Overview of the European Medicines Agency’s Experience With Biowaivers in Centralized Applications

Ines Lenic1, Kevin Blake1,*, Alfredo Garcia-Arieta2, Henrike Potthast3 and Jan Welink4,5

The waiver of the in vivo demonstration of bioequivalence (biowaiver) is an established tool in drug development and regulatory assessment. This study reviews the use of different biowaiver approaches in centralized applications for marketing authorization to the European Medicines Agency for generic and innovator medicinal products in 2016 and 2017. The focus was to provide insight into the applicability of biowaivers for medicines development. The results show that as expected, biowaivers were most frequently used in applications for generic medicines, in particular for the approval of additional strengths when in vivo bioequivalence has been demonstrated using a single, usually the highest, strength. Biowaivers have, however, also been used in applications for innovator medicines in different phases of clinical development. This review confirms the existing key roles and further potential for biowaivers in regulatory submissions in that they are useful in streamlining the often challenging processes of clinical development.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Biowaivers are a means of waiving bioequivalence studies in humans. Currently there are three types of biowaivers commonly described in EU regulatory guidelines.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ This study elucidates European Medicines Agency experience with biowaivers, their acceptability, and the frequency of their use in centralized procedures for innovator and generic medicinal products.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ This is the first European Medicines Agency review into their use in regulatory submissions for centralized marketing authorizations accompanied by an analysis on associated issues. This study provides transparency into the use of biowaivers and details frequency regarding which biowaiver approaches are applied.

HOW MIGHT THIS CHANGE CLINICAL PHARMA­COLOGY OR TRANSLATIONAL SCIENCE?

✔ This article provides information valuable to developers of new medicinal products to gain confidence that under certain criteria bioequivalence studies can be waived and also reflects some flexibility of biowaiver principles that are not specifically described in the European Medicines Agency guidelines, e.g., a biowaiver to investigate the impact of a different method of administration.

Facilitating access for European patients to high-quality, safe, and effective medicinal products is a core activity of the European Medicines Agency (EMA) and its scientific committees. This includes authorizing entirely new (innova­tor) medicinal products containing new active substances and generics of existing (reference) medicinal products.

There are different application procedures for submitting a medicinal product in the European Union. An innovator product (as defined in article 8.3 of Directive 2001/83/EC)1 can be evaluated under the centralized procedure in accordance with the relevant legislation in the European Union2,3 either because it falls within the “mandatory scope” (e.g., advanced therapy, orphan medicinal products as well as medicines for the treatment of cancer, diabetes, neurodegenerative disorder, acquired immune deficiency syndrome, autoimmune and viral diseases) or the criteria for eligibility under the “optional scope” are fulfilled. For all medicinal products that undergo a centralized procedure, a final scientific opinion on authorization is made by the EMA’s Committee for Medicinal Products for Human Use (CHMP). Once granted by the European Commission, the centralized marketing authorization is valid in all EU Member States and Iceland, Norway, and Liechtenstein.

Medicinal products can, however, also be submitted for marketing authorization in the European Union through a choice of three other application procedures, i.e., via a decentralized, national, or mutual recognition route. In these procedures, scientific assessment is concluded by the
National Competent Authorities in the Member States, facilitated where appropriate by the Co-ordination Group for Mutual Recognition and Decentralised Procedures–Human. Where a scientific issue arises in these procedures, the Coordination Group for Mutual Recognition and Decentralised Procedures–Human may request a CHMP opinion.

