Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"); Establishment of a Public Docket; Request for Comments
Federal Register Number: FDA-2020-N-1069

Docket Questions	Apotex's Response
• ***What types of people or entities use the Orange Book?***	A wide array of people use the Electronic Orange Book including but not limited to pharmacists, health insurance providers, drug product distributors, regulatory affairs professionals, R&D scientists, law firms, IP lawyers, patients, physicians, health care providers, public health students, other Federal and State agencies and other foreign regulators.
• ***What sections of the Orange Book do these different types of people or entities use?***	• Health insurance providers, drug product distributors, and pharmacists may use the Orange Book to identify products that are currently approved and marketed based on Active Ingredient, Dosage Form, Route of Administration, TE rating, Proprietary Name and Application Holder. • Regulatory affairs professionals, R&D scientists, and lawyers refer to the Reference Listed Drug and Reference Standard as well as currently listed patents and exclusivities in the OB. • Patients and health care providers may reference the Orange Book for Marketing Status, Active Ingredient, Proprietary Name, Dosage Forms, Route. Strength, TE code and Application Holder. • A Public health student may refer to sections like Active Ingredient, Dosage Forms, Route. Strength, TE code and Application Holder and Marketing Status. • Foreign Regulators may look for Marketing status, Approval date, RLD, RS and Application Holder. • Federal or State agencies may refer to Active Ingredient, Dosage Forms, TE code and Application Holder and Marketing Status.
• ***For what reasons do these people or entities use the Orange Book? What additional***	• Pharmacists will need to refer to TE rating to ensure proper substitution of brand to generic drugs, as well as to determine interchangeability among

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information or features (e.g., additional search functions) could be incorporated into the Orange Book to make it more useful?	generics when a patient may be switched to another manufacturer's product upon prescription refill. Regulatory affairs professionals and R&D scientists refer to OB to identify the associated patent and exclusivity information, approval dates and Reference Listed Drug (RLD) and Reference Standard (RS) and number of drug applicants, active and inactive status of applications for the purpose of product development and regulatory filing strategy. • Law firms and IP lawyers search for all of the above information in addition to specific patent-related information, dates of patent listing and patent delisting. • Patients and physicians may look for information pertaining to alternate approved medication options that are available, as well as the availability of generics. • A Public health student may refer to OB to identify products approved by FDA and product specific information, its prescription class and or therapeutic use and equivalence status and associated patents. • Health insurance providers and Federal or State agencies may use it qualify approved products that would fit into various formularies and insurance programs. • Foreign Regulators may look for all of the above information, but specifically the length of time a product has been approved in U.S and as well as a similar way to compile information within their regulated region. The Electronic Orange Book in its current format has a significant amount of information but does not provide all of the critical information researched by pharmaceutical firms, regulatory affairs professionals, IP lawyers, and R&D

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• ***Cont'd…For what reasons do these people or entities use the Orange Book? What additional information or features (e.g., additional search functions) could be incorporated into the Orange Book to make it more useful?***	scientists and the information, at times, may be organized in a way that is difficult to effectively utilize. As an example, an RLD may have multiple strengths and multiple patents may apply to one specific strength or all strengths. If the Orange Book could display this patent information in a single tabular format that includes all strengths, patents, use codes and exclusivities for the RLD, this information would be much clearer. In addition, when new use codes are added to a product, the date the patent was listed still reflects the original Orange Book patent listing date, and in no way is it possible to discern the date that the new use code was added to the patent. This can be challenging for regulatory affairs professionals to keep track of when new codes are added that would need to be addressed in the ANDA. The date that a patent was listed to Orange Book currently does not reflect if that patent was listed in a timely manner and thus has the potential to impose a 30 month stay on the approvability of an ANDA. This idea is further expanded upon in Apotex's comments provided to Docket No. FDA-2020-N-1127 - Listing of Patent Information in the Orange Book. Finally, there is a search function on the Electronic Orange Book to view newly listed patents. This is helpful for identifying when a new patent is listed for an RLD and can be the catalyst for the ANDA filer to update their patent

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• ***Cont'd...For what reasons do these people or entities use the Orange Book? What additional information or features (e.g., additional search functions) could be incorporated into the Orange Book to make it more useful?***	certifications. There is no option, however, to quickly identify any new exclusivities listed in the Orange Book, which also require a timely update to the ANDA. Either adding a search function for newly added exclusivities or adding exclusivities to the newly listed patent search function would be a welcomed improvement to the Electronic Orange Book. Regarding other stakeholders who use the Orange Book, it is not user friendly for a pharmacist or a patient to find a substitutable medication option. An option to view the Orange Book for consumers and health care providers or for industry professionals could be of use to view the Orange Book in a manner that provides appropriate language for the intended user's ease of access. Additionally, from a patient and common user perspective, Orange book can include a section of Drug Therapeutic Class to search therapies relevant to their condition of interest, as well as a general guide or "how to user manual" for navigating Orange Book for non-industry professionals. The law firms, researchers and students would potentially benefit with a link from the patent section of the OB to view the patent as listed on USPTO's website. The therapeutic equivalence codes and ratings indicated in the OB do not clearly indicate the related RS/RLD. The OB should provide an option to search all products approved based on a single RLD and the associated therapeutic equivalence codes. In addition, there should be an option to link the products in OB to Drugs@FDA for the product labeling.

