmatic and science-based regulatory approach for complex generics

Considering recent work by the FDA on reducing the hurdles of complex generic drug development, the FDA has published their definition of “complex generic drug products.” Complex drug products^c are defined as a product with:

- a complex active ingredient(s) (e.g., peptides, polymeric compounds, complex mixtures of APIs, and naturally sourced ingredients);
- a complex formulation (e.g., liposomes and colloids);
- a complex route of delivery (e.g., locally acting drugs, such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions, or gels);
- a complex dosage form (e.g., transdermals, metered dose inhalers, and extended release injectables).²⁴

^cThe views presented in this paper exclude drug–device combinations, which face different regulatory challenges. The FDA’s complex product category “drug–device combination products” (e.g., auto injectors and metered dose inhalers), as well as the category “other products where complexity or uncertainty concerning the approval pathway exists” are, therefore, omitted in the context of this discussion. However, the thoughts and ideas presented in this paper can potentially also be applied to drug–device combinations and other complex products.

Box 1. An overview of the regulatory frameworks of 505(j) vs 505(b)(2), from the FDA guidance document “Determining Whether to Submit an ANDA or a 505(b)(2) Application - Guidance for Industry.”¹⁷

505(j)

“An ANDA is an application submitted and approved under section 505(j) of the FD&C Act for a drug product that is a duplicate of a previously approved drug product. An ANDA relies on FDA’s finding that the previously approved drug product, i.e., the reference listed drug (RLD), is safe and effective. An ANDA generally must contain information to show that the proposed generic product¹ is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and² is bioequivalent to the RLD. An ANDA may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product.”

505(b)(2)

“A 505(b)(2) application is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.”

Publishing a definition of complex drugs by the FDA is an important milestone toward creating clear and consistent science-based regulatory approaches for complex drugs. Therefore, the regulatory approaches for complex drugs proposed in this paper build on the foundation of this definition and FDA guidance determining whether to submit a 505(j) or 505(b)(2) application.¹⁷

In line with the regulatory definitions of frameworks of 505(j) and 505(b)(2) shown in Box 1, we propose that if PE can be confirmed with additional physicochemical characterization and/or *in vivo* BE studies, the traditional generic paradigm through 505(j) may be considered appropriate (ANDA). But, when a complete characterization of the API is not possible, and therefore it is impossible to establish PE, we propose a mandatory 505(b)(2) application with additional clinical studies for safety and efficacy evaluations analogous to the totality of evidence approach for biosimilars.²⁵ An application via 505(b)(2) may also involve crossover comparative clinical studies to assess the safety of switching between RLD and the complex generic version. This approach was, for example, followed in the EU with the marketing authorization of complex generics of glatiramer acetate, sevelamer, and iron carbohydrate complex through the hybrid application procedure via Article 10(3).^{26,27} The hybrid pathway in the EU allows for the provision of addi-

tional (pre-) clinical data and can, therefore, be considered as a European equivalent to the 505(b)(2) application.^{28,29}

Table 1 provides an overview of brand-name complex drug products. Owing to the absence of a comprehensive overview of complex drug products approved for the U.S. market, this list is based on the GAO report.¹⁴ We compared this list with the FDA’s complex generic drug product definition from the GDUFA II Commitment Letter and classified each product according to the FDA complex drug product categories.²⁴ The overview presented in Table 1 illustrates the different forms of complexity and corresponding scientific and regulatory challenges that exist for different complex drug products, but more importantly provides a first outline of which regulatory application procedure could be viewed as most appropriate. In line with our suggestion for the pragmatic use of existing regulatory pathways, the 505(j) application procedure with additional physicochemical characterization and/or *in vivo* BE studies may most likely be applicable to complex drug products that fall within the FDA’s complex drug product categories “Complex Formulation,” “Complex Route of Delivery,” and “Complex Dosage Form” (Table 1 and Fig. 2), whereas the 505(b)(2) application procedure may most likely be applicable for complex drug products that fall within the FDA’s

Table 1. An overview of brand-name complex drug products approved^a by the FDA for U.S. market identified by the GAO, classified according to FDA’s complex drug product categories

