Regulatory pathways for development and submission activities

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Abstract
This article discusses how different regulatory requirements for a dossier requesting marketing authorisation for a medical drug affect the deliverables from development functions and the submission groups including medical writing. The content of the dossier submitted is strongly interlinked to the legal basis selected for a regulatory filing. This drives the requirements of data from different areas of development as well as of dossiers that can be summarised mainly into the general categories of Chemistry, Manufacturing and Controls (Common Technical Document (CTD) dossier Module 3), non-clinical (CTD dossier Module 4), and clinical (CTD dossier Module 5) reports. This article addresses different types of regulatory pathways in the EU and the US with case examples where possible. The pathways used in the generic and biosimilar industries are discussed regarding expectations of authorities in an application type. Although this article focuses on clinical research and clinical data requirements within the generic and biosimilar industries, it also addresses how other parts of the dossiers are affected.

Introduction
A thorough understanding of different regulatory pathways is indispensable from a regulatory perspective, as the regulatory submission strategy is a key decision before proceeding to development and submission activities. The focus on this area is self-explanatory in the broader sense, given that the effort invested in development and submission activities for any given medical drug can typically take as long as 15 years depending on whether it is a new active substance, a generic, a differentiated product such as a value added medicine, a biosimilar, or a combination of digital and/or device and/or medicinal product. The legal framework that lays out these regulatory pathways is comprehensibly different in the EU and the US. Energy and focus are needed early on to decide upon the legal basis, and where necessary, scientific advice and discussion with regulators need to be initiated in order to reach understanding and agreements on the project. This is the most important step as it determines the data needed for any successful regulatory submission. In turn, the data produced during development activities are placed in allocated slots in the Common Technical Document (CTD) structure supported by medical writing, development, and regulatory teams into the respective clinical (Module 5), non-clinical (Module 4), and quality (Chemistry, Manufacturing and Controls (CMC))(Module 3) components. Module 2 covers summaries of

Table 1. Different regulatory pathways in the EU[2,4,5]

Legal basis	Application Type	Needed clinical studies	Development and submission timelines
Art. 8(3)	Full application	Yes	8-15 years
Art. 8(3) mixed application	Full mixed application	Yes	8-10 years
Art. 10(1)	Standard Generic, abridged application	Mainly BE studies; may include PD/clinical endpoint studies for some products	2-5 years
Art. 10(3)	Hybrid Application, abridged application	Yes, in rare cases only BE also possible.	3-7 years
Art. 10(4)	Biosimilar Pathway, abridged application	Yes	5-8 years
Art. 10a	Well established use	No, generally only bibliographical references	1-2 years
Art. 10b	Fixed dose combination	Yes, depending on application.	2-5 years
Art. 10c	Informed consent (duplicate)	Reference to Modules 2 to 5	None

NB. Development and submission timelines above were collected through available public information and projected accordingly.[40, 41] Irrespective of the submission pathway, duration of regulatory procedure is always 210 days. In addition, national phase must be calculated for DCP/MRP procedures, which last between 4 weeks and 1.5 to 2 years.

Applicability	European reference medicinal product needed for submission	Data/ Market Exclusivity	Once approved can act as RefMP	SmPC	Need for PIP
New active substance	No, active comparator/placebo	Yes, 8+2+1 years (DP+ ME+ exclusivity for add indication)	Yes	New	Yes
No RefMP, no reference to any data from 8(3) dossier, may apply to differential products like VAMs	No, active comparator/placebo	Yes, 8+2+1 years.	Yes	New	Yes
Generics (mono and combos)	Yes, innovator of the same molecule, RefMp	No	No	1:1 similar to the RefMP	No
Strictly not generic	Yes, RefMp needed	No, only in case of orphan drugs 10 years ME.	No	Slight changes in SmPC compared to RefMP	Generally no, except for PUMA
Biosimilar product	Yes, innovator biologic as RefMp	No	No	1:1 to the RefMP possible	No
Old molecules /BCS I	None	Yes	No	Based on well-established use within EU	No
Fixed dose combination	Not needed	Yes	Yes	New	No
Duplicate of originator product	NA	No	NA	NA	No