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	The product use codes associated with patents and the exclusivity codes listed in the OB do not provide a meaningful correlation to what is documented in product labeling and therefore each code should specifically also direct to the RLD label being revised.
• ***Is the information in the Orange Book regarding therapeutic equivalence generally useful?***	The therapeutic equivalence information in OB is generally useful, however at times it is difficult to identify which applications are therapeutically equivalent to each other, specifically when there are multiple products with the same active molecule. Currently in the Orange Book it is not easy to determine the therapeutic equivalents for a specific RLD. The addition of features to clearly determine therapeutically equivalent products would help the users of the website. Users may have to switch between Drugs@FDA and Electronic Orange book to determine the therapeutic equivalents. In addition, when a product is moved to the discontinued section of the Orange Book, the TE code that was assigned to the application is removed. This can be problematic when multiple RLD's for a specific molecule exist and one RLD is moved to the discontinued section, making it more difficult to ascertain generic substitutability.
• ***How useful is the second letter of a therapeutic equivalence evaluation code?***	The second letter of a therapeutic equivalence evaluation code is useful to distinguish among dosage forms/route of administration, however at times it is difficult to interpret the correlation between the multiple RLD's that configure a two or three alphanumeric code to a dependent substitutable product application.

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• ***How could the therapeutic equivalence information be made more user-friendly or otherwise be tailored to meet the needs of people or entities that use the Orange Book (e.g., the therapeutic equivalence evaluation code)?***	The TE code is critical to ensure proper drug substitution at the pharmacy level. However, a mechanism to correlate the code to the RLD would be immensely beneficial. In addition, TE codes can be a powerful tool that the agency can put into use to further enhance generic drug competition. There is lack of clarity on the basis to assign TE codes for products that are approved as a 505(b)(2) application. The Agency could consider a clear guidance on how firms can seek therapeutic equivalence using the 505(b)(2) pathway. The TE codes identify situations when products are pharmaceutically equivalent and, if so, when they are also therapeutically equivalent. A product may be automatically substituted only if pharmaceutically and therapeutically equivalent. Currently, the Orange Book does not identify two products as pharmaceutically and therapeutically equivalent unless they contain the same amount of the same active ingredient, even if they contain the same amount of the same active moiety when metabolized (in the case of solid dose medicines) or reconstituted as instructed (in the case of parenteral drugs). Instead, they are considered "pharmaceutical alternatives" and therefore cannot be substituted without prescriber intervention. As explained below, other regulators across the globe have adopted broader standards for determining therapeutic and pharmaceutical equivalence. For the EMA and, as currently proposed by Health Canada, therapeutic equivalence can be assumed for different salts, esters, ethers, isomers, mixtures of isomers, complexes of derivatives of an active substance, clathrates, and co-crystals, unless they differ significantly in properties with regard to safety and/or efficacy.

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• ***Cont'd…How could the therapeutic equivalence information be made more user-friendly or otherwise be tailored to meet the needs of people or entities that use the Orange Book (e.g., the therapeutic equivalence evaluation code)?***	EMA's Directive 2001/83/EC Article 10(2)(b) indicates that generic drugs include the concept of different salts of the same "active substance": "'[G]eneric medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes of derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy." Health Canada has proposed to amend its drug regulations to incorporate the concept of a "therapeutically active component" as distinct from FDA's more rigid approach to pharmaceutical equivalence. Under the proposed regulations, Health Canada would treat different forms of active ingredients at the input stage to be "identical" if they converge into the same form in the approved dosage form. In particular, the proposal is currently considering different hydrated or solvated forms, different polymorphic forms, and different salt forms to be the same if they converge as the same active moiety in the administered dosage form.

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• ***Cont'd…How could the therapeutic equivalence information be made more user-friendly or otherwise be tailored to meet the needs of people or entities that use the Orange Book (e.g., the therapeutic equivalence evaluation code)?***	Accordingly, under Health Canada's proposed regulations, a "therapeutically active component" would supersede the current criterion of "identical medicinal ingredient." Instead, generic submission eligibility would be determined by a test of "identical therapeutically active component," defined as the following: A medicinal ingredient, *excluding those appended portions, if any, that cause the medicinal ingredient to be a salt, hydrate or solvate*. (emphasis added) We request the agency to consider extension of TE codes to 505(b)(2) applications which could result in earlier entry to generic drug products which can overcome the patent landscape in ways that may not be feasible via the ANDA pathway.
• ***If you use the information regarding therapeutic equivalence, how do you use it?***	We use the therapeutic equivalence information to study and research equivalent products.
• ***Does the information regarding therapeutic equivalence promote drug competition? And if so, how?***	Yes, information regarding therapeutic equivalence promotes drug competition. Drug competition would be further increased if the FDA took the position of the EMA and as proposed by Health Canada. If generic drug and 505(b)(2) NDA sponsors knew that they could submit ANDAs or 505(b)(2) NDAs and obtain A-type ratings for different salts, esters, ethers, isomers, mixtures of isomers, complexes of derivatives of an active substances when the final dosage form contained the same amount of active moiety, there would be increased competition for the same active moiety for the same indication.

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• ***Is there any other information regarding the Orange Book that would be useful for FDA to consider?***	FDA can include various other fields in OB such as: • Therapeutic class of a product • Patent issue date • Patent updated date (i.e. when use codes are added to patents) • Exclusivity listed date • Clarity on patent expiration date versus exclusivity expiration date is required. Currently in the OB the date listed for a patent expiration is the date that an applicant who filed a paragraph III certification can receive approval. However, the date listed for the exclusivity expiration does not reflect the date that the applicant could receive approval. For example, if a patent expiry date listed in the OB is January 1, 2021, this is the date an ANDA may be approved. If the expiry date listed for a patent with pediatric exclusivity is January 1, 2021, the earliest the ANDA approval may occur is on January 2, 2021. This inconsistency creates confusion. As such the dates listed in the OB columns titled "Patent Expiration" and "Exclusivity Expiration" should reflect the actual date an applicant can receive approval.