Regulatory Implications Using API Cocrystals for Generic Medicinal Products within the EU and US

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Contents

1 Abstract

The characterization of an active pharmaceutical ingredient (API) is one of the most important stages in the development of a medicinal product. Unfortunately, not all APIs posses ideal properties for their use in a pharmaceutical. For instance, many newly discovered active substances exhibit poor solubility. However, methods have been developed to alter and enhance various properties of an API. A strategy that is frequently applied to improve the solubility of an active substance is by generating salt derivatives. However, this approach has its limitations as not every API possesses the characteristics to be converted into a salt.

In recent years, a new engineering approach has been developed to generate new API forms with desirable properties. Pharmaceutical cocrystals are a results of these developmental efforts and enable medicinal product manufactures to modify already existing APIs or to generate new ones with tailored characteristics. Beside the scientific challenges that are associated with the development of a pharmaceutical, manufacturer are also confronted with regulatory requirements that have to be fulfilled in order to obtain an approval and enter the market. Since pharmaceutical cocrystals are a relative new API-form, not much regulatory guidance concerning cocrystals has been formulated for two of the biggest pharmaceutical markets, namely the United States of America (USA) and the European Union (EU).

This thesis shall analyze which regulatory requirements have to be fulfilled in order to use pharmaceutical cocrystals within generic pharmaceuticals that are intended for the USA and EU. This thesis will only discuss the requirements for immediate release and oral dosage forms containing an API cocrystal. Regulatory guidance documents published by the European Medicines Agency and the Food and Drug Administration will be consulted and discussed to see if pharmaceutical cocrystal are eligible for generic applications in both the USA and EU and if the outlined characteristics of this API form fit into the current legislation of both territories. Finally, this thesis will also discuss which data should be presented within the common technical document to justify the usage of cocrystal in a generic medicinal product.

2 Introduction

Cocrystals are not a new phenomenon within the supramolecular chemistry community. During the last 30 years, several advancements on growing, engineering and characterization of co-cyrstals have been made. Due to the possibility of engineering crystals with a wide range of physicochemical properties, cocrystals have only recently entered the scope of drug development.[1] As a result of this trend, cocrystals engineered for the purpose of using them in medicinal products have been termed pharmaceutical cocrystals.

What makes a pharmaceutical cocrystal so attractive for the industry? As mentioned previously, cocrystals can be designed to exhibit an array of different chemical and physical properties. This rational design process has the potential to be a valuable tool to improve certain aspects of active pharmaceutical ingredients (APIs). For instance the stability and solubility can be considerably enhanced through crystal engineering. Especially solubility is a property that is a critical aspect when developing new APIs. Recent publications point-out that approximately 40 % of currently marketed active substances and an estimated 70 % of new chemical entities display poor solubility.[2–4]

A classical approach to modify the properties of an API is by generating a salt derivative. For the formation of a salt an API has to harbor chemically functional groups that are ionizable. Prominent examples of molecules used for salt formation are acidic or basic molecules. This method of solid-state chemistry therefore has its limitation as not all pharmaceutical active substances posses such ionizable groups. The formation of cocrystal on the other hand, can be more widely used and relies on other physicochemical properties, which will be discussed in detail within the next sections.

3 Definition of Cocrystals

3.1 Scientific Definition of Cocrystals

Solids are one of the fundamental and classical states of matter, beside liquids and gases. Solids posses the characteristic that the atoms, ions or molecules are tightly packed and cannot move freely within a given space. This state of matter can be further divided into sub-groups depending on the arrangement of the components of the solid. Solids that do not display any form of order are know as amorphous solids. On the other hand, solids in which the compounds are arranged in regular patterns are known crystalline solids. Crystals are composed of a lattice in which the atoms, ions or molecules are arranged in a defined stoichiometric ratio and interact with each other via different types of atomic interactions.

The group of crystals can be further divided into several sub-groups. The categorization relies on the number of partners involved in the formation of the crystal lattice. Crystals composed of a single entity are the simplest example of a crystal. In contrast to single entity crystals, crystalline structures that are formed by two or more components can be formed by different interaction types such as covalent, non-ionic and van der Waals interactions. Crystals formed by ionic interactions are know as ionic solids, which are also often referred to as salts.[5]

Known examples of solids with crystalline character that are formed by non-ionic interactions are solvates, hydrates and cocrystals. Illustrated in Figure 1 are schematic representations of the different crystalline solids composed of two different compounds, whereas one of the compounds in the crystal lattice is an API. However, it should be noted that there are crystals known in the solid-state community that are formed through a combination of both ionic and non-ionic interactions. However, this thesis will only focus on the simplified classification of solids, as previously outlined in this paragraph.

Hydrates and solvates contain either water or a solvate molecule, respectively, that interacts with a different substance to form a crystal lattice.[6,7] Cocrystals, on the other hand, do not posses a clear-cut definition within the scientific community. Until today, it is still a matter of debate which types of solids can be considered as cocrystals. Table 1 lists the various definitions

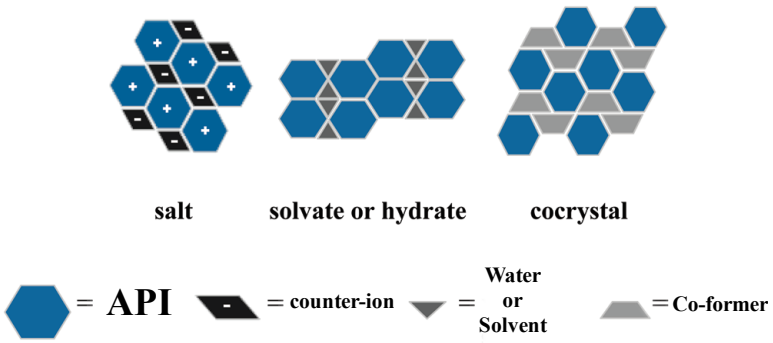

Figure 1 Schematic representation of salts, hydrates, solvates and cocrystals APIs present as a salt are composed of the active substance that posses a certain charge (either positive or negative) and interacts with a counter-ion (possesing the opposite charge as the API) to form the lattice. When the API interacts with water or a solvent then hydrate or solvate crystals are formed, respectively. When an API forms a crystal lattice with a co-former via non-ionic interactions, then pharmaceutical cocrystals a formed. Figure adapted from Schultheiss and Newman 2009[1]

that have been formulated within the scientific field for cocrystals.[8–14]

As shown by this table, cocrystals can posses completely different characteristics, depending on which definition is applied. For instance some scientists take into account the aggregate state of the compounds at ambient temperature, whereas other completely neglect this aspect. Another physical property that is either included or excluded into the cocrystal definition concerns the electric charge of the components. However, there is also a characteristic that all agreed upon, namely that a cocrystals are composed of two or more components that form a crystal.

In the literature, the term of pharmaceutical cocrystals can be found. Luckily, defining this type of cocrystal is rather simple. Cocrystals in which an API is incorporated into the lattice is considered a pharmaceutical cocrystal, independent of which scientific definition is used.[1] However, the vast amounts of definitions for cocrystals that have been formulated are counterproductive to formulate regulatory guidelines for this API form. Therefore, the following sections will elaborate on how the European medicines agency (EMA) as well as the United States Food and Drug Administration (FDA) have approached the topic of defining pharmaceutical cocrystals.

Table 1 Different definitions of cocrystals within the scientific community

Author	Definition of a co-crystal
Stahly, G. P.	"a molecular complex that contains two or more different molecules in the same crystal lattice"
Nangia, A.	"multi-component solid state assemblies of two or more compounds held together by any type or combination of intermolecular interactions"
Childs, S. L.	"crystalline material made up of two or more components, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule"
Aakeröy, C. B.	"compounds constructed from discrete neutral molecular species...all solids containing ions, including complex transition-metal ions, are excluded" "made from reactants that are solids at ambient conditions" "structurally homogeneous crystalline material that contains two or more neutral buildingblocks that are present in definite stoichiometric amounts"
Bond, A.	"synonym for multi-component molecular crystal"
Jones, W.	"a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, oftenincluding hydrogen bonding"
Zaworotko, M. J.	"are formed between a molecular or ionic API and a co-crystal fromer that is a solid under ambient conditions"

Table adapted from Schultheiss and Newman 2009[1]

3.2 EMA's scientific view of Cocrystals

The EMA has published a reflection paper concerning the usage of cocrystals as active substances within medicinal products.[15] Since a unifying definition of cocrystals is a matter of debate within the scientific community, the EMA has communicated what characteristics they consider essential in order for a substance to be accepted as a pharmaceutical cocrystal.

