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FDA Regulatory Implications for Co-crystals and recent Co-crystal Patents

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Abstract

One of the most crucial stages in the creation of a medicinal product is the characterization of an Active Pharmaceutical Ingredient (API). Unfortunately, not all APIs have the ideal characteristics for medicinal usage. Many freshly discovered active compounds, for example, have low solubility. However, various methods have been developed to change and improve an API's features to get desired physicochemical properties, which is an important tool in formulation development. The production of salt derivatives is a common technique for increasing the solubility of an active chemical. This method, however, has limits because not every API has the qualities to be transformed into a salt. In recent years, a novel engineering approach for creating new API forms with desirable features has been established. The development of pharmaceutical co-crystals is the result of these efforts which allow pharmaceutical companies to customise existing APIs or create new ones with specific properties. Aside from the scientific hurdles that come with developing a pharmaceutical, manufacturers are also faced with regulatory regulations that must be met in order to get approval and access the market. As pharmaceutical co-crystals are a relatively new API, little regulatory guidance for co-crystals has been developed for one of the world's largest pharmaceutical market the United States of America (USA).

This article will look at what regulatory standards must be met in order to employ pharmaceutical co-crystals in generic medications intended for use in the United States. It will also go over which data should be included in the common technical document to justify its existence. In addition to, a brief information of various patents on co-crystals have also been included for better knowledge of the reader.

Keywords: Pharmaceutical co-crystals, Coformer, Regulatory guidelines, Common technical document, FDA, Patent.

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1. Introduction

Co-crystals

Within the supramolecular chemistry world, co-crystals are not a new phenomenon. Several advances in the growth, engineering, and characterization of co-crystals have been made in the previous 30 years. Co-crystals have just lately entered the realm of medicine development due to the ability to design crystals with a wide range of physicochemical features. (1) Pharmaceutical co-crystals are co-crystals that have been created for use in medicinal products as a result of this trend.

Crystalline solids are solids in which the compounds are grouped in regular patterns. In the crystal lattice, a co-crystal is a multicomponent system including a drug and a coformer that are bound together by non-ionic contact and have a stoichiometric molar ratio of the same. Cocrystallization can improve the bioavailability of an API by changing its physicochemical properties such as solubility, dissolution, and stability. Protonation, which occurs in salts, does not occur in co-crystals, which work by intermolecular forces. (2)

The crystals can be grouped together in a variety of ways subdivided further into various sub-groups. Solvates, hydrates, and co-crystals are three well-known examples of crystalline solids generated through non-ionic interactions. Hydrates and solvates either comprise a molecule of water or a molecule of a solvate that interacts with another substance to form a crystal lattice. (3,4) Pharmaceutical co-crystals are those in which an API is included into the lattice, regardless of which scientific definition is utilised. The large number of definitions for co-crystals that have been developed, on the other hand, make it difficult to develop regulatory requirements for this API type.

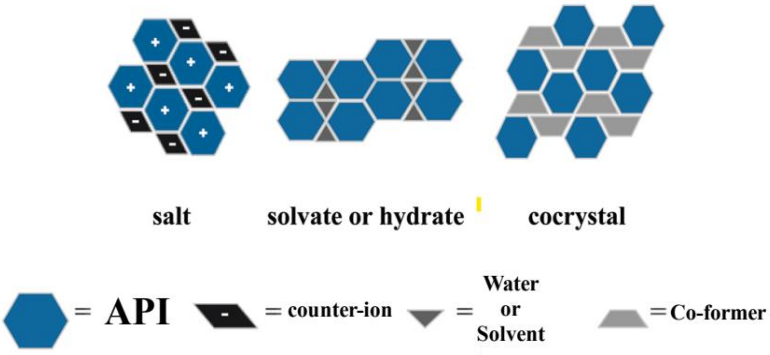

Figure 1. Schematic representation of salts, hydrates, solvates and co-crystals APIs present as a salt are composed of the active substance that possess a certain charge (either positive or negative) and interacts with a counter-ion (possessing the opposite charge as the API) to form the lattice. When 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 coformer via non-ionic interactions, then pharmaceutical co-crystals are formed. Figure adapted from Schultheiss and Newman 2009. (1)