	Active substance/formulation	U.S. originator drug name	FDA complex product category			
			Complex API	Complex formulation	Complex route of delivery	Complex dosage form
Liposomal formulations and lipid complexes	Amphotericin B (liposomal)	Ambisome [®]		X		
	Daunorubicin citrate (liposomal)	DaunoXome ^{®a}		X		
	Cytarabine (liposomal)	DepoCyt ^{®a}		X		
	Morphine sulfate (liposomal)	DepoDur ^{®a}		X		
	Doxorubicin hydrochloride (liposomal)	Doxil [®]		X		
	Bupivacaine (liposomal)	Exparel [®]		X		
	Vincristine sulfate (liposomal)	Marqibo [®]		X		
	Irinotecan hydrochloride (liposomal)	Onivyde [®]		X		
	Verteporfin (liposomal)	Visudyne [®]		X		
Amphotericin B (lipid complex)	Amphotec ^{®a}		X*		X	
Polymer-based drugs	Glatiramer acetate injection	Copaxone [®]	X			
	Sevelamer carbonate	Renvela [®]	X*		X*	
Low-molecular-weight heparins	Dalteparin sodium	Fragmin [®]	X			
	Tinzaparin sodium	Innohep ^{®a}	X			
	Enoxaparin sodium	Lovenox [®]	X			
Emulsions	Propofol	Diprivan [®]		X		
	Cyclosporine	Restasis [®]		X	X	X
Iron-carbohydrate complexes	Iron dextran	Dexferrum ^{®a}	X			X*
	Ferumoxytol	FeraHeme [®]	X			
	Ferumoxides	Feridex ^{®a}	X			
	Sodium ferric gluconate complex in sucrose	Ferrlecit [®]	X			
	Iron dextran	InFed [®]	X			
	Ferric carboxymaltose	Injectafer [®]	X			
	Iron sucrose	Venofer [®]	X			
Other	Paclitaxel (albumin bound)	Abraxane [®]		X*		
	Estradiol hemihydrate	Estrasorb ^{®a}		X*	X*	
	Paliperidone palmitate	Invega sustenna [®]				X*
	Lidocaine/prilocaine	Oraqix [®]			X*	

^a Products with marketing status “discontinued.”

Note: Where information on FDA’s complex drug product categories was not available, product categories were extrapolated based on the interpretations of the authors of this paper (extrapolations/interpretation by the authors marked with *).

complex generic drug product category “Complex API.”

How to deal with dynamics in a defined regulatory framework

While complexity is not new in medicines, the continuous progress in drug development will increase the level of complexity of novel drug products, including nanomedicines, whereas our technical capacity to measure and analyze data is also con-

tinuously increasing. This requires a determination of which measurements are relevant to demonstrate therapeutic safety and efficacy.³⁰

We believe several conditions for a robust approach via 505(j) and 505(b)(2) exist (each of these four conditions are further deliberated on below):

1. Understanding of all relevant critical quality attributes (CQAs);

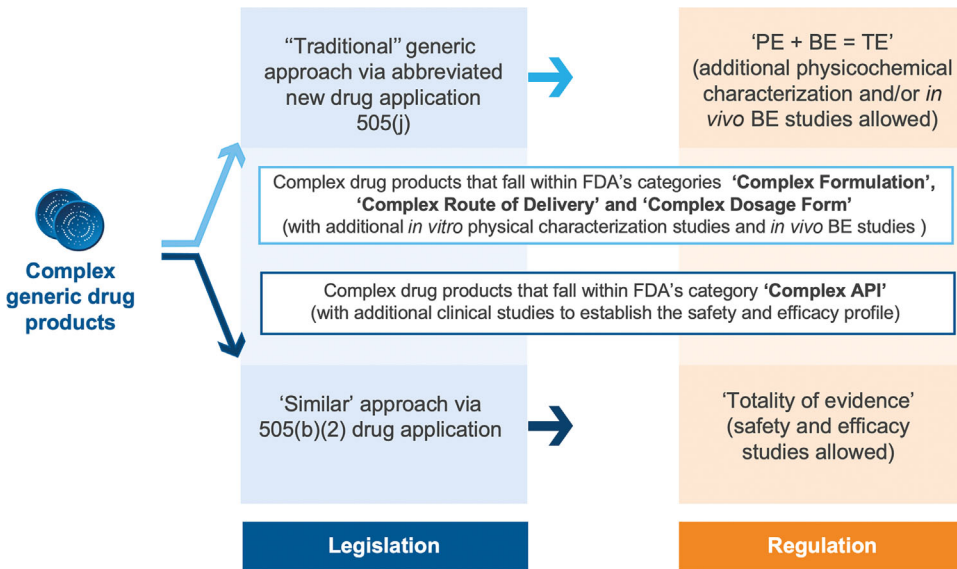


Figure 2. Two regulatory pathways 505(j) and 505(b)(2) within the FDA's regulatory framework that can be used for complex generic drug products depending on the types of characteristics and challenges of the product.

2. A certain amount of flexibility in the regulatory approaches for complex generic drug products;
3. A comprehensive and publicly available list of all complex products per GDUFA II Commitment Letter definition;
4. Further assessment of potential differences and barriers with regard to Orange Book listings or subsequent usage in clinical practice.