According to the EMA, pharmaceutical cocrystals"... *are in general defined as homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts). The components of a cocrystal may nevertheless be neutral as well as ionized*"[15]

This definition proposed by the EMA, mostly agrees on characteristics that are mostly shared by the numerous definition of cocrystals within the field of solid state chemistry (see section

3.1). As mentioned in the EMA definition, pharmaceutical cocrystals may contain substances that are present as ions. However, the charged moiety within the active substance or the co-former must not be involved in the crystal formation.

Interestingly, the EMA does not state if a component of the cocrystal has to be in a liquid or solid state. Beside the aggregate state, it is also not mentioned if the cocrystal definition is only valid at ambient temperature or not. Many in the scientific community argue that the components of a cocrystal must be present as solids at ambient temperature in order to be categorized as a cocrystal. This view would have the consequence that water, solvents or liquid active substances cannot form cocrystals. However, the EMA clearly states that according to their scientific point of view solvates (a solvent functions as a co-former) and hydrates (water functions as a co-former) are considered as subgroups of cocrystals. This view is further broadened for active substances that are present as liquids. Therefore, it is likely that both the API and coformers may be present as liquids and solids within the crystal lattice.

A key statement within the EMA definition is that pharmaceutical cocrystal formation does not rely on ionic bonds. Therefore, assembly of a crystal lattice must be established by weaker interactions such as hydrogen bonds, π-stacking, dipol-dipol- and van der Waals interactions. This aspect is essential in order for the agency to evaluate if a substance fulfills the requirements of a cocrystal (see section 5.2.1).

In summary, the EMA defines pharmaceutical cocrystals as solids that are composed of one or more components (at least one of them is the API) that interact with each other by non-ionic interactions and form a crystalline structure. Additionally, the components may be present in the crystal lattice as liquids, solids or ions.

3.3 FDA's scientific view of Cocrystals

In 2013, the FDA has published a first guidance concerning the regulatory classification of cocrystals.[16] Within this document the FDA defines a cocrystal as a solid with a crystalline morphology and the crystal lattice is composed of two or more molecules. One of these molecules is the pharmaceutical active ingredient and interacts, on a molecular level, with one or more so-called coformers. Within the same guidance it is stated that co-formers must interact with

the active ingredient via non-ionic interactions in order for the complex to be considered a cocrystal. Additionally, co-formers and API have to be neutral and be present within the same crystal lattice as the active substance.

By using the previously mentioned definition, cocrystals are distinct from other solid state forms such as polymorphs and salts. The FDA generally considers polymorphs as solids that only contain a single compound within their crystal lattice.[16] However, a single active substance can display different polymorphs. Salts, on the other hand, are formed through the interaction of oppositely charged molecules that result through acid-base reactions. As cocrystals consist out of two or more components and each posses a neutral charge, this solid state form creates a new distinct group within the classification of solids according to the FDA.

Even though cocrystals are considered a distinct solid state group, the United States (US) agency does not consider cocrystals as APIs. The FDA stated that the active substance cocrystallizes with an excipient to form an "API-excipient" complex and therefore should be treated as a drug product intermediate. As a consequence of this statement, these drug product intermediates solely have the purpose to improve the drug performance such as solubility, bioavailability, stability and dissolution. Therefore, cocrystals do not function as APIs but as a tool to achieve a certain functional outcome of the medicinal product.

The classification of cocrystals as a drug product intermediate generated criticism within the scientific community of both academia and the industry.[17] In addition to this critic, uncertainty on how to interpret the guidance as well as pratical problems arised. Regarding the latter, Cocrystal are normally manufactured in drug substance facilities. However, cocrystals are defined as drug product intermediates and this in return makes it necessary to apply additional current good manufacturing pratice measures that are norammaly not required for a drug substance manufacturer.[18]

These legal, regulatory and quality assurance challenges persuaded the FDA to revise the above-mentioned guidance paper. The revision was published in 2016 using the same title as the initial document and was then finalized in 2018.[19] Within this new guidance, a cocrystal is still defined as a crystalline material that is composed of two or more different molecules, whereas one of them is the API. However, the revised definition also mentions that the components of

the cocrystal are present in a defined stoichiometric ratio within the crystal lattice, which is formed by non-ionic and non-covalent bonds. This refined definition takes the defined ratio of both API and co-former(s) into account as well as how these interact with each other. However, the new guideline does not comment if a certain aggregate state of both API and coformer(s) have to be present, for example a solid at ambient temperature.

Interestingly, the revised guidance does not explicitly mention if API, co-former or both have to be neutral or can be present as an ion within the cocrystal (this comment is only valid if the resulting ions do not form bonds that in return result in crystal formation). Additionally, a definition is given on what characteristics a co-former has to posses. According to the FDA a co-former is a component that interacts with an API within the same crystal lattice, via non-ionic interactions, is not a solvent (including water) and is typically non-volatile.

Beside these new detailed and refined definitions of cocrystals and co-formers, the solid-state classification of cocrystals has been changed within the guidance. The FDA distinguishes cocrystals from polymorphs, which are now defined as substances that exhibit either crystalline, amorphous, solvate or hydrate forms.[20,21] However, from a scientific stand-point, cocrystals can be considered as a special case of solvates and hydrates. This in return leads to the conclusion that cocrystals should now be considered as a special case of polymorphs.[21] However, this is actually contradictory to the statement of the agency made at the beginning of this paragraph in which the FDA distinguishes cocrystals from polymorphs.

In summary, the FDA defines pharmaceutical cocrystals as crystalline solids that are composed of two or more components. The crystal lattice is formed through the non-ionic interactions between API and coformer, which are most likely neutral within the unit cell. Additionally, the coformer is not present as a solvent or water and is non-volatile. As a consequence of this definition, cocrystals can be viewed as a special case of a polymorph.

3.4 Comparison between the scientific views of the EMA and FDA

At first glance, both definitions of cocrystals from the EMA and the FDA share several common points. For instance, both agencies clearly state that a cocrystal are composed of one or more compounds that are present within the same crystal lattice and interact with each other via

non-ionic bonds to form the solid. However, when closely comparing both the reflection paper of the EMA and the guidance document of the FDA, one can find different standpoints of both agencies concerning the properties of both the API and co-former.

The EMA mentions that both the API and the co-former can be neutral or posses either a negative or positive charge. The only prerequisite is that the charged moiety of the compound is not involved in the formation of the crystal. The FDA on the other hand does not explicitly comment on this topic within the recent guideline. The outdated document from the FDA mentions that all molecules present within a cocrystal have to be present in a neutral state. This clear statement is missing in the new guidance document. Therefore, it is not known if charged compounds can be used in a cocrystal if the lattice is purely formed by non-ionic interactions.

In addition to the presence or absence of charged compounds within the crystal lattice, both the EMA and the FDA have different opinions concerning the aggregate state of the API and co-former. The EMA states that it has little scientific value to take the aggregate state into account for the definition of a cocrystal. The FDA does not clearly state its position on this matter, similar to the presence or absence of charged molecules described in the last paragraph. However, the FDA mentions in its latest guidance document that cocrystals are special cases of hydrates and solvates. Therefore, a conclusion can be drawn that the US agency distinguishes between hydrates, solvates and cocrystal and, therefore, the compounds of the cocrystal have to be present as solids at ambient temperatures. However, the best advice would be to contact the agency and discuss this topic during a scientific advice to receive a clear statement.

