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By Hand Delivery

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MUTUAL'S RESPONSE TO WEST-WARD'S COMMENTS


Despite the fact that Colcrys® is the designated Reference Listed Drug ("RLD") for single ingredient oral colchicine, West-Ward improperly submitted a 505(b)(2) application for a duplicate of Colcrys® for the prophylaxis of gout flares indication without referencing Colcrys® or certifying to the patents listed for Colcrys®. West-Ward claims that it can do this because it is identically situated to Mutual and is doing nothing different than Mutual did to obtain its approval for Colcrys®. Nothing could be further from the truth. There is a crucial difference between Mutual and West-Ward, which West-Ward studiously ignores. Unlike West-Ward, Mutual invested significant resources to conduct numerous studies that have advanced the science relating to the use of single ingredient oral colchicine, including for the prophylaxis of gout flares. Mutual's studies have benefitted both the medical profession and the patient community. As described below, this difference has changed the factual, scientific, and legal landscape, and it explains why West-Ward cannot travel the same path to approval as Mutual. In short, Mutual was the first company to obtain FDA approval for a single ingredient oral colchicine product and earned the exclusivity and other benefits (such as being the designated RLD) West-Ward now seeks to deny it.

According to West-Ward, it does not have to refer to Colcrys® or provide the related patent certification because it is not relying on Mutual's studies for the prophylaxis of gout flares...
indication it seeks. The facts show otherwise. Mutual conducted numerous studies to support the approval of Colcrys® that yielded important new information and discoveries necessary for the approval of colchicine for the prophylaxis of gout flares. The new information and discoveries are incorporated into the labeling for Colcrys® and are not found in the literature or in the labeling of Col-Probenecid, West-Ward’s proposed RLD. Those new discoveries are critical for the safe administration of colchicine, and no new applicant for a single ingredient oral colchicine product can now omit the information from its labeling. It is therefore apparent that West-Ward is relying on Mutual’s studies for approval and must certify to the patents listed for Colcrys®.

West-Ward also argues that FDA’s requirement that a 505(b)(2) application refer to the pharmaceutical equivalent drug, which for West-Ward’s product is Colcrys®, and certify to the patents listed for the pharmaceutical equivalent does not apply to West-Ward. As described below, Colcrys® is the proper RLD for West-Ward’s product from both a legal and scientific perspective. Additionally, West-Ward cites to the levothyroxine sodium situation to support its argument. However, West-Ward fails to disclose that FDA designated the first levothyroxine 505(b)(2) application as the RLD, and subsequent levothyroxine 505(b)(2) applications then relied on that RLD for approval. That is exactly what Mutual requested in its citizen petition with respect to colchicine and exactly what FDA must do here to avoid acting arbitrarily and capriciously.

Mutual’s citizen petition also explains why its three-year exclusivity prevents FDA from approving West-Ward’s application. In West-Ward’s comments, West-Ward simply asserts that Mutual’s exclusivity does not cover West-Ward’s product because Mutual did not perform any clinical trial relevant to the prophylaxis of gout flares. However, West-Ward’s comments fail to address Mutual’s cardiotoxicity study, which pertains to any use of colchicine. West-Ward also fails to explain why Mutual’s other studies are not relevant to the prophylaxis of gout flares. Indeed, West-Ward provides no response at all to Mutual’s showing that West-Ward cannot carve out important labeling information based on Mutual’s studies because it would render West-Ward’s product unsafe even for the prophylaxis of gout flares indication. No response is offered because none exists. The simple fact is that West-Ward’s proposed labeling carve-out would deprive prescribers and patients of essential safety information and would be obviously unsafe in light of the new scientific understanding discovered by Mutual.

Moreover, because West-Ward’s product is a duplicate (pharmaceutical equivalent) of Colcrys®, West-Ward must submit an Abbreviated New Drug Application (“ANDA”) pursuant to FDA’s policy, which has been in effect for over 12 years. The precedent cited by West-Ward to support its submission of a 505(b)(2) application instead of an ANDA is distinguishable, and there simply is no rational reason for FDA to depart from its longstanding policy.

Ultimately, in West-Ward’s zeal to circumvent Colcrys’s patents and exclusivities, West-Ward is bending the law and its underlying policies to the breaking point. FDA should grant the actions requested in Mutual’s citizen petition.
I. West-Ward Must Reference Colcrys® and Certify to the Patents Listed for Colcrys®

Despite West-Ward's legal and scientific acrobatics, it cannot escape the fact that its application for single ingredient oral colchicine must reference Colcrys® as the RLD and include certifications to the patents listed in the Orange Book for Colcrys®. First, Mutual conducted numerous studies that provided important new safety and effectiveness information regarding the use of colchicine, including for the prophylaxis of gout flares. Because the information from Mutual's studies is not in the literature or provided with West-Ward's proposed RLD, West-Ward must rely on Mutual's studies for approval. Second, Colcrys® is the only FDA-designated RLD for single ingredient oral colchicine and is legally and scientifically the proper RLD for West-Ward's product. Finally, the levothyroxine sodium situation, on which West-Ward principally relies, actually supports Mutual's Citizen Petition. Through the substantial investment of scientific and financial resources, Mutual has earned its status as the RLD with respect to single ingredient oral colchicine, and West-Ward must refer to Colcrys® and certify to the patents listed for Colcrys®.

A. West-Ward is Relying on Mutual's Studies

West-Ward argues that it does not have to reference Colcrys® or certify to the patents listed for Colcrys® because the literature and its asserted RLD, Col-Probenecid, contain sufficient information to support approval of West-Ward's product. Indeed, West-Ward admits that it would be necessary to rely on Colcrys® if "Mutual's approval contained data necessary to support the safe and effective use of West-Ward's product for prophylaxis." This admission should end the matter: that is exactly the situation now confronting FDA. Although West-Ward prefers to turn a blind eye to Mutual's contributions, Mutual performed numerous studies that provided new information and insight necessary for the safe and effective use of colchicine for any indication, including prophylaxis of gout flares. As detailed below, multiple FDA statements and actions have confirmed that this information is not provided in the literature or by Col-Probenecid. Accordingly, as West-Ward admits, FDA should require West-Ward to reference Colcrys® and certify to the patents listed for Colcrys®.

Colchicine is an old drug that historically has been used for the prophylaxis of gout flares and the treatment of acute gout flares. However, there had never been an FDA-approved application demonstrating safety and effectiveness for a single ingredient oral colchicine product until Mutual's application for Colcrys®. Rather, companies including West-Ward marketed unapproved versions of colchicine. During that time, colchicine was commonly administered to a patient for acute flares until the patient experienced adverse events. For example, West-Ward's labeling for its unapproved product stated that West-Ward's product should be given "until pain is relieved or nausea, vomiting, or diarrhea develops." The toxicity caused by colchicine is serious and can be fatal. Indeed, there have been 169 fatalities reported to FDA associated with the use of unapproved oral colchicine. Accordingly, the old paradigm for marketing colchicine

1 West-Ward Comments at 13.

2 See Mutual Citizen Petition at Tab 1.
was unacceptable, and FDA concluded that single ingredient oral colchicine products needed to have approved applications demonstrating safe and effective administration.³

Mutual was the first company to devote the resources necessary to obtain such an approval. In doing so, Mutual made surprising discoveries that changed and advanced the medical community’s knowledge of how to administer the drug safely and effectively. Contrary to West-Ward’s description, Mutual’s application was not a formality in which FDA simply acknowledged the prior use of colchicine and then rubberstamped an approval. Rather, it was an involved process that sought to reduce fatalities and adverse events related to the use of unapproved colchicine and to ensure the drug met modern approval standards. As FDA explained in a workshop regarding marketed unapproved drugs:

We all know that the regulatory standards and the science evolve over time so invariably if you are coming in referencing something that was approved many years ago or even just a few years ago you might find that the standards have changed. And, our reviewers are inclined to want to ask you to meet [current] standards.⁴

This is the situation with single ingredient oral colchicine. Although historically colchicine has been used to treat gout, the prior use was not demonstrated safe and effective in accordance with current FDA approval standards. As one commenter noted before Colcrys® was approved, “[c]olchicine is an ancient drug that would never pass the requirements of agencies operating today.”⁵ For example, FDA did not have fundamental safety information regarding colchicine, such as certain toxicity data, because colchicine was marketed before such data were required by FDA. As described by FDA, “[o]ral colchicine has been used for many years as an unapproved drug with no FDA-approved prescribing information, dosage recommendations, or drug interaction warnings.”⁶ Thus, when Mutual submitted the first application for colchicine, Mutual supported the application with studies that provided new information, beyond what then existed in the literature, to enable the safe and effective use of colchicine while minimizing the potential toxicities that plagued the prior use of colchicine. In addition to its research efforts to bring colchicine up to modern regulatory standards, Mutual made significant new discoveries that have revolutionized the safety of colchicine for all of its uses.

Cardiotoxicity studies. In particular, FDA requested that Mutual study the cardiotoxicity of colchicine because there was nothing in the literature or other approved colchicine products that provided such important information. As FDA explained, “[s]ince there is little information

⁴ Transcript of FDA’s Marketed Unapproved Drugs Workshop at 278-279 (Jan. 9, 2007) (Tab 1).
concerning colchicine’s potential cardiovascular toxicity, we recommend that the proposed cardiovascular safety studies be conducted.” FDA also “recommend[ed] ECG monitoring in all of the proposed PK studies.” Per FDA’s request, Mutual conducted at least five preclinical studies regarding the cardiotoxicity of colchicine. In addition, Mutual conducted at least one human in vivo trial to study cardiovascular toxicity.

Mutual completed study MPC-004-07-1002, which is titled “A Randomized, Double-Blind, Double-Dummy Pharmacokinetic and Exploratory ECG Safety Study of a Standard Acute Gout Regimen (Total Dose 4.8 mg over 6 Hours)” (emphasis added). The objectives of that study included determining “whether or not there is a trend toward the effect of this [dosing] regimen on ECG parameters, primarily the corrected QT interval and other ECG parameters.” As the QT interval represents the duration of ventricular depolarization and subsequent repolarization, this was an important clinical trial regarding the cardiotoxicity of colchicine. Cardiotoxicity studies are not limited to particular indications or uses of the drug; rather, they examine the potential effects on the heart of the compound itself, regardless of use.