Generic medicines are defined in the EU legislation (article 10.1 of Directive 2001/83/EC\(^1\)) as products that have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as a reference medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

In addition to the decentralized, national, or mutual recognition routes as outlined previously, eligibility to the centralized procedure can also be granted to generic medicinal products: (i) if the reference product has itself been centrally authorized, (ii) if it constitutes a significant therapeutic, scientific, or technical innovation, or (iii) if the granting of a centralized procedure can also be granted to generic medicinal products (i) if the reference product has itself been centrally authorized, (ii) if it constitutes a significant therapeutic, scientific, or technical innovation, or (iii) if the granting of a centralized authorization is in the interest of patients at a community level and allows access to medicines.\(^2\)

The overarching EU requirements for the design, conduct, and evaluation of bioequivalence studies for immediate release dosage forms with systemic action, irrespective of their innovator or generic status, are detailed in the CHMP Guideline on the Investigation of Bioequivalence.\(^3\) These requirements apply irrespective of regulatory approval route. The guideline also details where bioequivalence studies may not be required and an alternative scientific approach may be applied provided certain criteria are met and subject to regulatory scrutiny. A waiver may be applied in three different scenarios: (i) an additional strength(s), (ii) a specific type of formulation, or (iii) products containing class I or III drugs according to the Biopharmaceutics Classification System (BCS), based on the aqueous solubility and the absorption of the active substance (see Guideline on the Investigation of Bioequivalence section 4.1.6, Appendix II or Appendix III).

Additional-strength biowaivers are meant to reduce the repeating of the same in vivo studies for different strengths of the same product. In that case, it is implied that the in vivo bioequivalence that has been demonstrated by appropriate human clinical studies on one strength (i.e., the most sensitive to detect a potential difference) is extrapolated to the additional strength(s) based on the use of the same manufacturing process, qualitative and quantitative excipient composition of the different strengths, and similar in vitro dissolution data between product strengths.

On the other hand, biowaivers for specific types of formulations (e.g., aqueous parenteral solutions) could be used to waive bioequivalence studies if the composition of test and reference formulations containing the same active substance is similar, or, in case of differences in excipients, it can be justified that these differences will not affect the bioavailability of the active substance.

Similarly, BCS-based biowaivers represent a surrogate approach for in vivo bioequivalence in which an assumption of equivalence can be fully justified by satisfactory excipient composition and similar in vitro dissolution between the corresponding strengths of test and reference products.

As such, biowaver concepts provide evidence-based rationales to replace potentially time-consuming and expensive clinical studies in humans to facilitate access to medicines.

The present retrospective analysis has been undertaken to give detailed insight into the use of biowaivers in regulatory submissions to the EMA for centralized procedures with a focus on generic and new (innovator) medicinal products. The analysis is created to give further insight into the EMA’s experiences and perspectives on biowaivers rather than reiterating the technical and scientific requirements for specific biowaver approaches. Specifically, this work aims to evaluate experience with biowaivers in applications that obtained a positive opinion from the CHMP in 2016 and 2017 within the context of the three broad purposes previously outlined, i.e., for authorizing additional strengths, specific formulations, or BCS-based biowaivers.

**METHODS**

EMA annual reports were used as the reference sources to identify applications that received CHMP positive opinion in 2016\(^4\) and 2017\(^5\) according to Article 8.3 and Article 10.1 of Directive no. 2001/83/EC\(^1\) as the legal bases for innovator and generic medicines, respectively. The EMA electronic records management system was searched using the terms “biowaver,” “waiver,” “biopharmaceutics classification system,” “BCS,” “bioequivalence,” and “bioavailability” for relevant documentation, including the different assessment reports generated during the evaluation of procedures, to identify those that included reference to biowaivers. Additional searches were performed in the electronic common technical document dossiers that are submitted for marketing authorization applications, in particular for quality and clinical data for innovator medicinal products. The data lock point was December 31, 2017. A final list of procedures that included references to biowaivers was compiled. These were further categorized based on the intended purpose of the biowaver.

The assessment of each procedure on the list was subject to manual review to identify the type and time of application, the intended purpose of the biowaver, and the outcome of the biowaver request by the CHMP. Similarly, the EMA public website was also searched for relevant documentation, in particular European Public Assessment Reports and Summaries of Product Characteristics to identify where reference to biowaivers was in the public domain using the terms “biowaver,” “waiver,” “biopharmaceutics classification system,” “BCS,” “bioequivalence,” and “bioavailability” as keywords.