Interestingly, the fact that the FDA considers cocrystals as a special case of solvates and hydrates is another key difference to the view of the EMA. The EMA has the scientific opinion that cocrystals, solvates and hydrates share the same general concepts for the formation of crystals. Therefore, the agency does not distinguish between these three terms as they belong to the same solid state family. The definitions of cocrystals laid-down in the previous sections are the basis for both the EMA and the FDA to draw-up the regulatory framework for pharmaceutical cocrystals. The next chapter shall examine the legal and regulatory basis for generic medicinal products before discussing if cocrystal APIs fit into the EU and US legislation and fulfill the requirements for abridged applications in both territories.

4 Regulatory frame work for Generics

4.1 Within the European Union

Since the founding of the European Union (EU) all member states have focused on extensive collaboration efforts within different sectors such as finance and economy. One of the biggest achievements of the EU, however, was the endeavor to formulate EU legislative with a focus on medicinal products. The result of these efforts are a body of different regulations and directives concerning topics such as clinical trails, orphan drugs, post-marketing monitoring and the registration of medicinal products.

A great emphasis has been made to progressively harmonize the procedure of granting marketing authorizations across all member states. Marketing authorizations for medicinal products can be obtained by using either the centralized, decentralized, mutual recognition or national procedure. During the centralized procedure, the scientific evaluation is carried-out by the EMA and the market authorization is granted by the Commission. The other procedures involve the national competent authorities that cooperate with each other during the evaluation of the registration dossier (an exception here are purely national procedures).

Generics can use all of the previously mentioned regulatory pathways to enter either only certain national territories or the whole single EU market. Even though the different marketing authorization procedures vary, all of them rely on the same legal basis for the registration of generic medicinal products. This basis is laid-down within the Directive 2001/83/EC and represents one of the key legislative documents regulating pharmaceuticals within the EU.

4.1.1 Framework for Abridged Applications According to Directive 2001/83/EC

Within Directive 2001/83/EC, the regulatory foundation for medicinal products was formulated for the EU as well as the EEA. Within this legislation, various definitions were formulated such as what is considered an active substance, excipient or a medicinal product. The directive also describes the necessity of obtaining a marketing authorization (MA) before a medicinal product can be distributed. Additionally, the same directive also describes the regulatory pathways on

how to obtain a MA. Not only innovative medicinal products are introduced in the directive, but also the regulatory definition of a generic. Beside the definition of a generic, the exclusivity periods abridged applications have to consider before applying and receiving a MA are also outlined.

Within article 10(1) of the directive it is stated that an applicant for a generic medicinal product is not required to present results from non-clinical tests and of clinical trials, if it can be demonstrated that the medicinal product in question is a generic of a reference medicinal product. The reference product may only be referred to, however, if it is or has been authorized by the Community or a Member State of the EU for a period of at least eight years.[22] These eight years are often referred to as the data exclusivity period. Both the national competent authorities as well as the EMA are prohibited to accept any generic marketing authorization applications (MAA) before this period for the reference medicinal product has expired.

However, even after this data exclusivity period and after granting of a market authorization, the manufacturer of a generic my not place the medicinal product within the market before the market protection period has elapsed. This market protection period spans over a time of two years and starts at the end of the data exclusivity period. Only after this ten year period may a generic medicinal product be commercially launched within the community or EEA. This ten year protection of the reference medicinal product may also be extended by an additional year. The prerequisite for this is that the reference medicinal product is granted a marketing authorization for one or several new indications within the first eight years of its initial market authorization and has proven a significant clinical benefit in comparison to existing therapies.

In conclusion, reference medicinal products are protected for a total of ten years upon granting of a (the first) market authorization with the possibility of extension for an additional year. This legal framework has been known within the community as the 8+2(+1) rule. Article 10(1) outlines on how the reference medicinal product is protected by law, the time lines on when a generic application may be filed and which data do not have to be provided by the applicant. However, an exact definition on what a generic medicinal product exactly is cannot be found in this section of the directive. Nevertheless, the data and marketing exclusivity period are an integral part of identifying what is eligible for an abridged application within the EU as these define what can be considered a reference medicinal product for a generic application (see

section 4.1.2).

The previous paragraph highlighted at what time point an abridged application can be submitted and what requirements a reference medicinal product has to fulfill. But how exactly is a generic medicinal product defined within the legislation? According to the Directive 2001/83/EC Article 10 (2)(b):

"[a]"generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies."

In addition to this definition, the directive also mentions that variations of an active substance such as salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives may be considered as the same active substance and be used for a generic medicinal product. However, this statement is only valid if these active substances do not differ in terms of safety and efficacy compared to the parent API. If a newly developed medicinal product does not meet the criteria of a generic medicinal product, e.g. bioequivalence cannot be demonstrated (e.g. a lower amount of the active substance is needed to achieve the same plasma level as seen in the reference product), route of administration or the active substance(s) is changed, then an alternative regulatory pathway can be considered to obtain a market authorization.

This pathway is described in article 10(3) of Directive 2001/83/EC and is also known as a "hybrid application". The applicant has to present in this regulatory route to the authorities data that complement the data of the innovator and demonstrate safety and efficacy of the modified medicinal product, e.g. change in the active substance. However, this regulatory pathway is different from the generic route and will, therefore, not be further discussed in the following section.

4.1.2 Eligibility for EU Generic Applications using Cocrystal APIs

As outlined in Directive 2001/83/EC, generic medicinal products can contain APIs that deviate from the originator. Variations such as salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives according to the legislation in the EU are considered as the same active

substance. Even polymorphic forms of the mentioned API variations are suitable for a generic application. Do cocrystals fit into the EU definition of a generic and can they be used in an abridged application or do these API variants have to follow a hybrid application approach?

The lattice within cocrystals is formed by the non-covalent interactions of the API(s) with one or more co-formers. These weak interactions are thought to be disrupted upon dissolution. This case is highly similar to what happens to an API that is present as a salt within a medicinal product. The end result in both API variants is that upon dissolution the same active substance is released and can then be absorbed. Due to their behavior upon dissolution, the EMA mentions in their reflection paper that both salt and cocrystal APIs have the same regulatory status. Nevertheless, the hypothesis that the same API is released has to be demonstrated during dissolution experiments and bioequivalence studies. Therefore, cocrystals are eligible for generic applications as laid out in Article 10 (2)(b) of directive 2001/83/EC.

The dissolution concept of a crystalline API, may it be a single API, salt or cocrystal, is normally present with the oral administration of a medicinal product. However, abridged applications using cocrystals are not necessarily restricted to this route of administration. Other forms of administration may be eligible for generic applications if it can be demonstrated that there are no differences in terms of safety and efficacy compared to the originator when using a cocrystal API.

In conclusion, pharmaceutical cocrystals are considered similar to medicinal products containing an API that is present as a salt. This qualifies cocrystals to apply for an abridged application from a scientific and regulatory standpoint. If the reference medicinal product to which the generic product containing a pharmaceutical cocrystal is referring to has been present on the market within the community for at least eight years, then also the legal requirements are fulfilled for the submission of a generic application.

4.2 Within the United States of America

The legal framework for generic medicines within the United States was established in 1984. In this year, the "Drug Price Competition and Patent Term Restoration Act" came into force.[23] This act is also known as the "Hatch-Waxman-Act" and is the regulatory foundation for generics in

the US. This legislative in its core establishes the different exclusivity incentives for innovators and generics companies. Additionally, a new regulatory pathway for generics was introduced in order to overcome the lack of generic products within the US market.

4.2.1 The Hatch-Waxman-Act

As mentioned in the previous section, one intention of the Hatch-Waxman-Act was to serve the interests of both innovators and the generic industry. One measure to secure the interests of the innovator industry was to grant certain exclusivity rights for a new medicinal product.