Drug-drug interaction data. Additionally, Mutual conducted eight new studies directed toward reducing toxicity related to the co-administration of colchicine with other drugs. As West-Ward notes, the literature generally described toxicity caused by potential drug-drug interactions. At least 60 people have died from colchicine interactions with clarithromycin. However, the literature was incomplete and inaccurate. It contained conflicting information and did not suggest or provide any guidance regarding how to administer colchicine with the other

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7 Minutes from Type B Pre-IND Meeting Between FDA and Mutual on July 31, 2006 at 4 (meeting minutes prepared by FDA on Aug. 31, 2006) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 16).

8 Id. at 6; see also ICH Guideline (S7A): Safety Pharmacology Studies for Human Pharmaceuticals at 6 (July 2001) (“Effects of the test substance on the cardiovascular system should be assessed appropriately.”), available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129156.pdf. Based on the initial data generated by Mutual (including in vivo data), FDA did not require Mutual to pursue formal QT studies.

9 Effects of Colchicine on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (Study No. 1273HU21.001); Dose-Range-Finding (Pyramid) Intravenous Toxicity Study of Colchicine in Rabbits (Study No. 0406LU21.001); Effects of Colchicine on Electrocardiogram, Heart Rate and QTc in Anesthetized Rabbits (Study No. 1235LU21.001); Dose-Range-Finding (Pyramid) Oral Toxicity Study in Dogs with Colchicine (Study No. 0433DU21.001); Cardiovascular Evaluation of Colchicine in Conscious Telemetered Dogs (Study No. 1259DU21.001).


drugs to avoid toxicity and death. Those are of course just some of the many critical issues that West-Ward fails to mention.

Colchicine is a narrow therapeutic index drug, which means that it must be dosed precisely to be effective and avoid toxicity. Mutual studied the complex issues surrounding the administration of colchicine with other drugs. This was a significant undertaking. The medical literature is replete with conflicting and varying reports of elimination half-lives, ranging from 1 hour to over 50 hours, which resulted from inaccurate measurements of colchicine blood levels at later time points. Mutual used new analytical methods that were validated to picogram levels of detection to measure the correct elimination half life under normal conditions, at steady state, and in the presence of drug-drug interactions. Mutual also performed studies to dissect the differing contributions by CYP 3A4 versus P-gp towards metabolism and disposition of colchicine in the body. Mutual also dealt with the barrier to performing drug-drug interaction studies with colchicine that arises from the fact that colchicine’s adverse events occur before its effectiveness can be measured. Mutual dedicated the resources and ingenuity to overcome these obstacles and conducted numerous drug-drug interaction studies, which have substantially improved the safety profile of this drug including new dosing amounts and regimens for prophylaxis of gout flares as well as other indications.

Mutual’s drug-drug interaction studies yielded valuable information that has reduced unnecessary toxicity and fatalities. For example, Mutual discovered that co-administering colchicine with clarithromycin could increase colchicine levels in the bloodstream by an average of about 230%, with some patients blood levels reaching nearly 600%. Mutual also established dosing adjustments so that patients who need to take colchicine with clarithromycin can do so safely and effectively. This information is considered new and so important that it has been accepted for publication by the American College of Rheumatology.13

The new dosing instructions are included in the labeling for Colcrys®. In fact, there are specific dose adjustment instructions for patients taking colchicine for prophylaxis of gout flares.14 These are obviously directly relevant to West-Ward’s product. The dose adjustment for prophylaxis of gout flares provides that when colchicine is used with a strong CYP3A4 inhibitor, such as clarithromycin, the colchicine dose should be adjusted from 0.6 mg twice a day to 0.3 mg once a day. If the original intended prophylactic dose was 0.6 mg once a day, then the dose should be adjusted to 0.3 mg once every other day.

This information is not in the literature. Although the literature generally noted drug-drug interactions, Mutual’s studies corrected errors in the literature, discovered new information about those interactions and, importantly, provided a solution to the problem in the form of novel


14 Colcrys® Package Insert (revised Sept. 2010) at 5 (Table 1) and 6 (Table 2) (attached to Mutual’s Citizen Petition at Tab 2).
and appropriate dosing instructions. As FDA reviewers explained: "The additional studies conducted by the Applicant [Mutual] have provided data that permits dosage recommendations based on the degree of CYP3A4 inhibition exhibited by the concomitant medication."¹⁵ There is often a substantial patient need to administer colchicine with other drugs, such as clarithromycin, and Mutual's new information provides a significant benefit to the public health by allowing this co-administration to be done safely.

In addition to the labeling for Colcrys®, Mutual's drug-drug interaction discoveries have been deemed so important that FDA mandated that it be incorporated into the labeling for other drugs. In particular, Mutual studied the effect of the protease inhibitor, ritonavir, on colchicine blood levels. Mutual discovered that the co-administration of colchicine with ritonavir could increase average colchicine blood levels by nearly 185%, with some patients having increased levels approaching 450%. As a result of Mutual's work, FDA took the significant step of requiring all protease inhibitors approved for the treatment of HIV-1 infection to include in their labeling Mutual's reduced dosing instructions when co-administering these drugs with colchicine.¹⁶ That is true regardless of the purposes for which the colchicine is being administered, including prophylaxis of gout flares. As FDA explained in its press release announcing the new labeling, "The approved protease inhibitors for the treatment of HIV-1 infection now all include the following drug-drug interaction information: . . . New dosing recommendations for colchicine when prescribed for the prophylaxis of gout. . . ."¹⁷

Dosing data. Mutual performed another trial, the AGREE trial, that provided important new information regarding the optimal dose of colchicine for treatment of gout flares. The trial was a double blind, placebo controlled, multicenter (54 U.S. sites), dose-comparison study involving 575 trial participants that compared the effects of the traditional dose (limited to 4.8 mg of colchicine) versus a lower dose of just 1.8 mg. Through the AGREE trial, Mutual discovered that the lower dose is just as effective as the higher, traditional dose, but without the

¹⁵ FDA Summary Review for Regulatory Action for NDA 22-353 at 9 (Oct. 16, 2009) (emphasis added) (Tab 3). See also 75 Fed. Reg. 60768, 60769 (Oct. 1, 2010) ("These approvals [the approvals of Colcrys®] were based on extensive evaluation of studies and new data that permitted refinement of dosing regimens and labeling. When used in accordance with the approved labeling, single-ingredient oral colchicine was found to be well-tolerated and safe when taken at therapeutic doses and with appropriate dose reductions in susceptible populations or with potentially interacting drugs." (emphasis added)); id. ("Additionally, based on pharmacokinetic studies conducted in support of the approved NDAs, new specific-dose modification and reduction recommendations are provided in the approved colchicine labeling for its use with drugs that use certain enzymes, such as CYP3A4 or P-gp, for their metabolism or absorption." (emphasis added)); FDA, Questions and Answers for Patients and Healthcare Providers Regarding Single-Ingredient Oral Colchicine Products (Sept. 30, 2010), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm227961.htm ("Based on information submitted to the Agency, new specific dose modification and reduction recommendations are in the approved colchicine label. . . . The approved labeling reflects this newly discovered information." (emphasis added).

¹⁶ See FDA, New Label Information Affecting All Approved Protease Inhibitors for Treatment of HIV (attached to Mutual's Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 1).

¹⁷ Id.
serious adverse events of the higher dose. Nineteen percent of patients who received the higher dose experienced serious adverse events, whereas Mutual’s lower dose produced zero serious adverse events. Additionally, for the higher dose regimen, 77% of patients reported gastrointestinal adverse events, whereas the incidence dropped to 26% of patients using Mutual’s low dose regimen. Based on Mutual’s trial, FDA approved Mutual’s colchicine product with the low dose regimen as safe and effective for the treatment of gout flares. Additionally, the AGREE trial was deemed so important that its results were published by the American College of Rheumatology.  

Reliance on Mutual’s studies. West-Ward argues that “a large amount of other published literature also supports the safety and effectiveness of colchicine in the prophylaxis of gout flares”; however, the discoveries from Mutual’s studies are not in the public literature or available from Col-Probenicid. The available literature does not contain all of the information needed for West-Ward’s application. As such, despite West-Ward’s protestations to the contrary, its application necessarily relies on the clinical information discovered by Mutual and must therefore certify to the patents listed for Colcrys.

Mutual is aware of publicly available labeling for a marketed unapproved West-Ward colchicine product indicated only for prophylaxis of gout flares posted on the DailyMed site. Mutual believes this represents the proposed labeling that West-Ward submitted with its 505(b)(2) application and improperly seeks to use with its product (“West-Ward’s proposed labeling”). West-Ward’s proposed labeling cites to additional publications. However, none of the publications cited by West-Ward provides the information obtained from Mutual’s studies, such as colchicine cardiotoxicity data or specific dosing adjustments to avoid drug-drug interactions. Indeed, even West-Ward does not argue that such information is in the literature.

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19 West-Ward Comments at 4.

20 In an effort to make labeling information available to the public, the National Library of Medicine posts product labeling on its DailyMed section. Recently, Mutual discovered three package inserts posted on DailyMed for a West-Ward 0.6 mg colchicine tablet product indicated only for prophylaxis of gout flares. The package inserts are essentially the same in substance. They all identify West-Ward as the manufacturer of the product, while two of the package inserts identify repackagers (Rebel Distributors Corp. and RemedyRepack Inc.). See http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=36824 (Rebel Distributors Corp. labeling) (Tab 5); http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=33844 (RemedyRepack Inc. labeling) (Tab 6); http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=43702 (West-Ward archived labeling) (Tab 7).

21 In addition to FDA’s conclusion that Mutual’s drug-drug dosing information is new and not in the literature, Mutual received patent protection covering inventions stemming from those studies. To receive those patents, Mutual proved to the U.S. Patent and Trademark Office that the inventions are new and not obvious from the published literature. See 35 U.S.C. §§ 101, 102, and 103.
Because the new information resulting from Mutual’s studies is not in the literature or found with respect to Col-Probenecid, it is clear that West-Ward is relying on Mutual’s studies for approval. FDA can and indeed must take Mutual’s information into account when considering applications for approval of single ingredient oral colchicine products. And a comparison of West-Ward’s proposed labeling with Colcrys’s labeling confirms that West-Ward is actually relying on Mutual’s studies. The most telling proof of this fact is that West-Ward’s proposed labeling is consistent with Mutual’s studies and not the publications West-Ward cites and claims to rely on. Those publications in many instances actually would support language different or even opposite from that found in West-Ward’s proposed labeling.