Table 1. Different definition of co-crystals within the scientific community. (5-11)

Author	Definition of co-crystals
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, iconic compound or molecule"
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, often including hydrogen bonding"
Zaworotko, M.J.	"Are formed between a molecular or ionic API and a cocrystal cofomer that is a solid under ambient conditions"
Aakeroy ,C.B.	"Structurally homogenous crystalline material that contains two or more neutral building blocks that arepresent in definite stoichiometric amounts"

FDA's scientific view of Co-crystals

The FDA issued its first advice on the regulatory classification of co-crystals in 2013. (12) A cocrystal is defined by the FDA as a solid with a crystalline shape and a crystal lattice made up of two or more molecules. One of these molecules is the pharmaceutical active component, and it interacts with one or more so-called coformers on a molecular level. Coformers must interact with the active component via non-ionic interactions in order for the complex to be called a cocrystal

Co-crystals are distinguished from other solid-state forms such as polymorphs and salts by the definition given above. Polymorphs are solids that only contain one component within their crystal lattice, according to the FDA. (12) A single active chemical, on the other hand, can have several polymorphs. Salts, on the other hand, are generated by the collision of oppositely charged molecules produced by acid-base interactions. As co-crystals are made up of two or more components, each of which has a neutral charge, this solid-state form falls into a new category within the FDA's classification of solids.

Despite the fact that co-crystals constitute a unique solid-state category, the US government does not consider them to be APIs. As a result, co-crystals are used as a tool to help the pharmaceutical product reach a specific functional end. The designation of co-crystals as a medicinal product intermediary drew criticism from both academia and industry scientists. (13) In addition to this criticism, there was ambiguity about how to interpret the instructions, as well as practical issues. (14) The FDA revised the above-mentioned guidance document as a result of these legal, regulatory, and quality assurance problems. The rewrite was first released in 2016 under the same title as the original document, and it was finally completed in 2018. (15)

A cocrystal is still defined in this updated advice as a crystalline material made up of two or more distinct molecules, one of which is a single molecule. However, the revised definition also mentions that the components of the crystal lattice, which is produced by non-ionic and

non-covalent bonds, the cocrystal are present in a predetermined stoichiometric ratio. This updated description takes into account the established ratios of both API and coformer(s), as well as how they interact. However, the new rule is silent on whether a specific aggregate state of both API and coformer(s) is required, such as a solid at room temperature.

2. Regulatory framework for Generics

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. (16) This act is also known as the "Hatch-Waxman-Act" and is the regulatory foundation for generics. 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.

Eligibility for US Generic Applications using Cocrystal APIs

To be considered applicable for an ANDA, a drug must establish that it has the same method of administration, dosage form, strength, indication, and active ingredient as described in U.S.C. 505(j). (17)

The API of a drug must be the same as the one used in the RLD in order for it to be eligible for an ANDA. The word "same as" rules out the use of API derivatives such salts, ethers, and esters. On the other hand, different polymorphs of an API are nonetheless eligible for an ANDA. (17)

Co-crystals are considered unique examples of solvates by the FDA. Solvates are classified as one of three types of polymorphs. The FDA explicitly stated in the cocrystal advice that co-crystals have the same perspective as polymorphs of an API, and that these crystals aren't observed in new APIs as a result, pharmaceutical co-crystals can be deemed the same API and used in a medical product that will be filed utilising the ANDA method.

3. Considerations for Abridged applications using Pharmaceutical Co-crystals

The Common Technical Document

The common technical document is a template for presenting data for a marketing permission. The framework was created to ensure that application dossiers from different countries were consistent.

Modules 2 through 5 make up the CTD. Module 1 is not technically a part of the CTD. This is due to the fact that this module comprises administrative and country/regional data that is not internationally harmonised (e.g., country specific forms, declarations or fees).