**RESULTS**

**Requests for biowaivers within applications for generic medicinal products**

In 2016, 22 applications for generic medicines received a positive opinion from the CHMP (see Table 1). In 16 of these, a request for a biowaver was considered as an acceptable scientific rationale to approve the use of the biowaver for the intended purpose during the assessment by the CHMP.
The majority of the biowaivers (9 of 16) related to applications for additional strength(s) for products. Seven of these were for products with more than one strength. For two products with sildenafil as the active substance (Granpidam and Mysildecard 20 mg film-coated tablets), although the applications concerned only one strength, an additional strength biowaiver was applied as the relevant bioequivalence study was conducted with a different strength to the one applied for, i.e., the study was conducted with the 100 mg strength and a biowaiver was requested for the 20 mg strength.

Five of the 16 involved formulation-related biowaivers for parenteral solutions.

For one product with pregabalin as the active substance, both additional strength and BCS-based biowaivers consistent with section 4.1.6 and Appendix III of the Guideline on the Investigation of Bioequivalence, respectively, were sought for different strengths, i.e., the bioequivalence study was conducted with the highest strength, and because the lowest strength was not quantitatively proportional to the other strengths, a BCS-based biowaiver was sought for this strength only. Although this approach was considered acceptable, it was also pointed out by the CHMP that as pregabalin is a BCS class I drug, a BCS-based biowaiver for all strengths would have been acceptable.

Unlike the three scenarios described previously, a biowaiver was also used to waive a clinical study to investigate the impact of a different method of administration of a tablet, i.e., when disintegrated in water or juice compared with swallowed whole. This was for two products with tenofovir disoproxil as the active substance. It was considered that the additional method of administration would not have any impact because of the BCS classification of tenofovir (BCS III) and the comparative disintegration times of the test and reference products in water.

In 2017, a total of 21 generic medicinal products were granted positive opinion by the CHMP, and 15 of these requested a biowaiver (Table 2), all except one of which were endorsed by the CHMP.

Again, the majority were biowaivers for additional strengths (10 of 15). A further three involved formulation biowaivers for

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### Table 1 Listing of all generic products receiving a positive opinion from the Committee for Medicinal Products for Human Use in 2016 and whether biowaivers were requested

| Product name                  | Form                      | Strength(s)                                | Biowaiver | Biowaiver type          |
|-------------------------------|---------------------------|--------------------------------------------|-----------|-------------------------|
| Amlodipine–Valsartan Mylan    | Film-coated tablets       | 5/160 mg, 5/80 mg, 10/160 mg               | Yes       | Additional strength     |
| Atazanavir Mylan              | Hard capsules             | 150, 200, 300 mg                           | Yes       | Additional strength     |
| Darunavir Mylan               | Film-coated tablets       | 75, 150, 300, 400, 600, 800 mg             | Yes       | Additional strength     |
| Granpidam                     | Film-coated tablets       | 20 mg                                      | Yes       | Additional strength     |
| Ixabradine JensonR            | Film-coated tablets       | 5, 7.5 mg                                  | Yes       | Additional strength     |
| Ixabradine Zentiva            | Film-coated tablets       | 5, 7.5 mg                                  | Yes       | Additional strength     |
| Mysildecard                   | Film-coated tablets       | 20 mg                                      | Yes       | Additional strength     |
| Zonisamide Mylan              | Hard capsules             | 25, 50, 100 mg                             | Yes       | Additional strength     |
| Pregabalin Zentiva k.s        | Hard capsules             | 25, 50, 75, 100, 150, 200, 225, 300 mg     | Yes       | Additional strength + BCS|
| Tenofovir disoproxil Mylan    | Film-coated tablets       | 245 mg                                     | Yes⁴      | BCS                     |
| Tenofovir disoproxil Zentiva  | Film-coated tablets       | 245 mg                                     | Yes⁴      | BCS                     |
| Bortezomib Hospira            | Powder for solution for injection | 3.5 mg                          | Yes       | Formulation             |
| Bortezomib Sun                | Powder for solution for injection | 3.5 mg                          | Yes       | Formulation             |
| Palonosetron Accord           | Solution for injection    | 250 μg/5 ml                                | Yes       | Formulation             |
| Palonosetron Hospira          | Solution for injection    | 250 μg/5 ml                                | Yes       | Formulation             |
| Pemetrexed Fresenius Kabi     | Powder for concentrate for solution for infusion | 100, 500 mg | Yes       | Formulation             |
| Emtricitabine/Tenofovir disoproxil Krka | Film-coated tablets   | 200/245 mg                                 | No        | —                       |
| Emtricitabine/Tenofovir disoproxil Mylan | Film-coated tablets   | 200/245 mg                                 | No        | —                       |
| Emtricitabine/Tenofovir disoproxil Zentiva | Film-coated tablets   | 200/245 mg                                 | No        | —                       |
| Lifmior                       | Powder and solvent for a solution for injection or as a ready-made solution for injection | 10, 25, 50 mg | No        | —                       |
| Rasagiline Mylan              | Tablets                   | 1 mg                                       | No        | —                       |
| Talimanco                     | Film-coated tablets       | 20 mg                                      | No        | —                       |