For example, one publication cited by West-Ward notes numerous fatalities associated with the concomitant use of colchicine and clarithromycin and concludes that “clarithromycin and colchicine should not be prescribed concomitantly.” West-Ward’s proposed labeling, however, does not contraindicate colchicine and clarithromycin. Rather, West-Ward’s proposed labeling follows Mutual’s lead and states that “[t]he available data suggest a dosage adjustment is necessary with strong CYP3A4 and P-gp inhibitors.” Incredibly, West-Ward’s proposed labeling simply provides this general edict for prescribers without any guidance on how to adjust the dose to ensure the safe and effective use of colchicine. West-Ward’s omission of the actual dose adjustments is both a danger to public safety and a thinly veiled attempt to avoid acknowledging that West-Ward is in fact relying on Colcrys®. Given that the only source for the necessary dosage adjustment comes from Mutual’s studies, this statement clearly indicates that West-Ward is relying upon Colcrys®.

Indeed, West-Ward’s proposed labeling would be meaningless (and unsafe) to a practitioner without reference to the dosing adjustments provided in the Colcrys® labeling. FDA underscored this point and the necessary reference to Colcrys® when FDA explicitly stated that healthcare practitioners should “refer to Colcrys’ approved prescribing information for specific dosing recommendations and additional drug interaction information.” FDA’s statement is equally applicable to West-Ward, which must also refer to Colcrys® for specific dosing instructions. Given that is the case, West-Ward’s 505(b)(2) application must reference Colcrys® and certify to the patents listed for Colcrys®. It would be contrary to the public health for FDA to allow West-Ward to omit such critical dosing information from its labeling.

West-Ward also argues that it does not need to rely on Mutual’s studies because Mutual “did not perform any studies for its prophylaxis indication.” This is simply not true. As described above, Mutual’s drug-drug interaction studies led to the discovery of reduced dosage...

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24 West-Ward Comments at 6.
instructions that are specific to the prophylaxis of gout flares when colchicine is used with a strong CYP3A4 inhibitor, such as clarithromycin. Furthermore, Mutual’s other studies support the use of colchicine for the prophylaxis of gout flares and provide information essential for labeling the product for that use. For example, Mutual’s cardiotoxicity studies provide basic safety information regarding colchicine that is applicable to the use of colchicine for any indication, including the prophylaxis of gout flares.

Additionally, although Mutual’s AGREE trial was performed as part of the treatment of gout flares indication, it provides important information for the prophylaxis of gout flares indication as well, because patients taking colchicine for the prophylaxis of gout flares commonly suffer a break-through flare.25 The dosing regimen for treating a gout flare that occurs during prophylaxis is different than the dosing regimen for treating a gout flare that occurs when the patient is not being treated for prophylaxis. Based on the AGREE trial, the labeling for Colcrys® provides for the safe and effective dosing of Colcrys® to treat a gout flare during prophylaxis.26

The AGREE trial, moreover, provided basic safety information regarding colchicine that is applicable to use of colchicine regardless of indication. As FDA noted regarding Mutual’s application for the prophylaxis of gout flares indication, “The primary safety database for this application is comprised of the safety data that were submitted in support of the applications for the treatment of FMF and treatment of acute gout flares. It consisted of . . . data from a trial, MPC-004-06-001 [the AGREE trial], conducted by the Applicant in support of the application for the treatment of acute gout flares.”27 Similarly, FDA underscored the importance of Mutual’s new safety information for other applications, such as West-Ward’s NDA, at the pre-IND meeting for Colcrys®, where FDA stated that Mutual’s “safety information will be applicable to other NDAs.”28

West-Ward also references an old citizen petition (Docket No. FDA-2008-P-0442), which Mutual submitted and then withdrew, to support West-Ward’s argument that additional studies are not necessary for West-Ward’s application.29 In that petition, Mutual requested that


26 The labeling provides that “COLCRYS may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Wait 12 hours and then resume the prophylactic dose.” Colcrys® Package Insert (revised Sept. 2010) at 3-4 (attached to Mutual’s Citizen Petition at Tab 2).


28 Minutes from Type B Pre-IND Meeting Between FDA and Mutual on July 31, 2006 at 6-7 (meeting minutes prepared by FDA on Aug. 31, 2006) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 16).

29 West-Ward Comments at 6.
FDA require certain studies for the approval of colchicine for the “prophylaxis of gouty flare” indication. For example, the old petition requested that such applicants perform drug-drug interaction studies, similar to the studies that Mutual performed to support its application for Colcrys®. Obviously, Mutual still believes that such studies are necessary. Mutual withdrew its earlier petition without prejudice, and the withdrawal has no bearing on the actions requested in Mutual’s current citizen petition. West-Ward’s assertion that Mutual’s withdrawal of that citizen petition is proof of a Mutual position on the scientific merits is bizarre and incorrect.

Despite West-Ward’s mischaracterization of Mutual’s contribution, there is no question that Mutual’s discoveries significantly changed the treatment paradigm for single ingredient oral colchicine. Mutual’s efforts resulted in significant benefit to the public health by reducing colchicine toxicity and avoiding unnecessary potential fatalities. As FDA’s Director of the Center for Drug Evaluation and Research explained:

Without this review [of Colcrys®] by FDA, outdated assumptions of what is safe and effective for treatment with oral colchicine would have remained unchecked, and patients would have continued to suffer from adverse reactions such as severe gastrointestinal complications - and even death - needlessly.30

The “outdated assumptions” referred to by FDA in the above quote are those in the literature and the Col-Probenecid approval that West-Ward attempts to rely upon for its approval. The approval of Colcrys® set a new and safer standard for the use of colchicine for any indication based on the kind of innovator research that fully justifies exclusivity. Despite West-Ward’s attempt to pretend otherwise, it is clear that West-Ward is relying on Mutual’s new information in seeking approval of its duplicate colchicine product.31 As such, West-Ward must reference Colcrys® and certify to its patents.

West-Ward also suggests, especially in its more recent supplement of March 29, 2001, that concerns about patient access and the price increase that inevitably attends the entry of a product supported by new research should lead FDA to accept West-Ward’s legal contortions and approve its application despite the law’s clear requirements. Although such concerns have no proper place in FDA’s consideration of these issues, Mutual nonetheless wishes to make certain FDA understands that Mutual is dedicated to ensuring that all patients have access to its product. Mutual has implemented a robust Co-pay Assistance Program for most patients with health insurance. Additionally, Mutual has implemented a Patient Assistance Program (“PAP”) for patients who are uninsured or insured through Medicare Part D, and for anyone who

30 Open Letter from J. Woodcock Regarding Unapproved Colchicine at 3 (Mar. 3, 2010) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 2).

31 As further evidence that West-Ward is relying on Colcrys®, West-Ward requested that FDA provide West-Ward with parts of the Colcrys® NDA. See FOIA Request Log Control No. 2009-6835 (Aug. 20, 2009) (Tab 9). If West-Ward were relying only on the published literature and West-Ward’s proposed RLD (Col-Probenecid) as West-Ward claims, then there would be no reason for West-Ward to seek information from Mutual’s NDA.
otherwise does not have coverage. Using an average for the four weeks ending March 24, 2011, the monthly participation in Mutual’s assistance program was at least 43,116 patients compared to 19 contacts regarding access to Colcrys® (all price based). Thus, the ratio of patients receiving assistance from Mutual in a month, versus the number of patients contacting Mutual about price, is over 2000 to 1. And most, if not all, of the price inquiries were from individuals who were not aware of Mutual’s assistance plans.

Prior to FDA initiating its enforcement action against unapproved colchicine oral dosage forms, Mutual provided a written commitment to FDA that Mutual would continue its assistance plans until a generic product enters the market. Mutual believes that its assistance plans are not only among the most generous and comprehensive plans offered in the pharmaceutical industry, but that they are sufficiently comprehensive to address any patient access concern. FDA cited Mutual’s assistance plans in multiple FDA public announcements regarding enforcement action against unapproved colchicine, and the original assistance plans were sufficient to assure FDA that patients would have access to Colcrys® before FDA took enforcement action.32

But Mutual did not stop there. After the implementation of Mutual’s assistance plans, Mutual voluntarily made several enhancements that were not part of the original commitment to FDA. For example, Mutual routinely extends assistance even to those patients who do not qualify under Mutual’s plans without any diminution of benefits. Mutual believes that it has enrolled into Mutual’s PAP every U.S. citizen who has requested assistance with access to Colcrys® regardless of whether the patient qualified for assistance. 33 With respect to Mutual’s Co-pay Assistance Program, Mutual increased Mutual’s maximum contribution per prescription from $65 to $75 and lowered the co-pay floor for patients from $25 to $15 per prescription. Mutual believes that many patients now pay less for Colcrys®, which is FDA-approved and has enhanced safety benefits due to Mutual’s research, than other patients pay for West-Ward’s unapproved product.34

Mutual also is committed to ensuring that patients are aware of the available assistance offered by Mutual. Towards that end, Mutual embarked upon a “2 million contacts” program to inform physicians, pharmacists, and patients about Mutual’s patient assistance plans. Mutual’s contact program is completely voluntary and is not part of Mutual’s commitment to FDA. Thus

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33 Similarly, Mutual has provided assistance to certain dog owners who use colchicine even though it was not part of Mutual’s commitment to FDA. Although colchicine is not approved to treat dogs, Mutual asked FDA for permission to admit the dog owners into Mutual’s PAP as long as Mutual did not market Colcrys® for that veterinary use. FDA granted permission to Mutual, and the response has been overwhelmingly supportive.

34 Even though West-Ward is no longer manufacturing and shipping its unapproved colchicine product, West-Ward still has product on the market. In the years leading up to FDA’s enforcement notice, West-Ward significantly increased the market share of its unapproved product even as other companies with unapproved products acted responsibly by phasing out their products or, in the case of Mutual, by discontinuing marketing years earlier until receiving FDA approval.
far, Mutual has far exceeded its goal by sending over four million hard copy or electronic communications that inform about Mutual’s assistance plans, including over 280,000 co-pay pads, 281,000 MD Alert mailings, 300,000 Pharm Alert mailings, 84,000 post-teledetail nurse and pharmacist mailings, 210,000 Dear Doctor letters, 145,000 letters to patients, 165,000 PatientLink communications, and others. In addition to Mutual’s outreach program, information regarding the assistance programs is available to patients on the internet, directly from Mutual, and from health care providers.