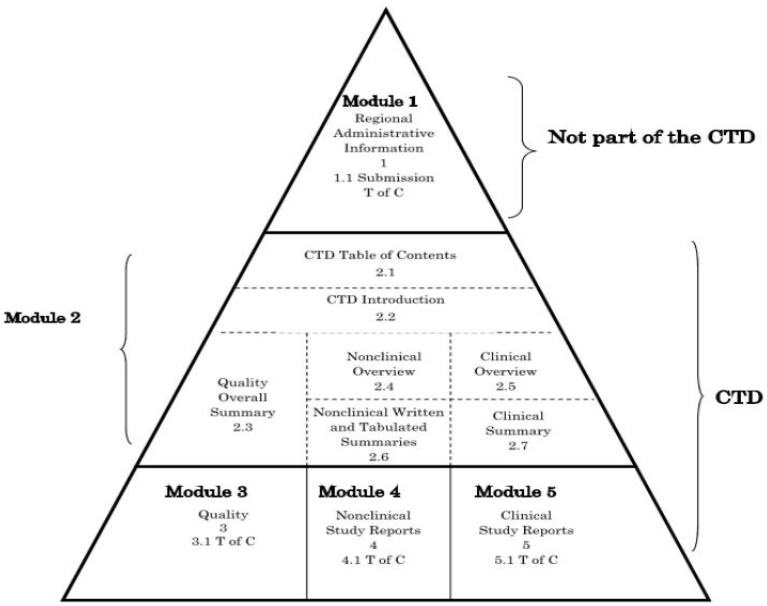

Figure 2. Overview of the CTD structure. (18)

Module 2 contains summaries of the information presented in modules 3, 4, and 5. Module 3 offers information about the medical product's quality features. This section contains details about the product's development, manufacturing, and specifications. Module 4 shows the data gathered throughout the product's non-clinical development. This portion of the dossier contains studies that were undertaken to determine the medicine's toxicity, pharmacology, and pharmacokinetics.

Finally, the findings of the clinical tests are presented in module 5, which demonstrate that the created product has the requisite safety and efficacy feature. (18)

a) Data for Module 3 - Quality have been addressed by FDA of certain quality aspects that should be met by pharmaceutical co-crystals.

- ***Cocrystal determination as recommended by the FDA***

With the US, pharmaceutical co-crystals can be used for the development of a generic medicine and can be registered using the ANDA regulatory pathway. In contrast to EMA, 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 substances as well as the coformer are present within the same unit cell. Techniques such as (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. 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 these approaches allows the classification of crystalline solids as a salt (pKa ≥ 1) or a cocrystal (pKa < 1) sol 0ely based on their theoretical potential to transfer or accept a proton. (19)

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.

Co-crystals are viewed by the FDA as a special case of solvates and hydrates Therefore, the interactions within the lattice of co-crystals 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.

- ***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: co-crystals composed of two components that are both APIs). 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. In general, it must be demonstrated that the utilized coformer is considered suitable for its use in a medicinal product. Both EMA and FDA 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.), could also be considered as a suitable justification for the intended use in a generic product. (20)

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 possess the status as Generally Recognized as Safe (GRAS). (21)

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 co-crystals 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) 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.

b) 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 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 co-crystals, 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 FDA 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. 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 it may be recommended to conduct toxicological studies (single and repeated dose toxicity studies) as well as safety pharmacology studies. Again, the issue should be discussed with the appropriate authorities to receive a case-by-case guidance on this matter.

c) Data for Module 5 - Clinical Studies

Minimizing or preventing the repetition of clinical studies that have already been performed 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 (Cmax), the area under the curve (AUC) and the time at which the maximum plasma concentration (Tmax) is reached. During these studies the mentioned pharmacokinetic parameters of the generic medicinal product are compared with those the reference medicinal product/RLD. By comparing the collected data, a definite conclusion can be made if both medicinal products are bioequivalent or not. The FDA has 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 FDA do not specifically exclude the use of pharmaceutical co-crystals. Therefore, the FDA BE guidelines should be valid for cocrystal generics. (22,23) 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. (24) 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. (25)