Abbreviations: Add, Additional; Art, Article; BCS, biopharmaceutical classification; BE, Bioequivalence; DCP, decentralised procedure; DP, data protection; RefMP, reference medicinal product; ME, marketing exclusivity; MRP, mutual recognition procedure; NA, not applicable; PD, pharmacodynamics; PIP, paediatric investigation plan; PUMA, paediatric-use marketing authorisation; SmPC, summary product characteristics; VAM, value added medicines

development activities and Module 1 the administrative information. In this article, all development, submission activities, and dossier writing (considering also individual study planning and reports) will be covered under the term *development and submission activities*.

European Union (EU)

Situation in the EU

In the EU, the legal basis to seek an approval of a medicinal drug product is under the European Directive 2001/83/EC as amended.[1] Table 1 summarises different regulatory pathways within the EU along with some general development and submission timelines and other regulatory requirements. All tables in this article provide an overview, and not all conditions and exceptions are considered.

There are two approval pathways within the EU irrespective of the legal basis used for submission. The first category is called national authorisation procedures, which include the Mutual Recognition Procedure (MRP), Decentralised Procedure (DCP), or national submission. The second category is the Centralised Procedure (CP), whose main objective is to provide: one marketing authorisation that is valid in all EU and European Free Trade Association countries, one invented name and one common product information, and centralised safety monitoring. Alternatively, DCP can be used for an approval within selected countries of the EU depending on the applicants seeking approval.

The scope and eligibility for the CP is defined in Article 3 of Regulation (EC) No 726/2004 as *mandatory*, *optional* or *generic/hybrid scope*. In a nutshell, *mandatory* includes biosimilars, advanced medicinal products like gene therapy, somatic therapy or tissue engineered products, medicinal products developed through biotechnological processes, and new active substances. *Generic/hybrid scope* products are in practice authorised through the DCP review procedure. However, the CP is also open for generics in case the originator product has been registered centrally. In addition, certain applications for Paediatric Use Marketing Authorisation can also be eligible for the CP.[2,3,4]

As shown in Table 1, there are specified regulatory pathways. The EMA and other national Health Authorities (HAs) advocate effective planning and discussions with authorities to facilitate development and submission activities.[4] It should be noted that data collection and presentation for illustrating the cases have been performed randomly, and no systematic review was done. This overview is intended for the sole purpose of informing.

A summary of collected information from different regulatory submissions is presented as case examples to illustrate how different regulatory pathways could be used to plan the development and submission activities within given financial budgets and timelines.

Directive 2001/83/EC Article 8(3) full application

Article 8(3) within the Directive No 2001/83/EC as amended requires a complete full and independent application. A complete full application means that the development and submission activities run over a period, which is longer than for any other regulatory pathway; an independent application here means that there is no European reference medicinal product required. Such an application or submission contains all administrative information, complete CMC and quality data, non-clinical and clinical data supported through own studies. Minimal amount of literature is used to support and substitute certain tests or studies that are already well established. These kinds of submissions and filing applications under Article 8(3) are generally used for new active substances.[6]