As detailed above, Mutual is committed to providing full access for anyone who needs colchicine and to making Mutual’s assistance available with minimal patient effort.  

B. FDA Designated Colcrys® as the RLD for Single Ingredient Oral Colchicine Products, and Colcrys® is the Proper RLD for West-Ward’s Product

West-Ward is also required to reference Colcrys® because Colcrys® is the proper RLD for single ingredient oral colchicine products like West-Ward’s product. Not only is Colcrys® the only FDA-approved single ingredient oral colchicine product, it is also the official FDA-designated RLD for such products.

Instead of referencing Colcrys®, West-Ward is trying to circumvent Colcrys’s exclusivity and patents by referencing a different drug as the RLD. Specifically, West-Ward references Col-Probenecid as the RLD, which is a combination product containing colchicine and probenecid. Although Mutual referenced a similar product as the RLD for Colcrys®, Mutual had to reference the combination product because no closer match was then available. Because Colcrys® was the first single ingredient oral colchicine product to ever be approved by FDA, there was no single ingredient oral colchicine RLD for Mutual to reference when it submitted the application for Colcrys®.

At the time Colcrys® was approved in 2009, the colchicine-probenecid combination product was the most similar listed drug to single ingredient oral colchicine. Accordingly, it was the proper RLD for Colcrys®. However, West-Ward submitted its application in 2010, after Colcrys® was approved and designated by FDA as the RLD. Furthermore, as described above and explained further below, Mutual has since discovered information necessary for the safe use of colchicine for the prophylaxis of gout flares that is reflected in the labeling for Colcrys® and that has rendered Col-Probenecid inadequate as the basis for any further approval of a single ingredient colchicine product, whether for the prophylaxis of gout flares or otherwise. Thus, West-Ward badly mischaracterizes the situation when it states that it is doing nothing different than Mutual did to obtain its approval for Colcrys®. Changed circumstances matter. In light of the changed circumstances brought about by the approval of Colcrys®, West-Ward must

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35 Mutual also notes that, after Colcrys® was approved by FDA, West-Ward itself increased the price of its unapproved product without undertaking any studies or other activities to advance the safe and effective use of colchicine.

36 West-Ward Comments at 12.
reference Colcrys® and certify to the patents listed for Colcrys®. To do otherwise would be both legally and scientifically improper.

FDA long ago decided which listed drug a 505(b)(2) application should reference and which patents a 505(b)(2) application should provide certifications to under the Hatch-Waxman Act. Colcrys® is the proper RLD for West-Ward’s product under these requirements. Specifically, FDA stated that:

If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

... If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug.


Under FDA’s regulatory framework, Colcrys® is the proper RLD for West-Ward because West-Ward’s product is pharmaceutically equivalent to Colcrys® and not to Col-Probenecid. Pharmaceutical equivalent products have the same active ingredient, strength, dosage form, and route of administration.37 Both West-Ward’s product and Colcrys® contain the same active ingredient (colchicine), while Col-Probenecid contains an additional active ingredient (probenecid). Additionally, both West-Ward’s product and Colcrys® have the same strength of colchicine (0.6 mg). In contrast, Col-Probenecid contains a lower strength of colchicine (0.5 mg). Although all three products have the same dosage form (tablet) and route of administration (oral), Col-Probenecid is administered differently than both West-Ward’s product and Colcrys®. Based on West-Ward’s proposed labeling, West-Ward’s dosing instructions for prophylaxis of gout flares is the same as Colcrys® (one tablet once or twice daily, with a maximum dose of 1.2 mg/day). In contrast, the dosing instructions for Col-Probenecid provide that the dose is “1 tablet of probenecid and colchicine daily for one week, followed by 1 tablet twice a day thereafter” and, in some circumstances, the dose can be increased up to four tablets per day (i.e., maximum dose of 2.0 mg/day of colchicine).38 Due to the fundamental differences between West-Ward’s product and Col-Probenecid, Col-Probenecid is not the appropriate RLD for West-Ward’s product.

37 21 C.F.R. § 320.1(c).

Col-Probenecid is not the proper RLD for West-Ward for another reason as well: because Col-Probenecid was approved before 1982, its labeling is outdated. In particular, the Col-Probenecid labeling directly conflicts with the new FDA-approved labeling for Colcrys®, which reflects Mutual’s significant discoveries and efforts to have colchicine meet modern approval standards. For example, the Col-Probenecid labeling provides that daily dosing may be increased for patients with renal impairment from two tablets per day to four tablets per day.\(^{39}\) This directly contradicts the FDA-approved labeling for Colcrys®, which recommends reducing dosing in patients with renal impairment.\(^{40}\) As FDA stated when it reviewed the application for Colcrys®: "Significant adverse events are often the result of inappropriate dosing in patients with renal . . . insufficiency . . . ."\(^{41}\)

The labeling for Col-Probenecid is also missing the important dosing instructions to avoid toxicity related to drug-drug interactions. In fact, the labeling for Col-Probenecid does not even mention that the use of colchicine with CYP3A4 and/or P-glycoprotein inhibitors increases the risk of colchicine-induced toxic effects. This is clearly insufficient and contrary to the updated approach to administering colchicine. Unless West-Ward is really relying on Colcrys®, West-Ward would have no basis to have labeling that is different than the labeling for Col-Probenecid. (As noted above, the literature is not sufficient to support the new information contained in the Colcrys® labeling.) Despite West-Ward’s supposed reliance on Col-Probenecid, West-Ward’s proposed labeling looks very similar to Colcrys’s labeling and very different from Col-Probenecid’s labeling. The only conclusion is that West-Ward must be relying on Colcrys®, and thus must certify to the patents listed for Colcrys®.

Incredibly, West-Ward argues that it should receive special treatment from FDA and that FDA’s requirement that a 505(b)(2) application should reference a pharmaceutically equivalent drug and certify to the patents for that drug does not apply to West-Ward because FDA implemented the requirement in a draft guidance document.\(^{42}\) However, FDA issued the draft guidance document in 1999 and has consistently followed it during the 12 years it has been effective. In fact, FDA confirmed its requirement in a 2004 citizen petition response. Letter from Galson (FDA) to Beers and Cavanaugh Regarding Docket No. 2004P-0386 at 9-10 (Nov. 30, 2004) (“FDA’s Fenofibrate Response”) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 7). Not only did the FDA’s Fenofibrate Response confirm FDA’s requirement regarding pharmaceutically equivalent products, it also expanded the requirement to provide that when there is no pharmaceutical equivalent listed drug, then the 505(b)(2) applicant should choose the most similar listed drug as the RLD, even if another drug could serve as the basis for the application. Id. at 9. FDA also routinely uses a “505(b)(2) Assessment” checklist to determine the appropriate RLD, which contains a series of questions to

\(^{39}\) Id.

\(^{40}\) See Colcrys® Package Insert (revised Sept. 2010) at 7, 13 (attached to Mutual’s Citizen Petition at Tab 2).

\(^{41}\) See FDA Cross Discipline Team Leader Review for NDA 22-353 at 5-6 (Oct. 15, 2009) (Tab 12).

\(^{42}\) West-Ward Comments at 11.
determine whether “there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.” Indeed, FDA used such a checklist with respect to Colcrys® and seemingly failed to employ it correctly with respect to West-Ward’s product.43

In its citizen petition, Mutual cited numerous examples where a 505(b)(2) applicant was required to reference the pharmaceutical equivalent listed drug. For example, FDA refused to approve a 505(b)(2) application for extended release metformin until the applicant certified to the patents listed for the pharmaceutically equivalent extended release product. Letter from Orloff to Andrx Labs, Inc. Regarding NDA 21-574 at 1 (Feb. 20, 2004) (“Because of the statutory requirement, your 505(b)(2) NDA must contain patent certifications for those patents listed in Approved Drug Products with Therapeutic Equivalence Evaluations for Glucophage XR (NDA 21-202).”).44 West-Ward does not dispute or distinguish this example.

Similarly, a court required a 505(b)(2) applicant for extended release diltiazem to certify to the patents covering the pharmaceutical equivalent listed drug. Marion Merrell Dow, Inc. v. Hoechst-Roussel Pharms., Inc., Civ. No. 93-5074, 1994 U.S. Dist. LEXIS 10024, 32 U.S.P.Q. 2d 1156 (D.N.J. 1994).45 West-Ward attempts to distinguish this case by stating that the case did not concern determining the proper RLD. However, the case does concern the proper patent certification for a 505(b)(2) application. In that case, an applicant submitted a 505(b)(2) application that included patent certifications for a pharmaceutically equivalent extended release product. The applicant then tried to circumvent those patents by withdrawing its certifications and relying only on the immediate release product. Despite referencing the immediate release product, the court still required the 505(b)(2) applicant to certify to the patents covering the more similar extended release listed product. Id. The situation here is no different in regard to patent certifications. Consistent with that case, FDA should require West-Ward to certify to the patents listed for Colcrys®.

West-Ward further attempts to justify receiving special treatment from FDA by arguing that the statute requires an applicant to provide patent certifications only to the drugs upon which the applicant relies. According to West-Ward, “‘Reliance’ is the touchstone for certification.”46 However, West-Ward’s argument misses the point. Improper reliance is not the touchstone. Because the statute does not address “what listed drug or drugs must a 505(b)(2) application cite” and thus rely upon, FDA directly addressed the issue of choosing the appropriate RLD and provided that a 505(b)(2) application should reference the pharmaceutical equivalent or, if there

43 See 505(b)(2) Assessment, Administrative and Correspondence Documents, Colcrys®, NDA 22-353, at 5-6 (Tab 13).
44 Mutual Citizen Petition at 12 and Tab 4.
45 Id. at 12 and Tab 3.
46 West-Ward Comments at 8.
is no pharmaceutical equivalent, the most similar listed drug. In either case, Colcrys® is the proper RLD for West-Ward’s product. West-Ward’s position essentially amounts to the claim that two wrongs (of its own) make a right: West-Ward clearly cannot entitle itself to avoid certifying to the patents by violating the Agency’s requirements for properly identifying an RLD.

