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Drug Information Association Pharmacovigilance and Risk Management Strategies 2017: Overview of the Generic Drug Program and Surveillance

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Abstract

The United States Food and Drug Administration's (FDA) generic drug program has dramatically increased the availability of affordable, high quality generic drugs. The foundation of generic drug approvals is a two-tiered regulatory framework of pharmaceutical equivalence and bioequivalence. Intrinsic to both of these is consideration of the clinical relevance of formulation and bioequivalence data to support an inference of therapeutic equivalence, based on clear evidence that there are no significant differences between the generic drug and the brand name drug. These analyses allow FDA to determine that the generic drug will perform in the patient in the same way, with the same safety and efficacy profiles, as the brand name drug. Allowable differences and the precise definition of what is meant by equivalence are critical to maintaining the quality, efficacy, and safety of generic drugs. The FDA Office of Generic Drugs' (OGD) Clinical Safety Surveillance Staff (CSSS) has developed investigative processes that complement the broader FDA safety efforts that focus on the potential impact of allowable differences and equivalence determinations for generic drugs. Two recent examples of the CSSS' processes include clonidine transdermal system and lansoprazole oral disintegrating tablet. Ongoing efforts of the CSSS result in improvements to the FDA's review processes and the quality of generic drugs in the U.S. market.

Index words

Post marketing; safety; surveillance; generic drugs; Office of Generic Drugs; bioequivalence; pharmaceutical equivalence

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Introduction

The United States Food and Drug Administration's (FDA) generic drug program has increased the availability of affordable, high quality generic drugs in the U.S. One of our nation's most effective healthcare cost-containment programs, the generic drug program has approved more than 16,000 generic drugs since its inception in 1984, resulting in $1.67 trillion in healthcare system savings over the past decade. Nearly nine out of 10 prescriptions for a wide variety of drugs are filled with a generic drug.[1, 2]

The foundation of generic drug approval is a two-tiered regulatory framework of pharmaceutical equivalence (PE) and bioequivalence (BE).[3] Intrinsic to PE and BE are considerations of the clinical relevance of the drug formulation and the BE data to support an inference of therapeutic equivalence (TE). This framework is also supported on clear evidence that there are no significant differences between the generic drug and the brand name drug, also referred to as the reference listed drug (RLD).[4] FDA's scientific standards for PE and BE analyses allow for determination that the generic drug will perform in the same way as the RLD, but also infers that the generic drug will have the same safety and efficacy profiles as the RLD.

While generic drugs are required to be the same as the RLD in many aspects, generic drugs are generally not required to be identical to their RLDs. "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book", states, "Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are formulated to contain the same amount of active ingredient, and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity)."[5] This definition allows for differences between generic drugs and the RLDs in "…characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration time, and, within certain limits, labeling."

Excipients are any inactive ingredients that are added to drugs during manufacturing. They are not specifically intended to exert a therapeutic effect but could aid in delivery by enhancing absorption or release[6]. Examples of excipients include fillers, extenders, solvents, preservatives, flavors and colors. Generally, excipients may be different in a generic drug compared to the RLD, but must not have physiological effects that conflict with the therapeutic effect of the active pharmaceutical ingredient (API) or change the adverse event profile compared to the RLD. Regardless, excipients require safety testing prior to marketing, as they could independently affect the safety profile of the generic drug.

Some of the legally allowable differences could be critical elements of drug formulation and carton and container packaging of the generic drug and may not be acceptable in certain circumstances. Some research suggests that other allowable differences, such as release mechanisms and inactive ingredients may, in some circumstances, contribute to differences in therapeutic performance, patient perceptions of therapeutic effect and/or drug safety profiles between different generic drugs and the RLD.[7, 8] These situations warrant careful examination.

Discussion

BE studies demonstrate that the generic drug and the RLD deliver the same amount of the active drug and any active metabolites into the blood stream at the same rate for distribution to the drug's pharmacological site of action. The goal of premarket BE studies is to establish that a PE generic drug will perform in the same way as the RLD in vivo. Most often, BE studies are conducted in healthy male and female volunteers with a single-dose pharmacokinetic (PK) study in either a crossover or parallel group design. Typically, these studies use the highest dose that can be safely administered to a healthy volunteer. Conversely, when BE is evaluated in a pharmacodynamic (PD) or clinical endpoint study design, the lowest dose that can demonstrate a PD or clinical response will be more sensitive and is typically used for showing possible differences in drug performance. For drugs with safety profiles deemed unacceptable for healthy volunteers (e.g., cytotoxic and radioactive drugs), BE studies enroll a defined patient population. Some of these studies are multi-dose studies conducted at steady state.