An applicant that has received an approval under Article 8(3) can later apply for a line extension application and such applications can differ in several ways. One example is leuprorelin acetate (Prostap® 3 DCS), which was approved as a line extension under mentioned Article. The difference between the current application as line extension (Prostap® 3 DCS) with the previous authorisation of Prostap® 3 was on the use of dual chamber prefilled syringe (DCS) instead of prolonged release powder for injection. The approval of Prostap®3 DCS was granted without changes in the proposed indications or route of administration. The aim of such submissions is to establish that the difference between the newly introduced product and the already authorised product has no impact on the quality, non-clinical, and clinical data, with the overall aim of achieving similar patient efficacy and safety. In the case of Prostap® 3 DCS, required quality data have been provided and given the slight change in its new product, there was no need to perform any additional non-clinical and clinical development activities. Normally, this kind of application may not require similar development and submission activities compared to a full-blown Article 8(3) application. This kind of line extension application is part of the same Global Marketing Authorisation; therefore, no new data exclusivity period applies. In case of leuprorelin acetate DCS, generic applications that intend to manufacture and/or market leuprorelin acetate DCS can establish similar quality and bioequivalence directly to Prostap® 3 DCS rather Prostap® 3.[7]

> A thorough understanding of different regulatory pathways is indispensable from a regulatory perspective, as the regulatory submission strategy is a key decision before proceeding to development and submission activities.

Directive 2001/83/EC Article 10(1) abridged application

Article 10(1) is generally known as the generic pathway. Submission of a generic product requires a European reference medicinal product with expired 8-year data exclusivity. Requirements for generic applications are highly standardised and several guidelines have been issued to guide generic applicants in the planning, development, and submission activities.[8,9,10]

The latter two still require effective planning, and in the case of unique scenarios, discussions with HAs and scientific advice are recommended. One example is the prasugrel product-specific guideline, which has been revised, and new comments have been collected to define the clinical requirements for generic applicants.[11,12,13] The updated guideline requests an additional clinical study under elevated gastric pH conditions in case of differences in salt or free base compared to innovator of prasugrel hydrochloride. As it can be understood, any change in the requirements of data from the development side may lead to a delay in submission and increase development costs.

Therefore, depending on the uniqueness of the product, certain discussions with HAs should be a part of development and submission activities. To better plan for these, EMA has issued general guidelines on clinical pharmacology and pharmacokinetics and in addition provides product-specific bioequivalence guidance on their website. [9,10]

Directive 2001/83/EC Article 10(3) abridged hybrid application

Article 10(3) as legal basis provides an opportunity for applicants to apply if their products are slightly different from existing innovator products that do not fall under the generic product category of 10(1). Buvidal® (Buprenorphine) subcutaneous injection, for example, was submitted under Article 10(3) and was granted marketing authorisation on 20 September 2018 by the Committee for Medicinal Products for Human Use. The application of Buvidal® was submitted for review under the CP per Article 3(2)(b) of Regulation (EC) No 726/2004. As required for any Article 10(3) submission, a reference to a European medicinal product was needed; in the case of Buvidal®, reference was made to Subutex® (Buprenorphine sublingual tablets) which were previously approved in Denmark and the UK using the DCP/MRP. Buvidal® subcutaneous depot injection differs from the reference medical product (Subutex® sublingual tablets) in terms of pharmaceutical form, strength, and route of administration. Therefore, this regulatory submission fits in the legal basis category of hybrid application 10(3). In terms of development activities and effort in preparing the dossiers, the major advantage of the 10 (3) is that it can still bridge the data to the European reference medical product. Given the possibility of bridging, the effort to produce non-clinical or clinical data is reduced (see Table 1 for overview of development timelines).[14]

In the case of Buvidal®, non-clinical and clinical data were supported by bibliographic information from the public domain to the extent feasible. Five clinical pharmacology studies were also conducted to support the proposed dosing of Buvidal® and for bridging data to Subutex®. Non-inferiority to Subutex® was established via a Phase III pivotal study. Overall, the development and submission plan was in line with the regulatory strategy of using a hybrid application 10(3), significantly reducing the development and submission activities compared to a full 8(3) application.[14]