FDA’s requirement that a 505(b)(2) application should rely on the pharmaceutical equivalent or most similar listed drug is based on public safety concerns. From a scientific perspective, FDA’s finding of safety and efficacy for a pharmaceutical equivalent is more applicable and provides better support for the approval of a 505(b)(2) product than another RLD that is different from the 505(b)(2) product. Furthermore, as West-Ward notes, it is in the interest of the public health to “avoid unnecessary duplication of research and review.” Indeed, concerns regarding unnecessary duplicative testing have been an overriding issue with respect to FDA’s implementation of § 505(b)(2) since it was enacted. According to FDA:

Since the Agency began implementing section 505(b)(2) with the 1987 Parkman letter, FDA’s approach to 505(b)(2) applications has been governed by consistent scientific principles. In enacting the Hatch-Waxman Amendments, Congress authorized FDA to rely on information about the safe and effective use of an approved drug product to approve another drug with similar characteristics, because duplicative clinical testing to reestablish what has already been shown is wasteful, unnecessary, and may raise ethical issues.

Requiring 505(b)(2) applicants to identify the pharmaceutical equivalent or most similar listed drug directly furthers these goals because, as FDA’s Fenofibrate Response explains, “it follows that the more similar a proposed drug is to the listed drug cited, the smaller the quantity of data that will be needed to support the proposed change.” There is a significant public interest in avoiding unnecessary research and allowing the agency to review and analyze the smallest amount of data necessary to support a proposed change to a listed drug.

West-Ward argues that this policy is not applicable to its application because West-Ward should not have to conduct any additional studies to support its application but, instead, can rely strictly on published literature and the Col-Probenecid approval. However, as detailed above, the new studies Mutual conducted to support the approval of Colcrys® provided important new information that is not available from Col-Probenecid or the literature. Accordingly, this

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47 FDA’s Fenofibrate Response at 6.

48 Id. at 9; see West-Ward Comments at 12.


50 FDA’s Fenofibrate Response at 9.
underlying policy is applicable to West-Ward's application because, if it did not rely on Colcrys®, West-Ward would have to perform its own studies to obtain that information, which would unnecessarily put patients at risk. West-Ward of course should not conduct duplicative and potentially unethical human studies where the information is already available with respect to Colcrys®.

FDA's requirement also is based on intellectual property concerns. Specifically, FDA justifiably prevents an applicant from using the 505(b)(2) process "to end-run patent protections." The Hatch-Waxman Act established a framework to resolve patent disputes before a product receives marketing approval. According to FDA, "[t]he act promotes competition by creating a process to expedite the filing and approval of ANDAs and 505(b)(2) applications and for resolving challenges to patents before marketing begins." Applications for FDA Approval to Market a New Drug (Proposed Rule), 67 Fed. Reg. 65448 (Oct. 24, 2002). As the patents most likely to cover a 505(b)(2) product are listed with the drug that is most similar to the 505(b)(2) product, requiring a 505(b)(2) applicant to reference the pharmaceutical equivalent or most similar listed drug prevents the applicant from circumventing the most relevant patents, as West-Ward is so blatantly attempting to do here, and is consistent with the statutory scheme.

Additionally, FDA has historically implemented the 505(b)(2) provisions consistent with parallel ANDA provisions contained in FDCA § 505(j). As FDA explained, the 505(b)(2) application "reflects the same principles as the 505(j) application," FDA Draft 505(b)(2) Guidance at 3; and requiring a 505(b)(2) applicant to certify to the patents listed for the most similar listed drug "ensures that patent certification obligations for 505(b)(2) applications and for ANDAs are parallel." FDA's Fenofibrate Response at 10; see also Abbreviated New Drug Application Regulations (Proposed Rule), 54 Fed. Reg. 28872, 28892 (July 10, 1989) ("An applicant submitting a section 505(b)(2) application must make the same certifications with respect to patents as an applicant submitting an ANDA."). Similar to 505(b)(2) applicants, FDA requires ANDA applicants to reference the closest listed drug to prevent the applicant from circumventing relevant patent protection. For example, FDA has stated that an ANDA applicant cannot use the suitability petition process to avoid a pharmaceutically equivalent reference drug and end-run relevant patent protection. As FDA stated:

[I]f a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug. It should not circumvent the patents on the tablet by citing the capsule as the reference listed drug and filing a suitability petition under section 505(j)(2)(C) of the Act and 21 CFR 314.93 seeking to change to a tablet dosage form.

51 Id.
FDA’s Fenofibrate Response at 9 fn 13 (emphasis added); see also Letter from Woodcock to Aikman Regarding Docket No. FDA-2008-P-0329 at 13 (Nov. 25, 2008) (requiring an ANDA applicant using a suitability petition to change the basis for the ANDA after an NDA is approved for the same drug product described in the suitability petition “to ensure that ANDA applicants do not circumvent the patent certification requirements”) (Tab 14). Furthermore, FDA requires ANDAs to reference only FDA-designated RLDs even when there are other pharmaceutically equivalent listed drugs that could serve as the reference drug. 

Consistent with FDA’s approach with ANDAs, FDA should prevent West-Ward from circumventing the patents covering single ingredient oral colchicine for the prophylaxis of gout flares by citing as its RLD a different drug that has not benefitted from updated and innovative scientific research (and which would therefore represent an unnecessary safety hazard for patients). FDA should, consistent with its longstanding policies, respect the needs of science, safety, and intellectual property law by requiring West-Ward’s application to reference the most similar listed drug, which is Colcrys®.

West-Ward, however, argues that FDA’s policy regarding RLDs is not applicable to drugs whose safety and efficacy already are established solely in the public literature. First, as described above, the literature does not provide all of the information necessary to support the approval of West-Ward’s application; Mutual conducted numerous new studies to support the approval of Colcrys® that have substantially improved the safe and effective use of colchicine for prophylaxis of gout flares as well as the other indications. Second, even if the literature did fully support West-Ward’s application, West-Ward’s argument that FDA’s RLD requirement is inapplicable to 505(b)(2) applications that rely solely on the literature is not supported by law, fact, or policy. FDA’s requirement itself contains no such limitation or condition. To the contrary, FDA has indicated that even a 505(b)(2) application that relies solely on the literature must identify an RLD. According to FDA, “Even if the 505(b)(2) application is based solely upon literature and does not rely expressly on an Agency finding of safety and effectiveness for a listed drug, the applicant must identify the listed drug(s) on which the studies were conducted, if there are any.”

Furthermore, West-Ward’s argument is not supported by the facts. West-Ward cites to the levothyroxine situation to conclude that 505(b)(2) applications that rely only on published literature do not have to reference an RLD. However, as detailed below, FDA designated the first approved levothyroxine 505(b)(2) application as an RLD, and subsequent 505(b)(2) applications for levothyroxine referenced that RLD, even though they relied solely on the literature. Thus, the levothyroxine situation supports Mutual’s position, not West-Ward’s.

52 To the extent that West-Ward is questioning FDA’s authority to designate appropriate RLDs for 505(b)(2) applications, West-Ward is also questioning FDA’s authority to designate appropriate RLDs for ANDAs.

53 West-Ward Comments at 12.

54 FDA Draft 505(b)(2) Guidance at 8.

55 West-Ward Comments at 12.
Additionally, West-Ward’s RLD argument is not supported by policy. The underlying purpose of having 505(b)(2) applications for similar drugs use one central RLD (even if other RLDs are available) is to ensure that similar products have similar performance. Patients often switch between pharmaceutically equivalent products, and there is an expectation that such products will perform the same. Allowing such products to use different RLDs could result in a drift of performance between the products.

West-Ward also attempts to support its RLD argument by referencing an obsolete FDA policy. Specifically, West-Ward attacks Mutual’s citizen petition as conflicting with FDA’s goal that reference be made to the underlying studies needed for approval. To support its argument, West-Ward quotes language from a footnote in FDA’s Fenofibrate Response. However, West-Ward fails to disclose that FDA changed the very policy cited by West-Ward in a 2010 citizen petition response. Contrary to West-Ward’s rhetoric, Mutual did not “ignore this issue altogether”; rather, it is West-Ward that ignored the Agency’s most recent pronouncement on the subject “altogether.”

West-Ward also salts its response with references to conversations and other informal communications with FDA employees, who it implies assured it in advance of the propriety of its approach. This is self-evidently ridiculous: no employee of the Agency is in the business of guaranteeing final marketing approval before FDA has completed its review of the marketing application and all related legal and scientific issues. Specifically, West-Ward emphasizes the fact that it apparently had a telephone conversation with three FDA employees in 2009 regarding the development of its colchicine product. To support its claim, West-Ward submitted unofficial minutes that West-Ward itself drafted. Of note, West-Ward’s version of the meeting minutes includes the assertion that FDA stated that West-Ward could use Col-Probenecid as its RLD and that West-Ward did not need to conduct any clinical studies. As West-Ward knows, even if such statements were made, oral communications of this sort by FDA are not binding. As explained by FDA’s regulations, “A statement or advice given by an FDA employee orally . . . is an informal communication that represents the best judgment of that employee at that time but does

56 Id. at 13.

57 See id. (citing FDA’s Fenofibrate Response at 10 fn 14).


59 West-Ward Comments at Exhibit A. It should be noted that the sworn declaration by one of West-Ward’s employees who attended the meeting contradicts the meeting minutes. In particular, the declaration states that FDA advised West-Ward that it could seek approval by conducting a “bioequivalence” study to Col-Probenecid, which means that the products would have similar rates and extent of absorption. However, the sworn statement seems unlikely to be true because the two products have different strengths of colchicine. In contrast, West-Ward’s meeting minutes state that FDA indicated that West-Ward could perform a “bioavailability” study to Col-Probenecid, which simply implies a comparison. Although this discrepancy seems minor, it has important scientific consequences and shows that West-Ward’s meeting participant is unable to accurately describe the meeting, which calls into question the veracity of West-Ward’s minutes and sworn declaration.
not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.60 This is particularly true with respect to preliminary communications regarding NDA submissions given that FDA is required by statute to examine an application once it is submitted to determine whether the conditions for approval have been met. See 21 U.S.C. § 355(c), (d). FDA cannot make such determinations until the agency receives the actual application at issue, and must be able to account for any changes or new issues that arise between the time of any pre-NDA meetings and the review of the actual application. Certainly tentative, oral statements by individual FDA employees cannot, under any circumstances, estop the Agency from applying the law correctly or justify unlawful agency action.