Innovators of pharmaceuticals, as many other industries within the US, profit from patent protection that last for a period of normally 20 years and start from the date of filing.[24] However, when a patent is filed, a pharmaceutical is normally still in development for several years and also goes through an extensive approval process. Innovators, therefore, have a reduced period of time to financially benefit from their patent when the medicine finally enters the market.

In order to minimize the protection gap that arises between patent filing and market entry, the Hatch-Waxman-Act grants the applicant of a new chemical entity (NCE) a period of data exclusivity for five years, which starts from the issue date of the market authorization. During post-approval, an additional three years of a clinical study data exclusivity can be granted to the innovator. The prerequisite for this exclusivity is that new clinical studies have been conducted and that the outcome of these studies lead to new formulations, new dosage regimes or the inclusion of new patient populations. The data exclusivity period is only granted to these innovative findings and not to the basis marketing authorization. Finally, the FDA may request from the applicant of a new drug application (NDA) that clinical studies are conducted with a pediatric population using the new drug. As a result of performing such studies, an extension of six months can be granted to any market or patent exclusivity.

The previous section mentioned that the NCE exclusivity period is primarily a method to protect the innovator from competition, once it has received approval from the FDA and has entered the market. During this period no generic application filing is accepted by the agency. However, the Hatch-Waxman-Act has introduced a regulatory mechanism to promote competition between innovators and generic companies. The manufacturer of a generic drug can circumvent

the five year exclusivity by submitting a generic application including a so-called paragraph IV certification. This certification allows the submission of a generic application after four years instead of the five year exclusivity period and rewards the first approved generic using this approach a 180 day market exclusivity.

A paragraph IV certification from the applicant of an abridged application claims that patents associated with the reference listed drug (RLD) are invalid or will not be infringed when the generic drug enters the market. The patents that are linked to the RLD and can be found within the *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the orange book). Therefore, clarification of any patent issues is an essential part for abridged applications within the US. Beside the paragraph IV certification, there are also paragraph I-III certifications. However, these certifications claim that no patents have been listed in the orange book, or that these have expired or will expire (including any exclusivities) before the FDA approves the application. Generic applications containing paragraph I - III certifications cannot file before the NCE exclusivity has expired. Interestingly, in the US both patent and exclusivity periods are tied closely to an abridged application, whereas in the EU only exclusivity periods are taken into account.

Before the Hatch-Waxman-Act there were only few generic drugs on the market. The reason for this was that the regulatory framework requested that generic companies conduct non-clinical and clinical studies to prove that their drug is safe and effective as the one from the innovator. Alternatively, the generic applicant may only make reference to scientific or medical literature showing that the active ingredient in scope of their application is considered safe.

However, these two pathways did not provide the anticipated rise of generic drugs within the market. The reason for this is that conducting non-clinical and clinical studies is a costly endeavor, which is not attractive for generic companies as they intend to offer their drug at a lower price than the innovator.[25] On the other hand, literature on the active ingredient were rather scarcely available or the innovator did not make its research accessible to the public.[23]

To overcome the drought of generic drugs within the US market, the Hatch-Waxman-Act introduced two distinctive regulatory pathways. The first pathway is described within Section 505 (j) of the Federal Food, Drug and Cosmetic Act. This regulatory procedure is also know as the

abbreviated new drug application (ANDA).

This section states that an ANDA has to provide information that a drug, to which the application is referring to, is listed within the orange book as a RLD. Additionally, the application should demonstrate that the generic drug contains the same active substance as the RLD. Furthermore, information shall be presented in the application showing that the new generic drug posses the same strength, dosage form, route of administration and same labeling (in terms of indication). Additionally as stated in 21 CFR 314.94(a)(9), a generic for parenteral use must contain the same inactive ingredients and in the same concentration as in the RLD. However, substances used as preservatives, antioxidants or buffers may differ from the RLD. These different excipients used in the generic medicinal product can be approved by the FDA if it can be demonstrated that these components do not have an impact on the safety or efficacy. If all of the previously mentioned conditions are met, then an ANDA can be submitted to the FDA, the earliest after the four years of the NCE exclusivity have passed and a paragraph IV certification is included in the application.

If any of the before mentioned conditions are not met, for instance a different active substance is used or a different dosage form, then the new drug is eligible for the second application process that the Hatch-Waxman-Act has installed. This regulatory pathway is described in Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. This process is known under the term 505(b)(2)-filing and represents a hybrid of a full NDA and an ANDA. This pathway is however, out the scope of this thesis as only pure generic applications are discussed.

4.2.2 Eligibility for US Generic Applications using Cocrystal APIs

As outlined in 21 U.S.C. 505(j) a medicine has to demonstrate that it has the same route of administration, dosage form, strength, indication and active substance in order to be considered applicable for an ANDA. A strong emphasis is made that for a medicine to be eligible for an ANDA the API is the same as the one used in the RLD. The term "same as" excludes the possibility of using API derivatives such as salts, ethers and esters.[21] Different polymorphs of an API, on the otherhand, are still eligible for an ANDA.[21]

The FDA views cocrystals as special cases of solvates (see section 3.3). Solvates are considered

one of three defined classes of polymorphs. Within the cocrystal guidance, the FDA clearly states that cocrystals have a similar standpoint as polymorphs of an API and that these crystals are not seen new APIs. Therefore, pharmaceutical cocrystals can be considered as the same API and can be utilized in a medicinal product that is intended to be filed using the ANDA pathway.

4.3 Comparison and Discussion of EU and US generic requirements towards cocrystal APIs

When generally comparing the eligibility of pharmaceuticals cocrystals for generic applications from the perspective of the EMA and the FDA, then it can be established that cocrystal APIs can be used for these type of applications. However, it must be kept in mind that the guidance and reflection papers published by both agencies only offer a framework on how pharmaceutical cocrystals can be developed. Divergence from these guidelines are possible and 3should be clarified beforehand in close collaboration with the authorities during scientific advises.

The scientific definition of pharmaceutical cocrystals provided by the EMA (see section 3.2) allowed a direct integration of this API form into European legislation. From the agency's point of view, cocrystals posses the same regulatory status as salts, which in return make them eligible for a generic application. This statement enabled the inclusion of the relatively new API form into the present regulatory landscape for generics and, thus, prevented the necessity of formulating new regulatory pathways.

This streamlining and integration of cocrystal APIs into the given legal framework is of course also backed-up by scientific arguments. Within oral immediate release dosage forms, both ionic and non-ionic interactions are disrupted upon dissolution and lead to the same pharmaceutical active substance being released after administration. Therefore, even though the formulations of generic medicinal products using either salt or cocrystal APIs differ, *in vivo* the same active moiety is released and can carry out its pharmacological purpose.

Another aspect worth mentioning is that the EMA explicitly mentions what characteristics of an active substance and co-former can be present in a cocrystal. The components that form the

lattice of the cocrystal can be neutral or be present in an ionized state. However, the formation of the cocrystal has to rely on non-ionic interactions even if ionic compounds are present in the cocrystal. Additionally, the European agency mentions in their reflection paper that both co-former as well as the active substance can be present as liquids within the crystal. Allowing a broad range of substances, aggregate and ionization states to be acceptable for pharmaceutical cocrystals is another point that facilitated the rapid inclusion of this API form into the current regulatory framework of generics.

The FDA initially defined in the first version of their guidance document that pharmaceutical cocrystals are composed of APIs and co-formes that both posses a neutral charge within the crystal lattice. This definition is clearly different from the one proposed by the EMA. However, the guidance document was revised as critic from scientists arose, as they did not agree on the classification that cocrystals are drug product intermediates. The new version of the document, however, does not comment directly on the ionization state of both API and co-former. Nevertheless, in the guidance on how to determine if a crystal is a salt or cocrystal (further discussed in section 5.2.2) mentions that APIs and co-formers possessing ionizable functional groups should be present in a neutral state in order to be classified as a cocrystal.