Directive 2001/83/EC Article 10(4) abridged application

Article 10(4) is meant to be used for biosimilar products within the EU and is coordinated through a centralised review process. A *biosimilar* is a successor to a biological medicine known as the *reference product*. It matches the reference medicine in terms of safety, efficacy, and quality. Using this regulatory pathway has the clear advantage of having condensed non-clinical and clinical programmes and clearly defined requirements of the quality programme, as defined by EMA biosimilar guidelines. Any submission made under this legal basis requires a European reference product with biologic origin, usually with a similar strength and same route of administration. In recent years, there have been several approvals in the EU that also included Pelmeg® and Ziextenzo® through 10(4) route. In general, biosimilar submissions are supported by at least one Phase III clinical efficacy and safety study; however in the case of Pelmeg®, pharmacokinetics and pharmacodynamics data were the bases for approval without any Phase III data. Tailor-made development plans in exceptional cases like that of Pelmeg® are encouraged and supported by EMA, if sponsors or applicants seek upfront discussions through scientific advice. Such unique development programmes also reduce the general development timelines proposed in Table 1. For cases like Pelmeg®, the fastest development period could be 5 years.[15,16] Extensive guidelines and support have been provided by EMA to biosimilar applicants as well as generic applicants on their website.[17]

However, there are certain products that fall under 10(4) which could still use more condensed clinical and non-clinical programmes compared even to classical biosimilar submissions mentioned above and may not even require a full-fledged efficacy and safety study. One example is enoxaparin (Crusia®), a low molecular weight heparin. The clear guidance issued by EMA for non-clinical and clinical development of low molecular weight heparins can be used by all applicants for submission of products in this category. As for the non-clinical programme of Crusia®, a pharmacodynamics study in rabbits and certain in vivo studies showing activities of anti-factors Xa and IIa were performed. Similarly, for the clinical programme, as conventional

pharmacokinetics studies could not be performed, and as per the above quoted guidelines, similarity at clinical level could be shown using pharmacodynamics endpoints thereby having overall abridged and targeted quality, non-clinical, and clinical development. The above examples represent how better planning and understanding between applicant and regulatory authority, supported by appropriate guidance, can offload considerable development and submission activities and lead to a targeted submission.[18]

There are also other examples, in which a version of peptide depending on its source, could be either a generic (synthetic origin) or a biologic (biological origin). As the case study of teriparatide shows us, there is a generic version (synthetic origin, teriparatide), and also a biosimilar (rDNA origin, Terrosa® and Movymia®) version, whereas the European reference medicinal product (Forsteo®) is of biological origin. Here, the generic version was approved using 10(3), whereas the biosimilar version was approved under 10(4).[19,20] Overall, one can add that development and submission activities required with different regulatory pathways may need to vary accordingly.

Directive 2001/83/EC Article 10a application

As per legal basis 10a, "the applicant shall not be required to provide pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety profile".[1] The applicant can use appropriate scientific literature to prove safety and efficacy. Reference to HA assessment reports from already approved products is, however, not acceptable for this purpose.

Directive 2001/83/EC Article 10b full application

Article 10b is the legal basis for the registration of combination products. However, the legal basis for registering combination products is open and can be decided on case-by-case basis. Moreover, applications can be submitted under alternative regulatory pathways to Article 10b. A specific guideline on clinical development of fixed-dose combinations (FDCs) is available.[21] Non-clinical and clinical data for the FDC need to be provided. Referencing publicly available data including assessment reports and Summary Product Characterstics is also possible in case of expiration of relevant data exclusivity. In addition, the current guidance on clinical development for FDCs proposes to establish that there are no drug-drug interactions at the pharmacokinetic level. If this cannot be supported by literature, a clinical study will be required.