Additionally, West-Ward could not possibly believe that the oral statements on which it purportedly relies constituted anything other than preliminary informal suggestions, because the meeting apparently did not include any legal counsel from FDA who could address the legality of the underlying issues. In fact, based upon West-Ward’s meeting minutes, it is clear that the participants did not consider all of the legal and factual issues related to West-Ward’s product, as described in Mutual’s citizen petition. Accordingly, such a conversation cannot provide West-Ward with the refuge it seeks. Ultimately, West-Ward is responsible for ensuring that its application meets all applicable standards, and FDA will make an official determination to that effect only after the Agency reviews the application and considers all relevant information and factors.

Finally, West-Ward makes the even more tenuous claim that a non-FDA employee, Dr. Cohen, was communicating on behalf of FDA with certain manufacturers of unapproved oral colchicine products and informed West-Ward that FDA would approve West-Ward’s application. According to West-Ward, Dr. Cohen stated that he was calling West-Ward and other manufacturers of colchicine, “with FDA’s knowledge and encouragement, to inform them that FDA would approve an NDA on the basis of a bioequivalence study between their products and Col-Probenecid.”61 This is particularly troubling. FDA clearly has not delegated its drug approval authority to individuals in the private sector, and West-Ward should have known that Dr. Cohen had no actual or apparent authority to make such promises, especially when individual FDA employees lacked such authority themselves. The purported comments also seem contrary to FDA’s dedication to transparency and the notice-and-comment procedures set forth in various governing statutes and regulations to ensure that FDA does not favor one manufacturer over others. In any event, if any such private communications were really made by Dr. Cohen, then clearly those statements are not binding on FDA.

60 See 21 C.F.R. § 10.85(k).

61 West-Ward Comments at 3.
C. The Levothyroxine Situation Supports the Conclusion that West-Ward Must Use Colcrys® as Its RLD.

Throughout its submission, West-Ward places principal reliance on the argument that the current situation is similar to and controlled by the prior situation concerning levothyroxine. Its central claim is that FDA should not require West-Ward to reference Colcrys® or certify to the patents for Colcrys® because FDA did not implement such requirements for levothyroxine. Once again, West-Ward blatantly distorts the facts. West-Ward incorrectly argues that FDA accepted multiple 505(b)(2) applications for levothyroxine without designating the first approved application as the RLD for subsequent applications. According to West-Ward:

> FDA’s willingness to accept multiple 505(b)(2) applications for levothyroxine, and to review all of them based entirely on literature in the public domain, is itself ample precedent for approving West-Ward’s NDA. Granting Mutual’s drug a preferred RLD status, when colchicine has been in the public domain for centuries, advances no rational objective and would conflict with FDA’s levothyroxine precedent.62

Contrary to West-Ward’s description, FDA did designate the first 505(b)(2) application for levothyroxine as an RLD, and subsequent 505(b)(2) applications referenced that application as the legal basis for approval and submitted related patent certifications. This is the same action that Mutual is requesting FDA take with respect to colchicine. Mutual’s 505(b)(2) product, Colcrys®, was the first approved single ingredient oral colchicine product and is the designated RLD. Consistent with the levothyroxine situation, subsequent 505(b)(2) colchicine applications must reference Colcrys® and certify to its patents.

The specific facts surrounding the levothyroxine sodium situation are as follows. Similar to colchicine, single ingredient levothyroxine products were marketed without an approved application for many years. There were, however, two approved combination products that contained levothyroxine, Thyrolar and Euthroid. On August 14, 1997, FDA issued a Federal Register notice announcing that single-ingredient levothyroxine sodium products are unapproved drugs and informing manufacturers that they would be required to submit applications if they wanted to continue marketing their products after a certain enforcement date.63

FDA approved Unithroid as the first single ingredient levothyroxine sodium product. Unithroid was approved under a 505(b)(2) application that relied solely on literature for all preclinical and clinical data. Contrary to West-Ward’s description, FDA designated Unithroid as an RLD. Subsequent 505(b)(2) applications for levothyroxine then referenced Unithroid as the

62 West-Ward Comments at 7.

legal basis for approval and provided related patent certifications. Examples of relevant language from the approval packages for subsequent levothyroxine 505(b)(2) applications are provided below.65

Synthroid: “LEGAL BASIS FOR SUBMISSION: 505(b)(2) application; RLD is Unithroid®”66

Levo-T: “The application is a 505(b)(2) NDA, which refers to Unithroid® (levothyroxine sodium tablets, USP); NDA 21-210 (Jerome Stevens, Bohemia N.Y.) as the reference listed drug (first approved levothyroxine sodium NDA)”67

Levoxyl: “[N]ow that an NDA has been approved for levothyroxine sodium tablets and there is a listed drug (Unithroid), applications that have been submitted or filed, but not yet approved, must be amended to contain a patent certification for each patent listed for the listed drug.”68

Levolet: “LEGAL BASIS FOR SUBMISSION: 505(b)(2) with reference to NDA 21-210 (Unithroid®, Jerome Stevens Pharmaceuticals, Bohemia, NY)”69

FDA’s action in the levothyroxine situation is consistent with its Draft 505(b)(2) Guidance and FDA’s Fenofibrate Response, which require 505(b)(2) applications to reference and certify to the pharmaceutically equivalent listed drug, or, if there is none, then to the most similar drug. As FDA stated with respect to the levothyroxine products, “Now that NDAs have been approved and there is a listed drug, applications that have been submitted or filed, but not

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64 After FDA approved subsequent products based on Unithroid, FDA designated certain subsequent products as additional RLDs based on anticipated or actual market leadership. FDA typically designates the market leader as the RLD. However, the market leader for levothyroxine, Synthroid, was not the first FDA-approved application. Accordingly, FDA designated additional RLDs because “it was unclear who would be the eventual market leader among the approved products.” Letter from Woodcock to Cerrito Regarding Docket No. FDA-2003-P-0337 (formerly Docket No. 03P-0097) at 5 (Oct. 1, 2003) (Tab 16). The fact that FDA designated subsequent levothyroxine products as additional RLDs does not affect the fact that the subsequent products relied on Unithroid for their original approvals. Similarly, West-Ward’s product should rely on Colcrys® for approval.

65 See also Levothroid (formerly Thyro-Tabs) (FDA Chemistry Review for NDA 21-116, at 6) (Tab 17) and Novothyrox (FDA Chemistry Review for NDA 21-292, at 6) (Tab 18). It seems that the only 505(b)(2) application for a single-ingredient levothyroxine product that did not reference Unithroid was Tirosint. However, Tirosint is a capsule product that is not pharmaceutically equivalent to Unithroid. Instead of referencing Unithroid, Tirosint referenced another single ingredient levothyroxine product and the historic market leader, Synthroid.

66 FDA Chemistry Review for Synthroid (NDA-21-402) (Tab 19).

67 FDA Chemistry Review for Levo-T (NDA 21-342) (Tab 20).

68 Patent certification from Jones Pharma Inc. for Levoxyl (NDA 21-301) to the patents listed for Unithroid (Mar. 19, 2001) (Tab 21).

69 FDA Chemistry Review for Levolet (NDA 21-137) at 7 (Tab 22).
yet approved, may need to be amended to include a patent certification for any patent listed for the listed drug.\textsuperscript{70} To quote West-Ward, the levothyroxine situation “provides an exact roadmap” for FDA action with respect to colchicine.

West-Ward also cites to a single unpublished district court opinion regarding a second phase of the levothyroxine situation that occurred after the relevant 505(b)(2) applicants had already received their original marketing approvals. That case is inapposite because, as the court stated, “this case presents both a factually and legally unique situation.”\textsuperscript{71} In that case, several levothyroxine manufacturers, Jerome Stevens, Inc. (Unithroid) and Mova Pharmaceuticals, Inc./Alara Pharm. Corp. (Levo-T), submitted supplements to their approved 505(b)(2) applications to obtain a therapeutic equivalence rating to another product – King Pharmaceuticals, Inc.’s levothyroxine product, Levoxyl.\textsuperscript{72} King argued that the supplemental applications were required to reference Levoxyl and include a certification to the related listed patents. Although the court rejected King’s arguments, the case concerned only supplemental applications that sought a therapeutic equivalence rating after their approvals as 505(b)(2) NDAs. As the court underscored, “The FDA points out that the NDA supplements submitted by Mova/Alara and Jerome Stevens simply asked for a bioequivalency determination.”\textsuperscript{73} Thus, the applications did not rely on any of FDA’s findings of safety or effectiveness. In contrast, West-Ward has submitted an initial marketing application (not a supplemental application) that seeks original marketing approval (not a therapeutic equivalence rating) by proposing to rely on FDA’s findings of safety and effectiveness for another drug product, Col-Probenecid. Accordingly, FDA should act consistent with the original approvals of the levothyroxine 505(b)(2) applications, where FDA designated the first approved application as the RLD and subsequent 505(b)(2) applications referenced the RLD and certified to the relevant patents. In fact, the initial marketing applications for the very levothyroxine products at issue in the King case, Levoxyl and Levo-T, did reference the RLD, Unithroid, and certify to the related patents when they were originally approved (see above).

Finally, consistent with the central point that West-Ward tries to ignore at every turn, it is vital to recognize that the original levothyroxine 505(b)(2) applications involved in the King case were approved solely on literature, which the court found critical.\textsuperscript{74} In contrast, as described above, Mutual conducted numerous studies that have provided important new information necessary for the safe and effective use of colchicine, including for the prophylaxis of gout.

\textsuperscript{70} FDA Guidance for Industry: Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications 4-5 (July 2001) (“FDA Levothyroxine Guidance”).


\textsuperscript{72} Therapeutic equivalence generally means that two products are pharmaceutically equivalent and bioequivalent, which indicates that the products can be substituted for each other.

\textsuperscript{73} King at 10.

\textsuperscript{74} Id.
flares. As such, West-Ward’s application must reference Colcrys® and include a certification to the related patents.