Closer examination reveals that this definition of cocrystals can cause some pitfalls. For instance, a medicinal product that contains a salt cocrystal are not eligible for an ANDA. Pharmaceutical salt cocrystals are crystalline solids formed by an API that is a salt (API with a counterion) that interacts via non-ionic interactions with a neutral co-former. Salt cocrystals formed by co-formers that are present as salts and interact with a neutral API are also a possible scenario.

Even though these are very special cases, various regulatory questions that arise when developing generics containing cocrystals cannot fully be answered by the FDA guidance document. An alternative approach could be the filling of a 505(b)(2) application to minimize the rejection of an ANDA. The framework provided by the EMA at the moment seems to provide more regulatory flexibility for generic medicines containing cocrystals. However, it should be kept in mind that guidance documents, independent of the agency that publish them, cannot and should not provide detailed instructions on how to obtain an approval and are, additionally, not legally binding. Therefore, it is highly recommended to address any uncertainties to the authorities in form of a scientific advise to receive a case by case guidance when developing

special medicinal products or using novel developmental approaches.

5 Data Considerations for Abridged Applications using Pharmaceutical Cocrystals

The previous sections analyzed the definitions of cocrystals given by the scientific community as well as the European and US regulatory authorities. In addition to what actually is a cocrystal, the last chapter presented and discussed the regulatory framework of both territories and investigated the regulatory status of pharmaceutical cocrystals. Finally, it was determined that cocrystals can be embedded into current legislation and that these solids are eligible for abridged applications.

The next sections now concentrate on the data that should be presented to the authorities in order to support a generic application. This will be discussed according to the modular structure of the common technical document (CTD) in which the data should be presented.

5.1 The Common Technical Document

The common technical document is a format in which the data for a marketing authorization should be presented. The structure was developed in order to harmonize application dossiers across different countries. Through the efforts of The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) the first countries (or regions) that adopted this structure were the USA, EU and Japan.

A brief overview of the content of the CTD can be seen in Figure 2. The CTD is composed of the modules 2 to 5. Module 1 is strictly speaking not a part of the CTD. The reason for this is that this module contains administrative and country/regional specific information that are not internationally harmonized (e.g. country specific forms, declarations or fees). The modules 2-5 display the data that has been collected during the development of a medicinal product and is the scientific basis for granting a marketing authorization application.

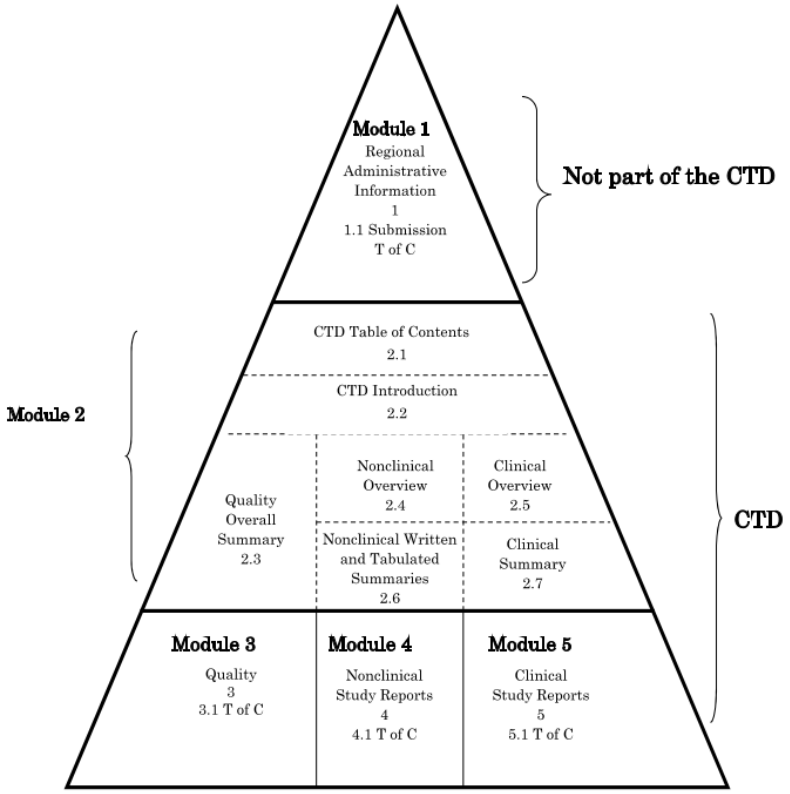

Figure 2 Overview of the CTD structure Applicants submitting a dossier for a medicinal product should present the data according to the CTD structure. Moulde 1 contains regional and administrative information. Module 1 is not considered a part of the CTD, since this section is not internationally harmonized. Module 2 contains the summaries of the modules 3 to 5. Module 3 concentrates on the quality aspects of both the drug substance and finished product. Module 4 contains the data gathered during non-clinical studies, which have been conducted during the development of the medicinal product. Finally, module 5 contains the clinical study reports providing the evidence that a medicinal product is safe and effective. (Legend: CTD = common technical document; T of C = table of content) Figure adapted from ICH guideline M4[26]

Module 2 contains the summaries of the data that is provided within the modules 3, 4 and 5. Module 3 contains information related to the quality aspects of the medicinal product. Within this section, information such as the development of the product, its manufacturing and the specifications are displayed. Module 4 presents the information that has been collected during the non-clinical development of the product. Studies conducted to determine toxicity, pharmacology and pharmacokinetics of the medicine are presented in this section of the dossier. Finally, in module 5 are the findings of the clinical studies conducted and provide evidence that the developed product posses the desired safety and efficacy characteristics.

5.2 Data for Module 3 - Quality

Both the FDA and EMA have addressed certain quality aspects that should be met by pharmaceutical cocrystals. This data shall be presented and discussed in the next few sections. However, beside the information provided by the competent authorities, further aspects will be drawn-up that should be considered when developing a generic medicinal product using a cocrystal as an API source.

5.2.1 Cocrystal Determination as Recommended by the EMA

The EMA defined within its reflection paper which substances can be considered as pharmaceutical cocrystals and that these solids can be used for abridged applications. One key aspect it that cocrystals are formed through non-ionic interactions between an API and a co-former, whereas salt crystals are formed through ionic interacts from acid-base reactions. A characteristic of acid-base reactions is the transfer of protons. The pKa value expresses if a given substance has the potential to carry-out such a reaction (accepting or transferring a proton).[5] It can be hypothesized that by analyzing the pKa values of the crystal components this could allow a prediction on how the lattice is formed, either via ionic or non-ionic interactions. The EMA, however, does not recommend this approach. The agency rather suggests that appropriate spectroscopic tools should be applied in order to determine if a given crystal is formed through the interaction of ions or of molecules interacting via non-ionic forces.

The EMA does not propose which specific methods shall be used to determine the interactions that form a potential cocrystal. One technique that is frequently used for the characterization of a crystal is single crystal X-ray diffraction (XRD).[27] This method cannot be applied to all substances, since not all form crystals suitable for this technique. Therefore, variations of XRD should be used, such as powder X-ray diffraction, or alternative spectroscopic methods such as solid-state nuclear magnetic resonance, Raman and infrared spectroscopy.[28] The data collected from these investigations should then be presented in the drug substance section (3.2.S) of the CTD.

Interestingly, the EMA noted within their reflection paper that categorizing solids into salts

or cocrystals using their formulated definition is only of theoretical nature from a material science point of view. The main goal of characterizing an active substance solid should be to determine if the substance is suitable for its use in a medicinal product in terms of quality, safety and efficacy and not necessarily to distinguish between a salt and a cocrystal.

5.2.2 Cocrystal Determination as Recommended by the FDA

With the US, pharmaceutical cocrystals can be used for the development of a generic medicine and can be registered using the ANDA regulatory pathway. The ANDA applicant has to provide sufficient evidence to the FDA that supports the claim that a pharmaceutical cocrystal is present within the product. In contrast to what the EMA has published in their reflection paper, the FDA has formulated a more detailed list of data that should accompany an ANDA application including a pharmaceutical cocrystal.