FDCs can also be approved under a legal basis

Table 2. Different regulatory pathways in the US [31,32,39]

Legal basis[a]	Application	Type of procedure	Needed clinical studies	Generally used for
FD&C 505(b)(1)	NDA	Full dossier, clinical safety and efficacy data required.	Yes, supported through several clinical pharmacology and efficacy/safety studies.	NME/NCE
FD&C 505(j)	ANDA	Abbreviated dossier, clinical mainly BE.	BE which may include clinical endpoint studies for some products	Generic application
FD&C 505(b)(2)	Hybrid between ANDA and full NDA	Full dossier, abbreviated clinical safety/efficacy studies may be needed to support the change.	Maybe – depending on the nature of the change	VAMs such as new dosage form, new combo, new indication
PHS 351(a)	BLA	Full dossier, clinical safety and efficacy data required.	Yes, supported through several clinical pharmacology and efficacy/safety studies.	BLA
PHS 351 (k)	Biosimilar/ interchangeable BLA	Full dossier, extensive CMC (analytical similarity) and at least one clinical efficacy and safety study.	Yes – at least one PK/PD study and in general one efficacy, safety and immunogenicity study. Interchangeable require one additional specific trial	Biosimilar or Interchangeable products

[a] In general, 505(b)(1), 505(b)(2), and PHS 351(a) target 10 months for approval. Whereas, 505(j) and 351(k) aim for 12 months, review period varies depending on classification as standard or priority review, in which the latter aims for 6 months. There is no clock stop during review in the US-FDA unlike in the EU.

[b] Other exclusivities from FDA include Generating Antibiotic Incentives Now (GAIN) and Qualified Infectious Diseases Product (QIDP), which would qualify product for additional 5 years of exclusivity from the time of approval.[42]

NB. Development and submission timelines above were collected through available public information and projected accordingly.[43, 44, 45]

Please refer also to Appendix 1 for differences among applications submitted and approved under FD&C Act Section 505.

8(3) full or mixed application. In certain cases, legal basis 10(1) has also been used to obtain an approval for an FDC. This has been achieved by referring to an already approved FDC, for which any relevant data exclusivity period has already expired. Important bridges of efficacy and safety, drug-drug interaction, and bioequivalence data are needed irrespective of the legal basis and accordingly development and submission activities vary. The requirement of more than one bioequivalence study may arise, if at least one of the FDCs contains a modified release component, in which case the EMA's guidance on pharmacokinetic and clinical evaluation of modified release has to also be taken into consideration.[22]

The approval of a new FDC of Glyxambi® (empagliflozin/linagliptin) is one of the examples under this category being filed under legal basis 10b. It required extensive non-clinical and clinical programmes, wherein several bridging studies and Phase III studies were performed. Another example is the FDC of amlodipine and atorvastatin, where non-clinical and clinical scientific arguments were supported by bibliographic references and bioequivalence was also shown for the proposed FDC in comparison to the mono-products given simultaneously, e.g., Norvasc® and Lipitor®.[23,24]

Directive 2001/83/EC Article 10c informed consent application

Article 10c can be used to introduce a duplicate of the originator product into the existing market without the need to perform any additional development activities. It is referred to as informed consent as all information provided comes from the Marketing Authorisation Holder of an already authorised product in the EU region. An example of this type of submission is olmesartan plus hydrochlorothiazide, where the applicant of the reference medicinal product introduced a generic of its existing OlmetecPlus® product.[25] By remaining as the applicant of the subsequent application and referencing the pharmaceutical, pre-clinical, and clinical documentations contained in the previously approved product, no additional requirements have to be fulfilled.

The Federal Food, Drug and Cosmetic Act (FD&C Act) and its subsequent amendments form the centre of all possible legal bases in the US.

United States (US)

Situation in the US

The category of submissions generally possible in the US are in Table 2. These mainly include new drug application (NDA); abbreviated new drug application (ANDA) for generics; hybrid applications for drugs falling in between an NDA and ANDA; and originator biologic license application (BLA) and biosimilar/interchangeable BLA. The table also provides other key information regarding other aspects of development and submission activities.