II. West-Ward failed to Provide any Meaningful Response to Mutual’s Exclusivity Arguments.

Mutual’s citizen petition explains at length why the three-year exclusivity granted to Colcrys® should prevent FDA from approving West-Ward’s single ingredient oral colchicine product. In response, West-Ward simply states that Mutual failed to submit any new clinical study reports with data that would be essential to approval for prophylaxis of gout flares. According to West-Ward, “[t]he only investigation that Mutual performed was for treatment of gout [i.e., the AGREE trial].” However, West-Ward completely ignores Mutual’s cardiotoxicity trials. In doing so, West-Ward effectively concedes the point.

As detailed in Mutual’s citizen petition, Mutual conducted six in vivo studies. Although the studies were primarily characterized as pharmacokinetic studies, they included other objectives unrelated to bioavailability. For example, Mutual’s trial MPC-004-07-1002 studied the cardiovascular toxicity of colchicine. Specifically, the MPC-004-07-1002 trial measured ECG parameters, such as “the corrected QT interval and other ECG parameters.” FDA specifically requested studies concerning colchicine’s potential to affect the heart. As FDA stated, “[s]ince there is little information regarding colchicine’s potential cardiovascular toxicity, we recommend that the proposed cardiovascular safety studies be conducted.” Additionally, FDA “recommended ECG monitoring in all of the proposed PK studies.” Another objective of the in vivo studies was to study the safety and tolerability of colchicine. As there was no previously approved single ingredient colchicine product, the safety information from Mutual’s clinical trials formed an important basis for the initial approval of such a product. It is fully applicable to the use of colchicine for any indication, including the prophylaxis of gout flares.

75 West-Ward Comments at 14. West-Ward also states that “FDA rightly denied Mutual’s request for exclusivity.” Id. This is simply not true; Mutual never made such a request. West-Ward apparently is referring to Mutual’s application for the prophylaxis of gout flares indication (NDA 22-353), where FDA did not act on its own to grant exclusivity when that application was approved. However, as Mutual explained in its Citizen Petition, the grant of exclusivity with that application was not necessary because the existing grant of exclusivity for “gout flares” covers the prophylaxis of gout flares. Mutual Citizen Petition at 14-15.

76 FDA Clinical Pharmacology Review for NDA 22-352 at 97 (Nov. 26, 2008) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 15).

77 Minutes from Type B Pre-IND Meeting Between FDA and Mutual on July 31, 2006 at 4 (meeting minutes prepared by FDA on Aug. 31, 2006) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 16).

78 Id. at 6. Based on the initial data generated by Mutual (including in vivo data), FDA did not require Mutual to pursue further QT studies.
Indeed, FDA expressly acknowledged that Mutual’s “safety information will be applicable to other NDAs.”

Furthermore, in attempting to dismiss trials such as the AGREE trial that were for “treatment of gout,” West-Ward fails to understand that the treatment of gout includes both the treatment of gout flares, either acutely or during prophylaxis of gout flares, and their continued prevention. Patients taking colchicine for prophylaxis of gout flares also commonly have breakthrough flares. Accordingly, the dosing information obtained from the AGREE trial is critical even for patients taking colchicine for prophylaxis of gout flares. Furthermore, the AGREE trial includes safety information that is applicable to any indication, including prophylaxis of gout flares. The determination that treatment of gout flares includes prophylaxis of gout flares is confirmed by FDA documents. As evidenced in FDA’s Orange Book, Colcrys earned exclusivity for “gout flares,” and the FDA-approved Colcrys labeling for “gout flares” clearly includes the prophylaxis of gout flares.

Mutual also conducted eight studies regarding drug-drug interactions. The studies yielded important new information regarding the administration of colchicine, including dosing instructions specifically for prophylaxis patients, that significantly reduces the risk of unnecessary toxicity and fatalities. The information was incorporated into the labeling for Colcrys. For example, the dose adjustment for prophylaxis of gout flares provides that when colchicine is used with a strong CYP3A4 inhibitor, such as clarithromycin, the colchicine dose should be adjusted from 0.6 mg twice a day to 0.3 mg once a day. If the original intended prophylactic dose was 0.6 mg once a day, then the dose should be adjusted to 0.3 mg once every other day. That information was so important that it formed the basis of a REMS (Medication Guide), an FDA MedWatch communication, an FDA video to healthcare providers, and was also incorporated into the labeling for other affected products (i.e., protease inhibitors for the treatment of HIV).

Mutual’s drug interaction studies resulted in important therapeutic innovations (e.g., new dosing instructions) that benefited the public health and apply to any use of single-ingredient colchicine, including the prophylaxis of gout flares. They are exactly the type of research that merits exclusivity.

79 Id. at 6-7.


81 For example, FDA acknowledged that Mutual’s application for the prophylaxis of gout flares indication is supported with safety data from the AGREE trial. See, e.g., FDA Summary Review for Regulatory Action for NDA 22-353 at 15 (Oct. 16, 2009) (Tab 3).

82 For example, MPC-004-07-1006 studied the effect of clarithromycin on the pharmacokinetic profile of colchicine.
III. West-Ward Failed to Address Mutual’s Labeling Carve-Out Arguments.

Based on Mutual’s efforts to bring the first single ingredient oral colchicine product to market, Mutual lawfully received certain market exclusivity periods and patent protection. The protected information is included in the labeling for Colcrys® and is necessary for the safe and effective use of colchicine for the prophylaxis of gout flares. One of the central arguments in Mutual’s citizen petition is that FDA should not permit West-Ward to omit or “carve out” the protected labeling information. Despite the critical nature of the labeling carve-out argument, West-Ward provides no response whatsoever. That is because no adequate response exists. As West-Ward tacitly admits by its failure to respond, allowing the labeling for West-Ward’s product to carve out the protected information would render West-Ward’s product unsafe. As such, it is ineligible for marketing approval.

As detailed above, Mutual discovered through its development program for Colcrys® essential information regarding drug interactions; dosage adjustments for the coadministration of colchicine with strong and moderate CYP3A4 inhibitors, P-gp inhibitors, and protease inhibitors; and information regarding the concomitant use of colchicine for both the prophylaxis of gout flares and treatment of gout flares, including new dosing instructions for treating gout flares that occur either acutely or during prophylaxis of gout flares. All of this information is included in the FDA-approved labeling for Colcrys®. In order to avoid prescriber confusion and potentially serious risks to patients, FDA must require that this information be included in the labeling for all single-ingredient oral colchicine products, including West-Ward’s product. Indeed, FDA already previewed the significant risk to the public health that would be posed if FDA allowed West-Ward to omit such information from its labeling when FDA described the labeling for the marketed unapproved colchicine products. As FDA explained:

The fatalities associated with unapproved oral colchicine products are among many other serious adverse events associated with unapproved drugs. These adverse events, in addition to being tragic and in many cases preventable, place a serious burden on the healthcare system. The Agency is particularly concerned because labeling of many unapproved drugs does not adequately convey the risks of the drugs and how to best use drugs safely, such as what kind of other medicines should be avoided at the same time to lower the chances of side effects. When a drug is not used properly because the labeling is inadequate, there is a cost to patients and the healthcare system because of the care required as a result of adverse events.

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83 It bears repeating that, compared to Col-Probenecid, Colcrys® contains very different dosing recommendations including the opposite dosing adjustments for renal insufficiency.

84 Open Letter from J. Woodcock Regarding Unapproved Colchicine at 3 (Mar. 3, 2010) (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 2) (emphasis added).
Despite West-Ward's attempt to downplay the underlying facts, Mutual's studies and innovation greatly improved the paradigm for the safe and effective use of colchicine. The improvements are reflected in the labeling for Colcrys®, and can be readily seen by comparing the Colcrys® labeling to the labeling for the marketed unapproved products (or to Col-Probenecid). FDA cannot allow West-Ward to move back to the old paradigm, where patients suffer unnecessary toxicity and physicians have drug labeling that denies them this critical safety information and instructions.


The labeling for Colcrys® includes important information related to drug-drug interactions that cannot be omitted from West-Ward's labeling. As noted, Mutual's research to support the approval of Colcrys® included conducting at least eight pharmacokinetic studies comparing the bioavailability of colchicine administered alone with the bioavailability of colchicine co-administered with other drugs. Mutual discovered that some drugs, such as clarithromycin, created serious toxicity problems by dramatically increasing colchicine concentrations in the blood. Importantly, based on its studies, Mutual determined dose adjustments for the safe use of colchicine with strong and moderate CYP3A4 inhibitors, P-gp inhibitors, and protease inhibitors, which are included in the Colcrys® FDA-approved labeling. The labeling for Colcrys® includes separate dose adjustment instructions for the prophylaxis of gout flares, treatment of gout flares, and FMF indications. Thus, this labeling information is directly relevant to West-Ward's product. Indeed, FDA stated as much when it reviewed the Colcrys® application. According to FDA, "The label should include information on drug-drug interactions and appropriate recommendations for dose adjustment."

The labeling for Colcrys® also provides similar dose adjustment information for the co-administration of colchicine with proteases inhibitors, such as ritonavir. Mutual studied the effect of ritonavir on colchicine and discovered that co-administration of the drugs could result in a dangerous increase in colchicine blood levels. FDA considered the new drug interaction and dose adjustment information for the use of colchicine with ritonavir to be so important that FDA

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85 As noted in Mutual's Citizen Petition, the labeling for Colcrys® includes a table summarizing Mutual's drug interaction studies. Mutual Citizen Petition at 6-7. Similar to the dosing adjustment instructions, the summary table provides important information necessary for prescribers to fully understand the risks associated with colchicine drug-drug interactions. For example, with respect to clarithromycin, the table notes that at least one subject experienced an extremely high 591% increase in colchicine blood levels, which is particularly noteworthy in light of the fact that colchicine is a narrow therapeutic index drug. To ensure the safety of all patients, FDA must require that the labeling for all single ingredient oral colchicine products, including West-Ward's product, include in their labeling the complete drug interaction information.