Table 2. Comparison between USFDA and EMA agencies guidelines (26)

Regulatory considerations	Food & Drug Administration guidance	European Medicines Agency
Regulatory category	Polymorph of the Active Pharmaceutical ingredient	Active Pharmaceutical ingredient
Composition	Active Pharmaceutical ingredient & a food or drug grade coformer	Active Pharmaceutical ingredient and coformer in fixed stoichiometric ratio
Interaction in crystal coformer role	Non-ionic / non-covalent interactions Excipient	Non-ionic / non-covalent interactions Reagent
New Chemical entity/New active substance registration	No	Possible if shown difference in efficacy/safety
Similarity with Active Pharmaceutical ingredient	Similar	Similar unless demonstrated different efficacy/safety
Classification	Polymorph of the Active Pharmaceutical ingredient	Active Pharmaceutical ingredient
Cocrystal & salt	Differences in interaction and regulatory pathway	Regulation depends on safety/ efficacy
US-Drug master files (DMF)/EMA-Active substance master file (ASMF)	Not feasible being DPI	Can be filed

4. Co-crystals Patentability concerns

Obtaining regulatory approval so that a pharmaceutical cocrystal can be commercialised is the next step after it has been developed and has shown promising results. A significant problem to address is the absence of precise regulatory guidelines. The last ten years have seen a tremendous increase in the development of co-crystals; a small number of cocrystal-related patents have even been issued. The three requirements of novelty, non-obviousness, and utility or usefulness must all be met for an invention to qualify for patentability.

Novelty

Pharmaceutical co-crystals are a novel composition of matter and should, thus, satisfy the requirement of novelty for the grant of a patent, according to Desiraju in his book "Pharmaceutical Salts and Co-crystals: Retrospect and Prospects." Pharmaceutical co-crystals should meet the novelty criteria much like salts, according to Andrew Trask in his article "An Overview of Pharmaceutical Co-crystals as Intellectual Property." Both Desiraju and Andrew emphasised that co-crystals may or may not form because coformers are chosen from a lengthy official list of GRAS compounds, coformer screening is a difficult task, and the outcome of co-crystallization is not always predictable.

In addition, it is impossible to predict the properties of the produced co-crystals. But the scenario is quite different; the FDA didn't even take crystals into account to the same class of salts or polymorphs in class.

Non obviousness

Non-obviousness refers to the fact that a "innovation" would be original but obvious to someone with the requisite technical expertise and familiarity if they created it relatively easily. According to Desiraju, identifying a co-former is rarely a routine process, unlike salt formation, in which an acid is required to create a salt with a base. Despite the existence of several co-crystal screening techniques, according to Trask, there is no reliable way to anticipate whether two molecules will form a hydrogen bond and a co-crystal. The co-crystallization process is governed by many variables, however more research is still needed to better understand it.

Furthermore, it is impossible to forecast co-crystal structure. Hence it accomplishes the Non obviousness criteria.

Utility

The only requirement that must be proven in the case of pharmaceutical co-crystals is utility or application of the invention in order to get a patent. Opportunities offered by co-crystals are comparable to those of polymorphs. They can be produced in greater quantities for any particular API, boosting the pharmaceutical market around it and, as a result, the range of beneficial characteristics that may be accessed, as they are unmistakably novel chemicals with fewer inherent anticipated problems likely to occur. According to Trask, an API's co-crystal has the same patented therapeutic usefulness as its parent API.

The extensive co-crystals research conducted over the past ten years suggests that co-crystals provide a wealth of chances for improving an API's features, which in turn boosts its usability and usefulness. (27)

5. Patents on Co-Crystals: Case Studies

Pharmaceutical co-crystals have grown significantly over the past ten years, and numerous research publications and patent applications have been made worldwide. To date, several patents relating to co-crystals and multi-drug co-crystals have been approved. Table 3, Table 4, and Table 5 list some of the newly approved pharmaceutical co-crystal formulations as well as a list of approved patents on pharmaceutical co-crystals in the USA, International (global), and multi-drug co-crystals.