BCS, Biopharmaceutics Classification System.

⁴Differs from the biowaiver concepts defined in the Guideline on the Investigation of Bioequivalence (see text).
parenteral solutions. The remaining two were BCS-based biowaiver requests. For one of these two (Lacosamide Accord), the biowaiver request was accepted.\textsuperscript{11} For the other (Yargesa), a biowaiver was originally requested to support the marketing authorization application based on Yargesa being considered a BCS III drug. According to the relevant product-specific EMA guideline on bioequivalence,\textsuperscript{12} this is in principle possible, i.e., if the applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, a BCS biowaiver could be applicable. However, the product-specific guidance also states that a BCS-based biowaiver might not be feasible because of the unacceptable differences in the excipient composition. During the assessment of the application, it was concluded by the CHMP that the criterion for the BCS biowaiver relating to the similarity of excipients was, in fact, not met, and a bioequivalence study was deemed necessary for the application to receive a positive opinion.\textsuperscript{13}

**Requests for biowaivers within applications for new (innovator) medicines**

In 2016 and 2017, there were 34 and 37 positive opinions, respectively, by the CHMP for initial marketing authorizations for new (innovator) medicines. For four products during the 2-year period there was explicit reference to seeking a biowaiver using the search criteria described in the Methods section. For two products (Lonsurf (trifluridine/tipiracil) and Galafold (migalastat)), biowaivers of a bioequivalence study for different formulations used in the clinical development program and the commercial formulations were requested. The BCS classification of these active substances as BCS class III compounds was taken into account as were the composition and the dissolution of the formulations (i.e., dissolution \(\geq 85\%\) at 15 minutes in all tested \(pH\) media).\textsuperscript{14,15}

A formulation biowaiver was applied for Parsabiv (etelcalcetide), where two different parenteral formulations were used in the clinical studies, i.e., a lyophilized powder for reconstitution for injection and a sterile liquid for injection. A biowaiver of a bioequivalence study between the two formulations was considered acceptable in light of both products being intravenous solutions containing the same active substance and no expected impact of excipients on bioavailability.\textsuperscript{16}

The fourth biowaiver was for a product with multiple strengths, Uptravi (selexipag), which is further described in the next section.