The first aspect that should be investigated by the applicant is if both the active substance as well as the coformer are present within the same unit cell. Techniques such as the ones mentioned in the previous section (e.g. XRD) can provide sufficient data to prove that both the API and coformer are organized in the same crystal lattice.

The second aspect that should be addressed is to demonstrate that the cocrystal present in the medicinal product is formed by non-ionic interactions. In the case that both API and coformer posses ionizable functional groups, which can possibly form ion bonds, the FDA has formulated a guide on how to determine if both components interact non-ionically within the crystal.

This guidance suggests that determining the pKa difference (ΔpKa = pKa (conjugated acid of base) - pKa (acid)) between both the API and potential coformer/counter ion allows a prediction if a given crystal is formed by ionic or non-ionic interactions. The FDA has defined that if a ΔpKa of ≥ 1 has been determined, then the components in the crystal lattice are likely to form ion bonds whereas substances with a ΔpKa of < 1 are considered to display non-ionic interactions. Using this approaches allows the classification of crystalline solids as a salt (pKa ≥ 1) or a cocrystal (pKa < 1) solely based on there theoretical potential to transfer or accept a proton.

However, additional experimental data should be provided in case a clear-cut conclusion using

the $\triangle$pKa approach cannot be reached. This is for instance the case if the $\triangle$pKa between API and coformer is barely bigger or smaller than 1. Various spectroscopical or equivalent methods should then be used in order to investigate the nature of the molecular interactions of the components within the crystal unit.

The third and final aspect mentioned within the FDA guidance document is to provide evidence that substantial dissolution takes place before the active ingredient reaches its intended site of pharmacological activity. Cocrystals are viewed by the FDA as a special case of solvates and hydrates (see sections 3.3 and 4.2.2). Therefore, the interactions within the lattice of cocrystals should behave in a similar manner as those seen in solvates and hydrates. The FDA considers it sufficient to present in vitro data from experiments evaluating the dissolution and solubility of the cocrystal to demonstrate that the crystal components dissociate from each other before the active substance reaches its site of pharmacological activity.

The data collected to classify and characterize the crystalline solid should then be presented in the drug substance format (3.2.S) of the CTD.

5.2.3 Considerations Towards Coformers

An API interacts with a coformer via non-ionic interactions to form a cocrystal. The coformer within the crystal lattice is mostly a substance with no pharmacological activity (exception: cocrystals composed of two components that are both APIs). In addition, a large number of substances can function as coformers with a variety of different chemical characteristics. Both the EMA and FDA have outlined in their respective guidance documents on how pharmaceutical cocrystals as a whole are viewed from a scientific and regulatory stand-point. However, one question that arises is what is the regulatory status of the coformer?

The EMA mentions within their reflection paper that the use of a coformer must be pharmaceutically acceptable for its use in a medicinal product. This statement follows the same premise that is set out for counter ions or in gerneal for excipients. Furthermore, the EMA makes a reference to the ICH guideline "Development and Manufacture of Drug Substances-Chemical and Biotechnological/Biological Entities" (Q11) and argues that coformers should be viewed as reagents for the manufacturing of the drug substance.[29] This classification as a reagent is, how-

ever, only valid for coformers that represent commonly available chemicals. This conclusion most likely arises from the description provide by Q11:

"Commonly available chemicals used to create salts, esters or other simple derivatives should be considered reagents.".

It is likely that the EMA adapted this sections for coformers since cocrystals have the same regulatory status as salts.

Interestingly, in the first published guidance document of the FDA, which is now outdated, actually classified coformers as excipients. In the newest revision, however, this status has not been confirmed. Nevertheless, the same argumentation as the EMA that sees coformers possessing a similar status as salts can most likely not be used. The rational for this is that cocrystals posses in the US the regulatory status of a solvate and not of a salt. It is not clear if a solvate can may be considered a simple derivative as stated in the Q11 guideline. Therefore, the question arises what are the alternative classification possibilities for coformers according to ICH guideline Q11?

During the manufacturing of an API different substance categories are used: starting material, raw materials, solvents and reagents. Coformers can be excluded from the category of starting and raw material due to the fact that the coformer is not a material used for the synthesis of the active ingredient. Categorizing coformers as solvents can also be excluded since the FDA does not accept coformers being solvents according to their definition of cocrystals (see section 3.3). Therefore, reagents remain the only option for coformers. It could be argued that a coformer is utilized as a crystallization reagent for the API. This definition would not infringe the regulatory definition that has been laid-out by the agency. Due to the fact that there is some uncertainty regarding this topic, a scientific advise should be arranged with the agency during the development of the medicinal product.

What kind of data should be presented to the authority concerning the coformer? In general and as previously mentioned, it must be demonstrated that the utilized coformer is considered suitable for its use in a medicinal product. Both agencies provide little guidance concerning which coformers can be used. The EMA mentions that if a substance that functions as a coformer has been previously used in a medicinal product (most likely as an excipient), then

this can be considered a sufficient justification for the use of the substance. Substances listed within the European pharmacopoeia (Ph. Eur.), a pharmacopoeia of a member state or a third country pharmacopoeia (z.B. US or Japanese) could also be considered as a suitable justification for the intended use in a generic product. If a coformer has not been previously included in a registered medicinal product or listed in a pharmacopoeia, then the applicant has to provide different data to justify the use of the substance as a coformer.

The EMA points out that such a novel-coformer should be documented in a similar fashion as a novel excipient.[30] This includes details of the manufacturing process, characterization of the substance, applied controls, specifications and cross referring to supporting safety data that are publicly available.[30] A feasible approach for a coformer that has been used as a food additive is to refer to the toxicological data that has been compiled during its evaluation for its use in foods. This could be another sufficient justification for the use of the substance as a coformer.

The FDA has not made a similar statement on what kind of data should be presented within an abridged application. However, a similar approach as outlined by the EMA may be a viable strategy. As stated within the "Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients", the FDA accepts excipients that have been previously approved in medicines or posses the status as generally recognized as safe (GRAS).[31] However, it has to be clarified if coformers and excipients are equivalent to each other. They should not be the same, as this might obscure the possibility of cocrystals being eligible for an ANDA. This is due to the fact that excipients between a RLD and the generic product should be identical (with a few exceptions; see section 4.2.1) and present at the same concentrations. Therefore, again all possible approaches should be discussed with FDA before submitting an ANDA with a drug containing a cocrystal.

Since the coformer and the API together form the pharmaceutical cocrystal, all the data collected concerning the coformer and the concluding justification for its use should be presented according to the drug substance format of the CTD.

As demonstrated in the last paragraphs, issues related to the coformer of the cocrystal have either been only briefly or not at all addressed. Due to the uncertainty towards coformers

that have never been used in a medicinal product, it may be a feasible strategy during the development of a cocrystal to first screen for substances that might function as coformers that have been associated with a medicinal product or that their use in a pharmaceutical is considered safe.

5.2.4 Eligibility of using ASMFs and DMFs for pharmaceutical cocrystals

A medicinal product generally consists of the API and one or more excipients. A pharmaceutical company does not necessarily have to carry out every manufacturing step in order to later market the finished pharmaceutical product. In some instances pharmaceutical companies purchase the API from another manufacturer. Information concerning the synthesis and control of the active ingredient are mostly regarded as confidential and are not shared with the manufacturer that purchases the API. However, the pharmaceutical company that intends to market a medicinal product has to take full responsibility of the finished product including the active substance that is utilized. Both the active substance mater file (ASMF) in the EU as well as the drug master file (DMF) procedure in the US allow the manufacturer of an API to protect their confidential intellectual property, while allowing an applicant for a marketing authorization application (EU) or ANDA (US) to take over responsibility of the finished product.