The Federal Food, Drug and Cosmetic Act (FD&C Act) and its subsequent amendments form the centre of all possible legal bases in the US. The entire FD&C and subsequent amending status are listed in Title 29 in Chapter 9 of the US Code (As Amended Through P.L. 115-271, Enacted October 24, 2018). Selected case studies are presented below with further explanation on how these different regulatory pathways are effectively used in practice. However, a detailed discussion as performed for the section on EU situation (see above) is not in the scope of this article.[26]

FD&C 505(b)(1)

In general, a 505(b)(1) application requires a full dossier. As per the process used by the US FDA, any submission under FD&C 505(b)(1) is assigned an NDA classification code that is also reassessed at the time of approval by US FDA. All applications under 505 (b)(1) would not mean a new molecule entity , i.e., classified as Type 1 under NDA classification codes. The NDA classification codes include Type 1 to Type 10, e.g., a new indication or claim for the same application has an NDA of Type 6. The purpose

	Reference to	Development and submission activities	Exclusivity and data protection[b]	Need for PSP
	Active comparator/ placebo	8-15 years	5 years for NCE, 7 years for ODE	Yes
	Yes, the US RLD or reference standard	2-5 years	180-day exclusivity possible for patent challenge, 180-day exclusivity for first to launch a competitive generic therapy	No
	Active comparator, generally the US RLD	5-8 years	0-7 years, depending on designation and the need for new clinical studies	Yes per PREA
	Active comparator/ placebo	8-15 years	5 years for NCE, 7 years for ODE	Yes Applications Covered by Section 505(b)(2)
	Reference product	7-10 years	No	Yes per PREA but limited scope based on reference product PREA requirements

Abbreviations: ANDA, abbreviated new drug application; BLA, biological license application; CMC, chemical manufacturing and controls; D&C, food, drug and cosmetic act; PC, patent challenge; PD, pharmacodynamics study; PK, pharmacokinetic study; PREA, paediatric research equity act; NCE, new chemical entity; NDA, new drug application; NME, new molecule entity; ODE, orphan drug exclusivity; PSP, paediatric study plan; RLD, reference listed drug; VAM, value added medicine.

of these codes is to help the US FDA to coordinate an effective review process at Central Drug Evaluation Research and to promote consistency across review divisions.[27] All new applications as NDA are approved using this legal basis.

FD&C 505(j)

This regulatory pathway is meant for generics and as noted in Table 2, some bioequivalence data are requested with no additional studies requiring pre-clinical, clinical efficacy, and safety data, or paediatric data. It could be directly compared to legal basis 10(1) in the EU. The FDA has issued several guidance documents over recent years for generic applicants in regard to the requirements including bioequivalence study requirements, 180-day exclusivity, and so on. The FDA also provides recommended dissolution methods and product-specific guidance for generic drug development.[28,29,30]

FD&C 505(b)(2)

The most relevant pathway for all applications aiming to obtain an approval for differential products, such as value added medicines, is the 505(b)(2) pathway, facilitated by the FD&C Act. Legal basis 505(b)(2) permits the US FDA to rely on data not developed by the applicant alone and therefore, sometimes the term hybrid application is used. Some of the scenarios where 505(b)(2) pathway could be used include change in dosage form, strength, route of administration, and substitution of an active ingredient in a combination product. The FDA has also provided guidance regarding regulatory and scientific consideration for applications using 505(b)(2).[31,32]

After an overview of different regulatory pathways with focus on generics and biosimilars, it is clear that there are different options available within the regulatory framework that could be used in both the EU and the US.

PHS 351(a) and PHS 351(k)

The Public Health Service (PHS) Act Section 351 is responsible for biological products. However, biological products are a subset of drugs and, as previously mentioned, all drugs in the US are regulated under provisions of the FD&C Act. In the case of biological products, these are licensed under section 351 of the PHS Act in view of specific requirements for manufacturing controls for such products regulated under this Act. In the case of biosimilars, an abbreviated licensure pathway for biological products was created through the Biologics Price Competition and Innovation Act of 2009. To use this licensure pathway, a biological product should be biosimilar to or interchangeable with an FDA-approved biological product. The original biologics used the approval pathway of 351(a), which is also referred to as the Original BLA pathway.[33,34]