### Table 2 Listing of all generic products receiving a positive opinion from the Committee for Medicinal Products for Human Use in 2016 and whether biowaivers were requested

| Product name                              | Form               | Strengths                      | Biowaiver | Biowaiver type |
|-------------------------------------------|--------------------|--------------------------------|-----------|----------------|
| Anagrelide Mylan                           | Hard capsules      | 0.5, 1 mg                      | Yes       | Additional strength |
| Darunavir Krka                             | Film-coated tablets| 400, 600, 800 mg               | Yes       | Additional strength |
| Darunavir Krka                             | Film-coated tablets| 400, 600, 800 mg               | Yes       | Additional strength |
| Entecavir Accord                           | Film-coated tablets| 0.5, 1 mg                      | Yes       | Additional strength |
| Entecavir Mylan                            | Film-coated tablets| 0.5, 1 mg                      | Yes       | Additional strength |
| Febuxostat Mylan                           | Film-coated tablets| 80, 120 mg                     | Yes       | Additional strength |
| Imatinib Teva                              | Capsules and film-coated tablets| 100, 400 mg | Yes | Additional strength |
| Ivabradine Accord                          | Film-coated tablets| 5, 7.5 mg                      | Yes       | Additional strength |
| Nitisinone MDK                             | Hard capsules      | 2, 5, 10 mg                    | Yes       | Additional strength |
| Tacforius                                  | Prolonged-release capsules| 0.5, 1, 3, 5 mg | Yes | Additional strength |
| Lacosamide Accord                          | Film-coated tablets| 50, 100, 150, 200 mg           | Yes       | BCS |
| Yargesa                                    | Capsules           | 100 mg                         | Yes       | BCS |
| Daptomycin Hospira                         | Powder for solution for injection/ infusion| 350, 500 mg | Yes | Formulation |
| Fulvestrant Mylan                          | Solution for injection| 250 mg                       | Yes       | Formulation |
| Pemetrexed Hospira                         | Powder for concentrate for solution for infusion| 100, 500, 1000 mg | Yes | Formulation |
| Efavirenz/Emtricitabine/Tenofovir disoproxil Krka | Film-coated tablets| 600/200/245 mg               | No        | – |
| Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan | Film-coated tablets| 600/200/245 mg               | No        | – |
| Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva | Film-coated tablets| 600/200/245 mg               | No        | – |
| Emtricitabine/Tenofovir disoproxil Krka    | Film-coated tablets| 200/245 mg                    | No        | – |
| Miglustat Gen.Orph                         | Capsules           | 100 mg                         | No        | – |
| Ritonavir Mylan                            | Film-coated tablets| 100 mg                         | No        | – |

BCS, Biopharmaceutics Classification System.
Approvals of multiple strengths within applications for new (innovator) medicines

Although the majority of initial marketing authorizations for new (innovator) medicines during the 2-year period (43 of 71) concerned a single strength, 28 concerned multiple strengths. The apparent low numbers of requests for biowaivers (4), in particular for additional strengths (1), led to further evaluation of the scientific rationale for how different strengths were approved. Of 28 multiple-strength products, 12 were parenteral products for which a waiver based on formulation is applied as soon as the company has shown that the drugs exhibit linear pharmacokinetics in that route of administration. Two were powders for oral suspensions that act locally in the gastrointestinal tract and for which the clinical studies were performed with all strengths. The remaining 14 were immediate-release, solid-oral forms. Two of these were combination products with the required comparative bioequivalence studies between combinations and single products. An in-depth review was therefore applied to the remaining 12 immediate-release, solid-oral, single-component products to see whether in effect biowaivers had been applied during assessment without explicit reference to the specific term. The results for these are present in Table 3.

For one product, Uptravi (selexipag), an additional strength biowaiver was applied. As bioequivalence between one tablet of the highest strength (1,600 μg) and eight tablets of the lowest strength (200 μg) had been demonstrated in a bioequivalence study in a bracketing approach, a bio- waiver for the intermediate dose strengths (400, 600, 800, 1,000, 1,200, and 1,400 μg) was considered justified taking account of the manufacturing process, the similarity of the qualitative and quantitative composition, and the dissolution profiles.17

For two products (Ongentys (opicapone)18 and Prevymis (ltemorvin)19), comparative bioavailability studies were performed to investigate bioequivalence between different strengths, i.e., for Ongentys (opicapone) bioequivalence was demonstrated between 5 × 5 mg and 1 × 25 mg strengths and between 2 × 25 mg and 1 × 50 mg strengths of the commercial formulations, and in the Prevymis (ltemorvin) application, a single-dose administration of a 1 × 480 mg tablet was compared with 2 × 240 mg tablets.