Entresto

On July 7, 2015, the US Food and Drug Administration (FDA) approved a sacubitril and valsartan combination cocrystal formulation (brand name Entresto, Novartis) to minimise the risk of cardiovascular and chronic heart failure. Entresto was a novel oral combination that received fast-track approval. (28)

Lexapro

Lexapro is a cocrystal formulation of escitalopram that was licenced in 2009 for the treatment of serious depressive and anxiety disorders under the brand name Lexapro. (29)

Steglatro

The Food and Drug Administration (USFDA) has approved Ertugliflozin cocrystal formulation (Ertugliflozin cocrystal with 5-oxo-proline) under the brand name Steglatro™. (30)

Suglat® (Ipragliflozin: L-proline)

Astellas Pharma and Kotobuki Pharmaceuticals created an Ipragliflozin: L-Proline cocrystal with a molecular ratio of 1:1. Ipragliflozin is a sodiumglucose co-transporter-2 (SGLT2) inhibitor. In Japan, the cocrystal formulation has been approved and is marketed as Suglat®. (31,32)

TAK-020—Co-crystals of gentisic acid

TAK-020 is a novel cocrystal-based formulation developed by Takeda Pharmaceuticals for the treatment of rheumatoid arthritis (Bruton's tyrosine kinase inhibitor). Phase I clinical trials for the cocrystal have been completed. (32)

Aripiprazole

Aripiprazole is a cocrystal formulation sold under the brand name Abilify®. Abilify is made up of co-crystals that contain aripiprazole and fumaric acid. Aripiprazole is a psychiatric medication used to treat schizophrenia. (33)

Tramadol- Celecoxib Cocrystal (1:1)

Enantia and Esteve, R&D, Spain, produced Cocrystal E-58425, which contains celecoxib and tramadol (1:1) and was patented by Laboratorios Del. This is an example of a multidrug cocrystal that is now in clinical trials. The synergistic impact of its components will aid in achieving therapeutic benefits at lower and more bearable levels for each component. A phase II proof-of-concept study in acute postoperative pain found that co-crystals outperformed placebo and a benchmark in terms of efficacy and safety. Clinical trials for the cocrystal-based formulation are currently in phase III. 48-50 Boehringer Ingelheim Pharma Gmbh Co and AstraZeneca received further patents for innovative co-crystals of tiotropium bromide and ticagrelor medicines, respectively. (34)

Table 3. Composition Patents issued IN USA for pharmaceutical co-crystals. (35)

US Patent No.	Date of Issue	Assignee	Compound
US6001996	14 Dec 1996	Eli Lilly & Co, Inc.	Complexes of (carba) cephalosporin with parabens
US7625910	1 Dec, 2009	Astra Zeneca AB	AZD1152; a phosphate prodrug and maelic acid cocrystal
US8124603	28 Feb, 2012	Thar Pharmaceutical	Meloxicam with various carboxylic acids, aliphatic and aromatic and maltol, ethyl

			maltol
US20170044176 A1	16 Feb, 2017	Euticals Spa	Co-crystals of tiotropium bromide and lactose monohydrate co-crystals
US20170224724 A1	10 Aug, 2017	University of South Florida	Co-crystals (ICC) of lithium and salicylic acid and 1- proline

Table 4. International Patents on Co-crystals. (27)

Patent No.	Date of Issue	Assignee	Compounds
WO2017191539 A1	9 Nov, 2017	Aurobindo Pharma Ltd.	di-proline cocrystal of dapagliflozin
WO2017144598 A1	31 Aug, 2017	Enantia , S.L	Co-crystals of Lorcaserin hydrochloride and organic diacid
WO2017115284 A1	6 Jul, 2017	Leiutis Pharmaceutical Pvt Ltd.	Adipic acid cocrystal of Agomelatine
WO2016156127 A1	6 Oct, 2016	Ratiopharm Gmbh	Cocrystal of ibrutinib and carboxylic acid