Before the 351(k) regulatory pathway was established for biosimilars, there had been approvals for "follow-on" proteins in the US, one of the case examples being somatropin (Omnitrope®), which was filed under the 505(b)(2) pathway. It was categorised under Type 5 – new formulation or new manufacturer submission classification for review – and was later approved in the US. In the absence of 351(k), choosing the 505(b)(2) regulatory pathway provided the applicant an opportunity to leverage existing data to reduce development requirements for these follow-on products. In addition, some follow-on protein approvals in the US were obtained using the regulatory pathway of the 351(a) of PHS Act, including insulin glargine (Lusduna® and Basaglar®). However, the introduction of the 351(k) pathway provided a dedicated pathway for the approval of biosimilars. Biosimilars in the US, following the implementation of this pathway, now have a well-defined legal pathway and clear guidance from US FDA with the possibility of targeted development and submission activities for applicant or sponsor. A review into recent approvals has shown that the requirements are clearly laid out and the review process by the FDA is well established.[35,36,37] It has also been announced by the FDA that Congress will implement a direction that certain biologics including insulins will be regulated under PHS 351 starting March 2020.[38]

Author's standpoint

After an overview of different regulatory pathways with focus on generics and biosimilars, it is clear that there are different options available within the regulatory framework that could be used in both the EU and the US. In certain cases, e.g., medicinal product or biologic or differential product (i.e., changes in dosage form or strength or combination of drugs or drug with device), there is more than one option that might be available to the applicant or sponsor. Any new development and submission strategy requires thorough planning and full understanding of the medicinal product itself, which could effectively be used to optimise effort for targeted development and submission activities. The case

examples presented also show that planning might have a direct impact on the financial budget and timelines of the projects. The impetus on planning lies completely on the applicant or sponsor as regulatory bodies encourage discussion on unprecedented cases. The development and submission activities irrespective of the kind of legal framework used either in the EU or the US are most essential activities for the applicant or sponsor. Therefore, it is in their best interest to plan these if possible, to perfection. The journey leading to a final submission-ready dossier is not an easy one. However, development and submission teams that have a good understanding of the legal framework, oversight of development activities, knowledge of the requirements of the CTD dossier, and submission writing expertise can bring results of cherished approvals. This also helps both pharma industry and regulators to achieve their aim, which is to have a safe and efficacious product complying all good practices for the patients.

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Conflicts of interest

The author declares no conflict of interest.

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Appendix

Appendix 1. Differences among applications submitted and approved under FD&C Act Section 505 [28,31,32,34,39,42]