For another product, Venclyxto (venetoclax), each of the three tablet strengths were shown to have different dissolution profiles, which meant a criterion for a biowaiver was not met. To address this, a detailed meta-analysis of the available clinical bioavailability data was performed, and it was concluded that the results did not indicate a relevant difference in bioavailability between the different tablet strengths.20

For another product, Ninlaro (ixazomib), although the dissolution profiles were similar, a different criterion for bio- waiver was not met in that composition between different strengths was disproportionate. However, all strengths were studied in the clinical program, and an analysis of the resulting pharmacokinetic data supported the conclusion that similar bioavailability was sufficiently demonstrated and no additional in vivo study was needed.21

For the remaining 7 of 12 products, bioequivalence between different strengths was not demonstrated based on a dedicated in vivo study or relevant human pharmacokinetic data. Although in these cases a biowaiver was not formally requested, the assessment was seen to have taken account of comparative dissolution profiles and proportional qualitative and quantitative composition of different strength formulations. In addition, consideration was made as to whether all strengths were produced by the same manufacturing process. It is also the case that different strengths are developed for a specific purpose in a clinical development program and as such are studied directly in the clinical studies. It would therefore seem that these additional strengths were approved based on the totality of the data without the need for a waiver of further specific studies being explicitly required.

DISCUSSION

Impact of biowaivers on authorization of medicinal products in the European Union

If the EU guideline is followed, a variety of possibilities emerge in terms of waiving in vivo bioequivalence studies. Bioequivalence is the fundamental concept in applications

Table 3 Multiple-strength, single-component, immediate-release, solid-oral, innovator products receiving positive Committee for Medicinal Products for Human Use opinions in 2016 and 2017

| Product (INN)       | Form             | Strengths                        |
|---------------------|------------------|----------------------------------|
| 2016                |                  |                                  |
| Ibrance (palbociclib) | Hard capsules   | 75, 100, 125 mg                  |
| Kisplyx (lenvatinib) | Hard capsules   | 4, 10 mg                         |
| Ninlaro (ixazomib)  | Hard capsules   | 2.3, 3, 4 mg                     |
| Ocaliva (obeticholic acid) | Tablets | 5, 10 mg                         |
| Olumiant (baricitinib) | Tablets       | 5, 10 mg                         |
| Ongentys (opicapone) | Hard capsules   | 25, 50 mg                        |
| Truberzi (eluadoline) | Film-coated tablets | 75, 100 mg             |
| Uptravi (selexipag) | Film-coated tablets | 200, 400, 600, 800, 1,000, 1,200, 1,400, 1,600 μg |
| Venclyxto (venetoclax) | Film-coated tablets | 10, 50, 100 mg               |
| 2017                |                  |                                  |
| Fotivda (tivozanib) | Hard capsules   | 890, 1,340 μg                    |
| Prevymis (ltemorvin) | Film-coated tablets | 240, 480 mg              |
| Reagila (cariprazine) | Hard capsules | 1.5, 3, 4.5, 6 mg                |

INN: International nonproprietary name.
*Available also as a concentrate for solution for infusion.
for generic medicines that allows bridging to the clinical and nonclinical data for the reference product. Therefore, as perhaps could have been expected, a request for a waiver of in vivo bioequivalence studies was found in more than 50% of the generic applications in the past 2 years (2016–2017), and given that bioequivalence is usually determined based on one strength (most often the highest), the most frequently used approach is an additional strength biowaiver. This may also be considered as a consequence of the relative ease in applying this approach following well-established principles from the guideline. An alternate approach could be a “bracketing” approach in which bioequivalence studies would be performed on strengths that represent the extremes. However, the present review suggests that a “bracketing” approach is not such a popular concept in drug development (only one example), and this may be because of the criteria for proportional composition being generally easy to meet to apply a respective biowaiver.