First, the understanding of all relevant CQAs, which is especially important for those products for which the mode of action of the API is unknown.³¹ According to the International Conference on Harmonization (ICH), a CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.³² For complex drug products containing complex APIs, there is a clear need to increase the knowledge on those product characteristics that have an impact on the quality and the clinical profile of the product. Next to CQAs, a better understanding of other relevant characteristics is needed to increase the robustness of assessments for complex drug products. This includes critical process parameters, as the properties of complex drug prod-

ucts can be substantially altered by the manufacturing process, and qualitative and quantitative (Q1/Q2) sameness requirements for inactive ingredients, which is especially relevant for certain types of complex drug products, such as liposomal formulations. Innovator, generic product developers as well as regulators have a responsibility to further our common understanding of these import parameters and characteristics.

Second, a certain amount of flexibility in the regulatory approaches for complex generic drug products. As the continuous progress in scientific understanding and technology further evolves, such as a better understanding of CQAs or improved methods for better characterization of the API, it could allow for more flexibility by the FDA to receive, review, and approve complex drug products via a 505(j) application where it previously lacked the scientific basis to do so.¹⁷

Third, a comprehensive and publicly available list of all complex products per GDUFA II Commitment Letter definition. Such overview currently, to the best of our knowledge, is not publicly available. Therefore, we based Table 1 on the list of complex drug products from the GAO report.¹⁴ This provides only a snapshot of the entire complex drugs landscape. For example, FDA provides many other examples of complex drug products via public

communications and presentations.^{33–37} Examples are oligonucleotide drug products (eteplirsen, nusinersen, and patisiran lipid complex), non-absorbed potassium binder (e.g., patiomer), or synthetic peptides (e.g., teriparatide and exenatide), which are all categorized by the FDA as Complex APIs. An up to date, publicly available comprehensive list of all complex drug products on the U.S. market, together with the corresponding FDA complex drug product categories (e.g., Complex API), is a very valuable resource. It allows generic product developers to identify potential challenges, as highlighted by the FDA's complex drug product categories, earlier in the drug development and marketing authorization process.

Finally, although therapeutic equivalence ratings can be achieved via both the 505(j) and 505(b)(2) routes, potential differences and barriers with regard to Orange Book listings or subsequent usage in clinical practice (i.e., substitution practices) may need to be further assessed. However, this was outside the scope of this paper.

Conclusion

This paper contributes to the discussion to increase the clarity of appropriate science-based regulatory approaches for complex generic drug development. We, therefore, propose a clear regulatory approach for approving complex generic drug products within the existing U.S. abbreviated regulatory pathways of 505(j) and 505(b)(2). Our proposed regulatory approach, summarized below, builds on FDA's complex drug product classification, which should be leading in determining whether to submit a 505(j) or 505(b)(2) application:

- Complex generic drug products can be evaluated through a 505(j) application if it is possible to establish PE with physicochemical characterization and *in vivo* bioequivalence studies are sufficient to demonstrate BE. This most likely refers to complex drug products that fall within FDA's complex generic drug product categories "Complex Formulation," "Complex Route of Delivery," and "Complex Dosage Form."
- Complex generic drug products should be evaluated through the 505(b)(2) application if a complete characterization of the API is not possible, and therefore impossible to estab-

lish PE. This would require clinical studies to establish the safety and/or efficacy of the follow-on product, comparable to the totality of evidence approach used for biosimilars. This would most likely concern complex drug products that fall within the FDA's complex generic drug product category "Complex API."

With this paper, we hope to add to the scientific and regulatory discussions allowing for the evolution of regulatory approaches and to manage current and future challenges from complex drug products. This will hopefully facilitate access to much-needed complex generics and further promote sustainability within the healthcare system.

Acknowledgments

The authors thank Sesha Neervannan for his invaluable input during the several workshops on this topic.

Competing interests

All authors are members of the steering committee of the Non-Biological Complex Drugs Working Group, an initiative hosted by Lygature. Current partners are the University of Geneva, Allergan Plc (Abbvie), Vifor International Inc., Foundation Lygature, and the University of Basel. The working group consists of experts from industry, academia, and knowledge institutes. In addition to in-kind contribution of all partners, funding is provided by Allergan Plc and Vifor International Inc. B.F. is employee of Vifor Pharmaceuticals, Ltd. G.B. received funding for a research project from Vifor Pharmaceuticals, Ltd. S.E.M. is a consultant for Vifor Pharmaceuticals. J.S.B.d.V. and K.K. are employed by Lygature, an independent Netherlands-based not-for-profit organization facilitating the NBCD Working Group. <https://nbcds.info/>

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