	505 (b) (1) Application	**505 (b) (2) Application**	**505 (j) Application**
Patent and Exclusivity Information	Submit information on patents claiming the drug or a method of use; exclusivity request claiming exclusivity	Submit information on patents claiming the drug or a method of use (if any); generally, a patent certification (Paragraph I, II, III or IV) or "section viii" statement is required; exclusivity request claiming exclusivity and exclusivity statement the listed drug is subject to exclusivity (if any exists)	Patent certification (Paragraph I, II, III or IV) or a "section viii" statement is required; exclusivity statement the RLD is subject to exclusivity (if any exists)
Five-Year Exclusivity Subject to five-year exclusivity for 505(b)(1) or 505(b)(2) applicants.	Prevents the submission of an ANDA or 505(b)(2) application for 5 years after NDA approval, except an ANDA or 505(b)(2) application with a Paragraph IV certification to an Orange Book-listed patent may be submitted after 4 years	Only for applications for NCEs; prevents the submission of an ANDA or another 505(b)(2) application for five years after application approval, except an ANDA or other 505(b)(2) application with a Paragraph IV certification to an Orange Book-listed patent may be submitted after 4 years; also subject to NDA holder's exclusivity	No Exclusivity
Three-Year Exclusivity Subject to three-year exclusivity for 505(b)(1) or 505(b)(2) applicants.	Only if one or more of the clinical studies, other than BA/BE studies, was essential to the product's approval; prevents FDA from making effective an ANDA or 505(b)(2) application for the conditions of approval of the NDA	Only if one or more of the clinical studies, other than BA/BE studies, was essential to the product's approval; prevents FDA from making an ANDA or other 505(b)(2) application effective for the conditions of approval of the 505(b)(2) application; also subject to NDA holder's exclusivity	No Exclusivity
Orphan Drug Exclusivity Subject to 7-year exclusivity for 505(b)(1) or 505(b)(2) applicants.	Prevents FDA from approving an application for the same condition for 7 years	Prevents FDA from approving an application for the same drug for the same condition for 7 years; also subject to NDA holder's exclusivity	No Exclusivity
Antibiotic Exclusivity Subject to 5-year exclusivity for 505(b)(1) applicants.	Provides an additional five-year exclusivity for qualified infectious disease products	Not Applicable	Not Applicable
Paediatric Exclusivity Subject to 6-month exclusivity for 505(b)(1) or 505(b)(2) applicants.	Extends by six months all other types of patent and non- patent market exclusivity an NDA holder may have under the FD&C Act for a particular active moiety	Extends by six months all other types of patent and non-patent market exclusivity an NDA holder may have under the FD&C Act for a particular active moiety; also subject to NDA holder's exclusivity	No Exclusivity

Continued opposite

	505 (b) (1) Application	505 (b) (2) Application	505 (j) Application
180-Day Exclusivity Subject to 6-month exclusivity for 505(j) applicants.	Not Applicable	Not Applicable	Available to any "first applicant" that files an ANDA with a Paragraph IV certification; prevents FDA from approving other ANDAs submitted by applicants that are not "first applicants"
Orange Book Listing	Included in the Orange Book as a listed drug; may be identified as an RLD	Included in the Orange Book as a listed drug; can be identified as a therapeutic equivalent (e.g., "AB-rated") to the listed drug if BE is demonstrated and also is a pharmaceutical equivalent	Included in the Orange Book as a listed drug; can be identified as a therapeutic equivalent (e.g., "AB- rated") to RLD if BE study(ies) is/are demonstrated and also is a pharmaceutical equivalent; listed in the Orange Book as a "pharmaceutical alternative" without a therapeutic equivalence evaluation code if approved under an approved suitability petition

NB. Biologics (innovator) under 351(a) Act will get 12 years of market exclusivity. Under Biosimilar 351(k) Act, the period of exclusivity for biosimilar depends on a number of factors and can range between 12 months and 42 months.
Abbreviations: ANDA, abbreviated new drug application, BA/BE, bioavailability and bioequivalence; FD&C, food, drug and cosmetics act; NCE, new chemical entity; NDA, new drug application; RLD, reference listed drug.

Appendix 2. Registered trademarks referred to in this article with their respective owners

Trademark	Company
Basaglar	Eli Lilly & Co.
Buvidal	Camurus AB, Sweden
Crusia	Laboratorious Pharmaceuticos Rovi
Farmprojects	Farmprojects S.A.
Forsteo	Eli Lilly & Co.
Glyxambi	Boehringer Ingelheim International GmbH
Lusduna	Merck Sharp & Dohme
Movymia	Stada Arzneimittel AG
Novarsc and Lipitor	Pfizer, Inc. and Pfizer Ireland Pharmaceuticals
Olmetec Plus and Daiichi Sankyo	Daiichi Sankyo Co. Ltd.
Omnitrope and Ziextenzo	Novartis AG
Pelmeg	Comfa Biotech S.L.
Prostap	Takeda Pharmaceutical Co.
Ratiopharm	Ratiopharm GmbH
Subutex	Indivior UK Limited
Terrosa	Richter Gedeon Nyrt