For parenteral solutions, bioequivalence studies can be waived following the rules from the Appendix II of the guideline. According to the current overview, companies can easily comply with the biowaiver requirements for parenteral solutions, as demonstrated by formulation biowaivers being applied in all cases where it was possible. It is noted, however, that no application for a marketing authorization for a generic oral solution was submitted in 2016 and 2017. Biowaivers could also be used for aqueous oral solutions. In the case of aqueous solutions containing completely solubilized active substances, neither the manufacturing process nor the formulation affects drug release, and the formulation impact on absorption should be minimal. However, clarification of guidance on the requirements for composition of excipients when waiving in vivo studies for oral solutions, in appearing to make the requirements more stringent, may have negatively impacted on companies’ development strategies for generic oral solutions, at least in the short term.

What differentiates BCS-based biowaivers when compared with additional-strength waivers is that they may represent a surrogate for bioequivalence without conducting any in vivo bioequivalence study within the clinical development program. As for any biowaiver request, although the applicability of a BCS biowaiver according to Appendix III of the guideline is critically reviewed by EU regulators for each application, products are approved applying the scientific rationale of the BCS-based biowaiver approach. Moreover, it has also been noted how BCS classification can be used to support additional types of biowaivers such as the waiver of an in vivo study of different methods of administration. For most of the innovator products, BCS classification was done as a part of development that might be a basis for future biowaiver applications.

On the other hand, during innovator product development, most applications (43 of 71) concern only one strength or companies tend to do full characterization of the compound and usually all strengths are studied in clinical programs. Most often bioequivalence studies in a development of an innovator product are concerning changes in formulations (e.g., final commercial formulation differs from the formulation used in clinical trials) or manufacturing processes (e.g., change of a manufacturing site) in which case the bioequivalence has to be demonstrated between two or more concerned formulations. A biowaiver can be applied in these cases if relevant scientific data can justify that approach. For multiple-strength products, similar bioavailability has to be established between multiple strengths at the same dose. Although this can be done, in principle by appropriate bioequivalence studies, the present review suggests that such direct comparative bioavailability studies between strengths are not very often used in development, i.e., they were found in only two applications for innovator products during the 2-year period (Ongentys (opicapone) and Prevymis (letemovir)). Instead, it appears that companies tend to demonstrate comparative bioavailability by providing appropriate dissolution data together with evidence of proportional qualitative and quantitative compositions and the same manufacturing process that complies with the guideline’s requirements for biowaivers. In fact, a number of different ways of demonstrating bioequivalence of multiple-strength doses were found in the applications for innovator medicines. This reflects the CHMP approach of reviewing case by case every application for a marketing authorization, allowing different scientific rationales. This approach is the direction of travel of drug development toward more complex medicinal products and associated clinical programs. The decisions are taken based on the totality of evidence.

Limitations of the performed analysis
The results of the present study underestimate the number of procedures containing biowaivers in the European Union. Only centralized procedures have been selected, and this excludes biowaivers submitted to the National Competent Authorities for noncentralized procedures. This impacts on the numbers of procedures for generic products as the vast majority of these in the European Union are noncentralized applications. Only waivers described in the Guideline on the Investigation of Bioequivalence are addressed, and other types of waivers, e.g., for locally acting products, are not. It is also acknowledged that biowaivers may be applied for in other contexts, e.g., the development of appropriate pediatric formulations that may be submitted as variations to an existing marketing authorization, and these have also not been included in the analysis. With reference to the data set, the fragmentation of data and the use of a variety of terms in the assessment reports may complicate the identification of references to the use of biowaivers.