Within the EU, pharmaceutical cocrystals are viewed as "classical" APIs. Therefore, cocrystal API manufacturer can use the ASMF procedure as laid down in the *"Guideline on Active Substance Master File Procedure"*.[32]

Within the US, it was initially not possible to submit a DMF to support an ANDA using a pharmaceutical cocrystal. The reason for this was that the FDA classified cocrystals as drug product intermediates within the first version of their guidance paper (see section 3.3). A drug product intermediate is not eligible for a type II DMF that is used for a drug substance, drug substance intermediate, a material used in the preparation of the intermediate or drug substance, or a drug product.[33] However, after revision of the first guidance, cocrystals are viewed as an API in the classical sense and, therefore, are eligible for a type II DMF.[33]

Information provided by both the ASMF and DMF procedure shall be presented using the drug substance format of the CTD.

5.2.5 Other Quality Aspects that Should be Considered during the Development of a Generic using Cocrystal APIs

Both the FDA and the EMA provide regulatory guidance towards the usage of pharmaceutical cocrystals. However, there are several aspects not addressed within the guidance documents (e.g. questions related to coformers mentioned previously). Generics incorporating a pharmaceutical cocrystal mostly have the same challenges that standard generic medicinal products encounter during their development. However, the next paragraphs shall highlight a few quality topics that should be addressed that only concerns the development of a generic using a cocrystal as an API.

The pharmaceutical cocrystal represents the biggest difference when compared to a "classical" API (e.g. single entity or salt API) used in generic medicines. Therefore, great efforts should be made in the characterization of the cocrystal. Primarily the physicochemical properties of the cocrystal shall be thoroughly investigated in order to estimate if a certain cocrystal is suitable for generic medicinal products in the EU and US as well as comply to the regulations associated with these territories.

Properties such as melting point, stability and dissolution should be closly examined since these might largely differ between the parent API and the pharmaceutical cocrystal.[1] The melting point is a parameter that is frequently used to determine the purity of a substance or identify different polymorphic forms of a crystalline substance.[34,35] Additionally, the melting point has to be taken into account when developing the manufacturing process of both drug substance and the finished product. Many pharmaceuticals incorporate a drying step during the manufacturing process. If in this case the melting point of the cocrystal is too low, then the components of the crystal might dissociate from each other and thus change the API content within the finished product. Agencies such as the EMA require data which demonstrates that the intact pharmaceutical cocrystal is still present within the finished product.[15]

A high stability of the drug substance is highly desirable during its development. Stability towards thermal, humidity and chemical stress should be analyzed. The association of a coformer with an API might decrease the stability of the resulting crystal and has to be evaluated in order to estimate if certain impurities/degradation products are later present within the

medicinal product. Additionally, the information obtained from these stability studies are also required to determine the retest period or shelf-life of both the drug substance and finished product, respectively (like for classical generics).

Finally, dissolution is a vital aspect during the development of a generic using a pharmaceutical cocrystal. The dissolution behavior of the API within the reference medicinal product (EU) or RLD (US) should be similar to the dissolution observed with the cocrystal. This aspect is essential since differences in dissolution might have a clinical significance that might prevent the registration of a generic pharmaceutical containing a cocrystal (see section 5.4 for more details). However, comparable dissolution between parent and cocrystal API also have an advantage to pursue different regulatory pathways to obtain an approval from the agencies (see section 5.4 for more details).

These are of course not all points that should be taken into account when developing a generic using a cocrystal API. However, it should give a brief guidance on the different parameters that can have a significant impact on the success on the registration of a generic medicine. Together with the regulatory framework defined by the EU and US authorities concerning pharmaceutical cocrystals, there are many aspects that have to be considered and several challenges that have be tackled during the development of the product.

5.3 Data for Module 4 - Non-clinical Studies

Generic medicinal products normally do not have the obligation to conduct non-clinical studies such as safety pharmacological or toxicological studies. The basis for this rational is that the applicant of a MAA (EU) or an ANDA (US) refers to the non-clinical studies that have been conducted by the innovator. Therefore, it is mostly sufficient to include published literature that demonstrates the safety of the API used in the medicinal product. In the case of pharmaceutical cocrystals this approach is also applicable. If studies have been conducted using the cocrystal then these should be included into the CTD. However, literature that focuses solely on the parent API and not the cocrystal should be sufficient to demonstrate the safety of the cocrystal within the EU.

The reason for this assumption is that the EMA mentions in their reflection paper that salts and

cocrystal should behave similarly in terms of dissolution for an oral immediate release product. Upon dissociation of the crystal components the same active substance is released. The same argumentation could be used for an ANDA. However, as mentioned for different aspects not directly addressed by the FDA, these should be discussed with the agency during a scientific advise.

Referring to published literature is a viable approach to circumvent the necessity of conducting additional non-clinical studies. However, in the case of novel coformers (see section 5.2.3) it may be recommended to conduct toxicological studies (single and repeated dose toxicity studies) as well as safety pharmacology studies. Again, these issue should be discussed with the appropriate authorities to receive a case by case guidance on this matter.

5.4 Data for Module 5 - Clinical Studies

Minimizing or preventing the repetition of clinical studies that have already been preformed is a common goal that both the competent authorities and the pharmaceutical industry have. Since the applicant is referring to the studies conducted by the originator, manufacturers of generic medicinal products do not have to carry out the full-battery of clinical studies to prove that their product is safe and effective.

Generic manufacturers have to collect clinical data during the development of their product in which they demonstrate that their product is equivalent to that of the innovator. Evidence that two medicinal products are equivalent to each other is provided through the performance of bioavailability (BA) and bioequivalence (BE) studies. Bioavailability studies investigate how much of the initially administered active substance is later present at the site of its pharmacological activity. For products that have an oral route of administration (e.g. immediate release tablets) the blood concentration of the active substance is measured at certain time intervals after administration.

BE studies, on the other hand, have the goal to determine pharmacokinetic parameters such as the maximum plasma concentration (c_{max}), the area under the curve (AUC) and the time at which the maximum plasma concentration (T_{max}) is reached. During these studies the mentioned pharmacokinetic parameters of the generic medicinal product is compared with those

of the reference medicinal product/RLD. By comparing the collected values a definite conclusion can be made if both medicinal products are bioequivalent or not.

Both the FDA and EMA have not mentioned any special considerations towards BA and BE studies for generic medicinal products that have incorporated a pharmaceutical cocrystal. Vice versa, the BE guidelines published by both agencies donot specifically exclude the use of pharmaceutical cocrystals. Therefore, both the FDA and EMA BE guidelines should be valid for cocrystal generics.[36,37]

There is also an alternative strategy for manufacturers of a generic medicinal products to prove the equivalence of their test product with that of the originator without conducting in vivo BA and/or BE studies. A procedure termed as the Biopharmaceutics Classification System (BCS) based biowaiver process has been installed as an alternative regulatory pathway to scientifically argue that two products are equivalent to each other.[37,38] This process has been developed in order to further minimize unnecessary human testing, if possible, and facilitates the availability of medicines without compromising the safety of the patients. However, only immediate release solid oral dosage forms can utilize this procedure and the product has to fulfill several requirements.

For instance, the medicinal product applying for a biowaiver has to have an API that dissolves rapidly and which does not precipitate in the gastrointestinal tract after the API is dissolved.[39] Additionally, excipients of the test product that can have an impact on the bioavailability should be quantitatively and qualitatively the same as the reference medicinal product/RLD. Other excipients present in the test product shall be in terms of quantity very similar and in terms of quality the same as in the reference product. Furthermore, only medicinal products that do not have a narrow therapeutic index are eligible for this regulatory procedure.

Besides the previously mentioned factors, one of the most essential requirements of a BCS biowaiver is the classification of the active substance into one of the four BCS classes. The classification of the active substance is based on its solubility in aqueous solutions and its intestinal permeability. Substances belonging to BCS class I display high solubility and high permeability whereas representatives of BCS class II display low solubility and high permeability. Active ingredients belonging to the BCS class III display high solubility but low permeability. Finally, BCS

class IV APIs posses low solubility and permeability.