Table 5. Patents on Multi-drug Co-crystals. (36-39)

Drug Combination	Therapeutic category
ASA-theanine	NSAID and psychoactive
Cyprodinil-dithianon	Fungicides
Mesalamine with alpha amino acids, flavones and nutraceuticals	Anti-inflammatory
Metformin-oleoylethanolamide	Antidiabetic and anti-obesity

Patent Ever-greening and Co-crystals

Patents that are filled to protect the additional aspects of later advancements to an invention are referred to as ever-greening and follow-on patents. This provision of follow-on patents to an existing innovation was enacted into law to stimulate further research as a means of obtaining pharmaceutical items that are far safer and more effective. While the terms "ever-greening patent" and "follow-on patent" are both used to refer to patents that protect pharmaceutical formulations, new forms of active agents, processes for manufacturing active agents, new uses for pharmaceutical products, new combinations of active agents, and new dosing regimens, the majority of pharmaceutical companies have abused this provision and have built picket fences of minor improvements that have been filled over the parent patent, successfully preventing generic entrance into the market and retaining their monopoly for long periods of time. While cocrystallization is a method that appears to produce drug products that meet the criteria for innovation, non-obviousness, and utility, it may encourage the research of earlier APIs for new benefits, which could lead to the ever-greening of current medication patents. (40)

6. Conclusion

Cocrystallization is a burgeoning field of research having immediate implications for the pharmaceutical sector. New design solutions have been developed during the last 20 years to circumvent the limitations associated with API salt production. These new approaches also open up new opportunities for customising APIs to meet specific requirements. One of these freshly discovered strategies in pharmaceutical sciences is the utilisation of pharmaceutical cocrystal. The development of these crystalline solids is a rapidly emerging topic that has attracted a lot of industry attention.

A pharmaceutical cocrystal is an API that interacts with a coformer via non-ionic interactions within a unit cell, according to the FDA. Initially, the FDA believed that co-crystals should not be considered an API in the traditional sense. These solids were classified as drug product intermediates by the FDA. This point of view sparked a heated debate among scientists in both academia and industry. As a result, the guidance document on the classification of pharmaceutical co-crystals was revised.

Co-crystals are considered a special case of solvates in the FDA's current view. Solvates, on the other hand, are one of three types of polymorphs. This property explains why pharmaceutical co-crystals may be suitable for shortened applications under the Hatch-Waxman-ANDA Act's process. When comparing the regulatory situation for co-crystals in the United States and Europe, it appears that the European Medicines Agency (EMA) has a more flexible basis to work with when it comes to generics. This is because different API derivates can be utilised in a generic pharmaceutical product as long as the safety, efficacy, and quality are not harmed.

The regulatory position of coformers still needs to be addressed by the authorities, which is one of the largest possible problems when using co-crystals in the creation of a generic. The FDA does not state if coformers have the same status as excipients or have a distinct regulatory status. This is particularly problematic for shortened applications in the United States. The excipients in the generic product must be qualitatively and quantitatively identical to those in the innovator's product. When coformers are considered excipients, the similarity between the generic and innovator is no longer evident. As a result, the FDA may reject an ANDA application because the generic product's composition differs from the innovators. Pharmaceutical co-crystals, on the other hand, could be used to get around patents related with the parent API.

Pharmaceutical co-crystals look patentable when the criteria of innovation, utility, and non-obviousness are applied as evidenced by the amount of patents submitted by many pharmaceutical companies all across the world.

Despite the fact that there are still various issues to be considered and resolved regarding the use of pharmaceutical co-crystals, the debut of these solids has sparked a spirited debate in the regulatory arena. The ramifications of this new API form have prompted new regulatory methods for new medicinal items, but they could also be accommodated into the existing legal framework in the United States. It will be fascinating to observe how many new novel medications and generic pharmaceuticals will have a cocrystal API in the future, as well as what regulatory challenges these goods may face.

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Conflict of interest

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