CONCLUSION
The present review confirms that biowaivers are used more frequently for generic medicines than for innovator products. For example, biowaivers were applied for all additional strengths for generic products. On the contrary, for innovator products, a formal demonstration of bioequivalence or at least with the extremes of the strengths in a bracketing approach is preferred. This is taken to reflect that there are other alternatives for innovators such as testing all strengths clinically and combining the available data, including on composition and dissolution, to conclude that the bioavailability of the different strengths is similar.
Therefore, although not claimed explicitly, the principles of biowaivers are also employed for innovator products. The EMA endorses a variety of different approaches in terms of biowaivers as they comply with the agency’s mission to facilitate development and provide access to high-quality, effective, and safe medicines to all patients in the European Union. The agency is supporting efforts in harmonization of biowaiver and marketing authorization requirements, which will further contribute to the interests of patients and public health, regulatory agencies, and the pharmaceutical industry.

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1. European Parliament and the Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 <https://www.ema.europa.eu/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf>. Accessed December 13, 2018.

2. European Parliament and the Council of the European Union. Annex to Regulation No 726/2004 of the European Parliament and of the Council of 31 March 2004 <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:033:en:PDF>. Accessed December 13, 2018.

3. European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure (version dated 4 May 2018). EMA/821278/2015 <https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en.pdf>. Accessed December 13, 2018.

4. European Medicines Agency procedural advice for users of the centralised procedure for generic/hybrid applications (version dated 12 May 2017). EMEA/CHMP/225411/2006 <https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency-procedural-advice-users-centralised-procedure-generic/hybrid-applications_en.pdf>. Accessed December 13, 2018.

5. European Medicines Agency. Annual report 2016 <https://www.ema.europa.eu/documents/annual-report/2016-annual-report-european-medicines-agency_en.pdf>. Accessed December 13, 2018.

6. European Medicines Agency. Annual report 2017 <https://www.ema.europa.eu/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf>. Accessed December 13, 2018.

7. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/Corr ** <https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf> (2010). Accessed December 13, 2018.

8. Pregabalin Zentiva EPAR <https://www.ema.europa.eu/documents/assessment-report/pregabalin-zentiva-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

9. Tenofovir disoproxil Zentiva EPAR <https://www.ema.europa.eu/documents/assessment-report/tenofovir-disoproxil-zentiva-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

10. Tenofovir disoproxil Mylan EPAR <https://www.ema.europa.eu/documents/varia­tion-report/tenofovir-disoproxil-mylan-h-c-004049-0000-epar-assessment-rep­ort_en.pdf>. Accessed December 13, 2018.

11. Lacosamide Accord EPAR <https://www.ema.europa.eu/documents/assessment-report/vimpat-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

12. Miglustat product-specific bioequivalence guidance <https://www.ema.europa.eu/documents/scientific-guideline/miglustat-hard-capsules-100-mg-product­specific-bioequivalence-guidance_en.pdf>. Accessed February 24, 2019.

13. Yargeas EPAR <https://www.ema.europa.eu/documents/assessment-report/yargeas-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

14. Lonsurf EPAR <https://www.ema.europa.eu/documents/assessment-report/lonsur­f-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

15. Galafold EPAR <https://www.ema.europa.eu/documents/assessment-report/galaf­old-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

16. Parabiv EPAR <https://www.ema.europa.eu/documents/assessment-report/parsa­biv-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

17. Uptravi EPAR <https://www.ema.europa.eu/documents/assessment-report/uptra­vi-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

18. Ongentys EPAR <https://www.ema.europa.eu/documents/assessment-report/ongen­ty­s-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

19. Prevymis EPAR <https://www.ema.europa.eu/documents/assessment-report/prevy­mis-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

20. Venclyxto EPAR <https://www.ema.europa.eu/documents/product-information/venc­lyxto-epar-product-information_en.pdf>. Accessed December 13, 2018.

21. Ninlaro EPAR <https://www.ema.europa.eu/documents/assessment-report/ninla­ro-epar-public-assessment-report_en.pdf>. Accessed December 13, 2018.

22. Clinical pharmacology and pharmacokinetics: questions and answers (biowaivers, 6.3) <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharm­acokinetics/clinical-pharm­acology-pharmacokinetics-questions-answers_en.pdf>. Accessed December 13, 2018.

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