An active ingredient that belongs to either BCS class I or III is eligible for a biowaiver, whereas an API belonging to the other two classes is not suitable for this approach. Both the FDA and EMA have published guidance documents that outline what kind of data should be provided to investigate which BCS class an active substance belongs to.[37,38] If sufficient evidence is presented that a pharmaceutical cocrystal can be classified at least as a BCS class I substance, then it should be possible to utilize this regulatory pathway. So far both agencies have not mentioned any specific restrictions concerning cocrystal pharmaceuticals using the BCS biowaiver approach. On the contrary, the EMA has recently published a product-specific bioequivalence guidance in which it has been noted that cocrystals can be accepted for a biowaiver in case the substance belongs to BCS class I.[40] However, a similar statement has not been published yet by the FDA.

6 Discussion and Outlook

During the development of a medicinal product, much emphasis is made on the characterization of the API. Physicochemical properties such as melting point, solubility, dissolution, stability and polymorphism are extensively investigated and have a tremendous impact on various attributes of the finished product. Not all APIs posses desired characteristics to translate them into a medicinal product. As a consequence of this, solid state design strategies have been developed to engineer API crystals that have improved properties such as rapid dissolution or desirable melting points. A classical technique used in the field to engineer improved APIs is by generating salt derivatives. However, this approach has its limitations since there are only a certain amount of counter ions that are suitable for their incorporation into a medicinal product. Another limitation of this approach is that not every API possesses functional groups that are ionizable, which is essential for salt formation.

During the last 20 years, new design strategies have been developed to overcome the limitations that are associated with the salt formation of APIs. These new approaches also provide new possibilities of tailoring APIs with desired properties. The usage of pharmaceutical cocrystal is one of these newly developed techniques used in pharmaceutical sciences. Development of these crystalline solids is a fast growing field and has drawn much attention in the industry. Within the scientific community, a unifying definition of cocrystals has not been formulated yet and is under constant debate. This lack of an exact definition for pharmaceutical cocrystals has the potential to create diverge regulatory pathways that are formulated by different authorities such as the EMA in Europe and the FDA in the United States.

The EMA defines pharmaceutical cocrystals as solids that are composed of one or more APIs that interacts with one or more coformers to form a crystal lattice. The formation of the crystal is driven by non-covalent and non-ionic interactions and the components are present in stochiometric amounts. Both the API and the coformer may be neutral or present as an ion within the crystal. In case of the presence of ions, these must not promote the crystal formation in order for the solid to be classified as a cocrystal.

The FDA generally also has formulated a similar definition. The agency classifies an API that in-

teracts with a coformer via non-ionic interactions within a unit cell as a pharmaceutical cocrystal. However, details such as that all the components within the crystal lattice have to be neutral and that the coformer cannot be a solvent and is normally non-volatile are aspects that differ from the European definition.

Not only do the definitions of both agencies vary from one another, but also the regulatory status of these solid are different. The FDA had at first the viewpoint that cocrystals should not be considered as an API in the classical sense. The agency declared these solids as drug product intermediates. This view initiated a large debate within the scientific community within both academia and the industry. This lead to the revision of the guidance document concerning the classification of pharmaceutical cocrystals. Within the current view of the FDA, cocrystals are considered a special case of solvates. Solvates in return are one of three different flavors of polymorphs. This characteristic is the reason why it is possible that pharmaceutical cocrystals are eligible for abridged applications according to the ANDA pathway described in the Hatch-Waxman-Act.

Within Europe, cocrystals have a similar regulatory status as salts. This view has been justified by the EMA due to the fact that salts and cocrystal containing the same API moiety behave similar upon dissolution. Different salts of an API are considered the same active substance within European legislation and may, therefore, be used in generic applications according to Article 10(1) of Directive 2001/83/EC. Due to their similar regulatory status as salts, this in return also allows medicinal products containing a pharmaceutical cocrystal to use the generic regulatory pathway.

These different viewpoints on how to classify a cocrystal and how they fit into the regulatory framework of both territories is a great challenge for professionals working in the field of regulatory affairs. When comparing the regulatory situation of cocrystals in the US with that in Europe, then it seems that the EMA has a more flexible basis to work with when it comes to generics. This is due to the fact that various derivates of an API can be used in a generic medicinal product as long as the safety, efficacy and quality is not compromised. Additionally, the EMA's definition of cocrystals allows the industry to generate more solids that are eligible for generic applications than with the cocrystal definition present in the US. For instance, the FDA only allows the use of neutral components and non-solvents to form the lattice of cocrystals.

This fact, therefore, greatly reduces the amount of possible API-coformer combinations that can be used for the generation of cocrystals.

One of the biggest potential pitfalls when using cocrystals in the development of a generic is that the regulatory status of coformers still has to be addressed by the authorities. Both the EMA and FDA do not claim if coformers have the same status as excipients or have a special standing within their regulatory framework. This fact is especially problematic for abridged applications within the US. Here the excipients within the generic product have to be qualitatively and quantitatively very similar to the innovator. If coformers are viewed as excipients, then the similarity aspect between the generic and innovator is not present anymore. Thus, the FDA might reject an ANDA application due to the different composition of the generic product when compared to the innovator. The classification of coformers as excipients would not have a dramatic impact for generics applying for a marketing authorization within the EU. Within Europe, the composition of a generic may differ from that of an originator as long as these differences do not have an impact on the safety and efficacy of the product.

The conclusion that can be made from the previous paragraphs is that the use of pharmaceutical cocrystals is possible in both the US and within the EU. However, some regulatory risks might arise when submitting an ANDA to the FDA. Therefore, it is highly recommended to be in frequent contact with the agency in order to identify these risks and to mitigate them during the development of the generic product. On the other hand, a positive recommendation can be made for seeking marketing approval within the EU, since a high degree of regulatory flexibility towards pharmaceutical cocrystals is present. Nevertheless, close collaboration with the EMA and/or competent authorities should be sought during development as the use of cocrystals is still rather new and not all regulatory circumstances have been covered by the regulatory authorities. One of the biggest challenges that the authorities should address concerns the coformers. Both the EMA and FDA should revise their cocrystal reflection and guidance paper in order to provide more regulatory support on this topic.

Beside the regulatory complexity, there are also several other aspects that make pharmaceutical cocrystals attractive to work with. For instance, the field of pharmaceutical process engineering can greatly profit from the use of cocrystals. This is due to the fact that pharmaceutical cocrystals can be designed to posses desired properties that are advantage for the manufac-

turing process, for example to withstand high temperatures that might occur during the production of the finished product. On the other hand, pharmaceutical cocrystals might be useful to circumvent patents that are associated with the parent API. As an example, many originators hold various patents that protect the various polymorphic forms of an API. Cocrystals do not infringe these patents and therefore generic companies get an early start to develop and launch a generic medicinal product before the polymorph patents have expired.

Even though there are still several aspects that have to be discussed and resolved concerning the use of pharmaceutical cocrystals, the introduction of these solids has, nevertheless, facilitated a lively discussion in the field of regulatory affairs. The implications of this new API form have lead to new regulatory strategies for new medicinal products but also could be incorporated into the present legal framework within the USA and EU. For the future it will be very interesting to see how many new innovative medicines as well as generic products will harbor a cocrystal API and what regulatory issues these products will face. The introduction of cocrystal could also nicely demonstrate that not only the pharmaceutical sciences are constantly evolving and adapting but also the regulatory environment in which new APIs try to find their place.

List of Tables

List of Figures

List of Abbreviations

ANDA	Abbreviated New Drug Application
API	Active pharmaceutical ingredient
ASMF	Active substance master file
AUC	Area under the curve
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulations
CTD	Common technical document
DMF	Drug master file
EEA	European Economic Area
EMA	European medicines agency
EU	European Union
FDA	Food and Drug Administration
GRAS	Generally recognized as safe
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	Marketing authorization
MAA	Marketing authorization application
NCE	New chemical entity
NDA	New drug application
RLD	Reference Listed Drug
T_{max}	Time at which the maximum plasma concentration is reached
U.S.C.	United States Code
US	United States
USA	United States of America
XRD	X-ray diffraction

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Hamburg, 10.12.2018
Ort, Datum

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