86 Colcrys® Package Insert (revised Sept. 2010) at 5-6 (attached to Mutual's Citizen Petition at Tab 2).

87 Id.

88 FDA Cross Discipline Team Leader Memorandum for Colcrys® (NDA 22-351) at 17 (July 1, 2009) (Tab 23).
required all approved protease inhibitors used to treat HIV-1 infection to amend their labeling to include the new Colcryst® information.89

FDA also required the drug interaction information to be included in the REMS for Colcryst®. The Medication Guide for Colcryst® prominently warns patients regarding the potential for drug interactions. FDA’s approval of Colcryst® with a REMS reflects the Agency’s determination that the REMS is necessary to ensure that the benefits of the drug outweigh the risks of the drug. 21 U.S.C. § 355-1(a)(1). To have practical meaning, the warning in the Medication Guide regarding drug-drug interactions must be read in conjunction with the reduced dosage instructions to avoid the drug-drug toxicity. If FDA permitted West-Ward to exclude from its labeling any of the drug-drug interaction information, the Agency would be allowing West-Ward to carve-out what the Agency views - under the statutory definition - as essential risk information necessary for the safe use of the product. Indeed, without the information, a patient taking West-Ward’s product could receive a four-fold overdose of colchicine. Accordingly, the drug interaction information, including the dose adjustment information, is essential to the safe use of colchicine and must be included in West-Ward’s labeling. Without the information, FDA cannot approve West-Ward’s product, and, if West-Ward includes the information, then West-Ward must certify to Mutual’s patents.

B. The Labeling for Any Single-Ingredient Colchicine Product for Prophylaxis of Gout Flares Must Contain Certain Information Protected by Exclusivity.

As explained in Mutual’s Citizen Petition, even if FDA interprets Colcryst’s three-year exclusivity as not including the prophylaxis of gout flares, FDA should not allow West-Ward to carve-out labeling information protected by the exclusivity because it would render West-Ward’s product unsafe even for the prophylaxis of gout flares indication.90 Patients taking colchicine for prophylaxis of gout flares commonly suffer from a break-through flare.91 When a break-through flare occurs in a patient already taking colchicine for prophylaxis of gout flares, prescribers and patients need to know how to safely and effectively coordinate the administration of colchicine for both treatment and prophylactic purposes. Indeed, the labeling for Colcryst® has specific information directed to patients who are already using colchicine for prophylaxis of gout flares and then need to use additional colchicine to treat a break-through flare. For example, the labeling provides that “COLCRYS may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Wait 12 hours and then resume the prophylactic dose.” (Emphasis

89 See FDA, New Label Information Affecting All Approved Protease Inhibitors for Treatment of HIV (attached to Mutual’s Supplement to the Citizen Petition (Dec. 23, 2010) at Tab 1).

90 Mutual Citizen Petition at 14-19.

This safety and efficacy information for the dosage of Colcrys® to treat a gout flare during prophylaxis of gout flares resulted from Mutual's AGREE trial research.

Additionally, due to potential toxicity, the labeling for Colcrys® provides that patients with renal impairment who are taking colchicine for prophylaxis of gout flares should not receive colchicine for the treatment of break-through gout flares.92 Similarly, the labeling provides that prophylactic patients who are also receiving CYP3A4 inhibitors should not use colchicine to treat break-through gout flares.93 The labeling also provides information regarding missed doses when a person is taking Colcrys® for both prophylaxis of gout flares and treatment of gout flares.94,95

The labeling information described above is necessary for the safe and effective use of colchicine. Allowing West-Ward to carve-out the information from its labeling would make West-Ward's product unsafe for the prophylaxis of gout flares indication, particularly in light of the fact that the prophylaxis of gout flares indication is a chronic indication necessitating colchicine use for months to years. Accordingly, FDA cannot approve West-Ward's application to the extent that it seeks to omit this important safety information.

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92 Colcrys® Package Insert (revised Sept. 2010) at 7 (attached to Mutual's Citizen Petition at Tab 2).
93 Id. at 6.
94 Id. at 22-23.
95 Mutual also notes that West-Ward's proposed labeling seems to improperly carve-out language from the CONTRAINDICATIONS section of the labeling. In particular, the CONTRAINDICATIONS section of the Colcrys® labeling provides:

Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors, except Fosamprenavir). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

However, West-Ward's proposed labeling fails to inform prescribers and patients that the contraindication regarding individuals with impaired renal or hepatic function includes those taking all protease inhibitors except fosamprenavir. Moreover, the proposed labeling fails to inform prescribers and patients that life-threatening and fatal toxicity has been reported with colchicine taken in therapeutic doses by contraindicated patients.

FDA's prescription drug labeling regulations provide that the CONTRAINDICATIONS section of the physician labeling "must describe any situations in which the drug should not be used because the risk for use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit." 21 C.F.R. § 201.57(c)(5). By approving the labeling for Colcrys®, including the CONTRAINDICATIONS section, FDA has determined that the benefits do not outweigh the risks for all of the patient populations described. Accordingly, West-Ward should include such information in its labeling.
IV. **West-Ward's Product is a Duplicate of Colcrys®, and West-Ward Must Use an ANDA**

Finally, in its citizen petition, Mutual details the reasons why West-Ward must submit an ANDA for its product given that West-Ward’s product is a duplicate, as FDA defines that term, of Colcrys®. According to FDA, “section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval under 505(j).” *FDA Draft 505(b)(2) Guidance* at 3-4 (citation omitted); see also id. at 6 (“What Can’t Be Submitted as 505(b)(2) Applications? An application that is a duplicate of a listed drug and eligible for approval under section 505(j).”). Although FDA issued this edict in a draft guidance, it has been in effect for 12 years without change, and FDA has consistently followed it except in special circumstances distinguished below. According to FDA, applications for duplicate products should be submitted as ANDAs. See *Abbreviated New Drug Application Regulations (Proposed Rule)*, 54 Fed. Reg. 28,872, 28,890 (July 10, 1989) (“The agency intends to treat any application for a duplicate of a listed drug eligible for approval under an ANDA as an application under section 505(j) of the act because it believes that Congress intended the ANDA provisions to, among other things, assist the agency in avoiding duplicative reviews of safety and effectiveness information about already approved drugs.”). West-Ward has now confirmed that its product is a duplicate of Colcrys®. Accordingly, West-Ward should withdraw its 505(b)(2) application and submit an ANDA referencing Colcrys® as the RLD.

West-Ward argues that there is nothing in FDA’s governing statutes or regulations that require an applicant to submit an ANDA for a duplicate product. In fact, West-Ward notes that FDA’s regulation governing FDA’s filing of 505(b)(2) applications provides that FDA “may” refuse to file a 505(b)(2) application for a duplicate product. To support its argument, West-Ward cites to the *King* levothyroxine decision, in which the court rejected an argument that the supplemental levothyroxine applications had to be submitted as ANDAs and not 505(b)(2) applications.

Although the *King* court may not have required ANDAs, the levothyroxine situation concerned “a factually and legally unique situation” that is distinguishable from the colchicine situation. Importantly, FDA provided public notice and the opportunity for comment in the levothyroxine situation by issuing a guidance document stating that FDA intended to deviate from its longstanding policy and allow multiple 505(b)(2) applications for levothyroxine up to a certain date. In contrast, FDA has not issued such a guidance document with respect to

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96 FDA uses the term “duplicate” to refer to a drug product having the same active ingredient, dosage form, strength, route of administration, and conditions of use as a previously approved listed drug. See *Abbreviated New Drug Application Regulations (Proposed Rule)*, 54 Fed. Reg. 28,872, 28,877 (July 10, 1989).

97 See *King* at 1.

98 In the guidance document, FDA indicated that it would accept 505(b)(2) levothyroxine applications for filing until the enforcement date, after which time FDA would exercise its authority to refuse to file 505(b)(2) applications for products that are eligible for approval under ANDAs. *FDA Levothyroxine Guidance* at 4. If, as West-Ward requests, FDA uses the levothyroxine situation as a model for colchicine, then FDA should require West-Ward to submit an ANDA because FDA filed West-Ward’s 505(b)(2) application on November 1, 2010, after the October 1, 2010 enforcement date for colchicine.
colchicine, indicating that applicants must submit ANDAs for duplicate colchicine products in accordance with FDA’s underlying policy. Further, the levothyroxine applications were based solely on literature. In contrast, Mutual performed multiple new studies to support the approval of Colcrys® that West-Ward must rely upon for approval of its product. Accordingly, the circumstances that existed with levothyroxine do not exist with colchicine, and there is no reasonable explanation to justify FDA departing from its longstanding ANDA requirements. 

V. Conclusion

West-Ward’s comments fail to provide any valid reason why West-Ward should not have to reference Colcrys® as its RLD and certify to the patents listed for Colcrys®. Mutual performed numerous studies that West-Ward must rely upon for approval. Colcrys® is also the designated RLD for single ingredient oral colchicine products and is the proper RLD for West-Ward’s product from legal, scientific, and safety perspectives. West-Ward’s product necessarily must include information derived from Mutual’s studies in its labeling to be safe and effective.

West-Ward’s failure to dispute some of Mutual’s most significant arguments, including those relating to exclusivity and West-Ward’s attempted labeling carve-outs, constitute a silent but eloquent admission that Mutual is correct. Even as far as it goes, West-Ward’s response depends almost entirely on pretending that many of the important studies conducted by Mutual do not exist.

Ultimately, Mutual conducted research studies that advanced the science and improved the safety and efficacy of colchicine, while bringing this molecule into regulatory compliance. West-Ward now seeks approval to sell the same basic product as Mutual. West-Ward had every opportunity to be the first company to bring an FDA-approved product to market. However, West-Ward waited for Mutual to conduct the necessary studies and pave the way for subsequent manufacturers, such as West-Ward. Based on Mutual’s work, Mutual lawfully and legitimately earned exclusivity and patents that cover West-Ward’s product. West-Ward cannot bob and weave around the scientific, legal, and safety issues arising from Mutual’s costly, valuable, and innovative work. As FDA has allowed West-Ward to market its unapproved product for over a year during Mutual’s three-year exclusivity period, it is particularly important that FDA now vigilantly enforce Mutual’s rights and exclusivity. FDA should not allow West-Ward to twist the law and facts to undermine the Congressionally mandated incentives that lead to the advancement of science and increased safety for patients.

Mutual’s citizen petition should be granted.

VI. Verification

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the

99 See Teva Pharms., USA, Inc. v. FDA, 182 F.3d 1003, 1010 (D.C. Cir. 1999) (FDA violated the APA by acting contrary to its Guidance for Industry).
action requested herein first became known to me on or about the following date: March 4, 2011. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Mutual Pharmaceutical Company, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

[Signature]

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