BE analysis includes a robust statistical comparison of PK data for the generic and the RLD, including maximum concentration (C_{max}) and area under the curve (AUC). These measures serve as surrogates for the rate and extent of absorption of the API. To demonstrate BE, the statistical analysis must show that the ratios (generic to RLD) of these parameters remain strictly within a 90% confidence interval of 0.80 to 1.25.[9] This is the same standard used to achieve consistency between manufactured batches of the RLD. A retrospective study of more than 2000 generic drugs demonstrated that, using these criteria, the average differences in C_{max} and AUC between generic drugs and their RLDs were 4.35% and 3.56% respectively[10]. Nonetheless we recognize that BE is not always a straightforward evaluation of PK and BE studies must consider aspects of clinical relevance with a thorough understanding of the clinical use of the RLD, including the indication, the patient population to be treated, the chronicity of the therapy, the adverse event profile of the RLD, and the intended physiological behavior of the RLD. These considerations are particularly important and challenging for complex dosage forms and modified-release formulations.

TE is an inference made for generic drugs that meet PE and BE criteria. TE implies that the generic drug and the RLD can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. To evaluate TE, FDA clinical reviewers consider the data used to establish PE and BE of the generic drug and its RLD, as well as other characteristics that may alter the generic drug's safety profile or effectiveness in clinical use when compared to the RLD. Although PE and BE analyses, along with inference of TE, build a strong coherent and concise model for generic drug assessments, there is always a possibility of unexpected safety considerations and concerns that occur before and after marketing of a generic drug. This is especially true when the generic drug begins to replace the RLD in the marketplace and use of the generic drug increases in a larger, more diverse patient population.

The 2007 FDA Amendments Act[11] and the 2012 FDA Safety and Innovation Act[12] provided FDA with regulatory authorities and mandates to enhance drug safety and surveillance. To address safety and surveillance of generic drugs, OGD developed a Safety Team, which

became the Clinical Safety Surveillance Staff (CSSS), as the point of contact for other Center for Drug Evaluation and Research (CDER) offices regarding safety and surveillance of generic drugs.[13] The CSSS serves as the OGD liaison to CDER's Office of Surveillance and Epidemiology (OSE) and other drug surveillance groups within CDER, to obtain and coordinate information in order to ensure the safety of generic drugs on the U.S. market. These CSSS safety and surveillance efforts focus on identifying unanticipated issues that may impact the safety or efficacy of generic drugs and provide a clinically and scientifically based complementary function to the safety and surveillance led by OSE.

Generic drug safety and surveillance differs from RLD safety and surveillance because it focuses on problems with the formulation design, methodology of equivalence determination, and quality of the generic drug, along with any new unanticipated adverse events not seen with the RLD. In contrast surveillance of the RLD is focused on the physiological effects of the API in the context of a specific disease process. While generic drug safety and surveillance encompasses the entire lifecycle of the generic drug, the CSSS focuses its safety and surveillance efforts primarily on the prior to ANDA submission (premarket) and post-marketing phases.

Premarket safety and surveillance is a limited but useful effort to screen for potential safety signals prior to a generic drug application being submitted to the FDA for review. In development of a new drug there are many meetings between the FDA and the applicant to discuss the safety of the drug and how that can be effectively studied. Premarket safety clinical studies are not a part of the generic drug application, because safety is inferred for a generic drug that is PE and BE to an RLD. This inferred safety limits the need for premarket communications and meetings between applicants and the FDA. Instead of such meetings, OGD issues product-specific guidances (PSGs) to incorporate safety concerns into the recommendations, along with details on BE methodology or other scientifically supported methods of demonstrating BE. At the, "Product-Specific Guidances for Generic Drug Development" website, FDA recommends consistent approaches to BE listed by active drug ingredient and dosage form. To date, FDA has published more than 1,600 PSGs to aid generic drug applicants in BE study design and data analysis.[14]

The requirement for expedited reporting of a serious adverse event (SAE) in bioavailability (BA)/BE studies is relatively new. The Final Rule (75 FR 59936), published on September 29, 2010, added new safety reporting requirements for investigational new drug (IND) exempt BA/BE studies[15]. Most BA/BE studies that meet the requirements for IND exemption are generally safe and the occurrence of an SAE is relatively unusual. Since the Final Rule became effective on March 28, 2011, the CSSS has received more than 1,000 expedited safety reports from these BA/BE studies. These reports could reflect a problem with the generic drug formulation, subject inclusion/exclusion criteria, or other aspects of the BE study design or conduct. The CSSS safety and medical officers evaluate these safety reports, request additional information from submitters when needed, determine probable study-related risks to subjects, and formulate appropriate recommended actions.

The CSSS reviews spontaneously (i.e., voluntarily, non-required) submitted MedWatch[16] reports concerning potential safety issues from generic drug quality-only issues, quality

issues leading to adverse events (AEs), formulation issues related to excipients and impurities, and perceived therapeutic failure. The CSSS also reviews generic drug concerns and reports[17] from individuals, consumer groups and other private sources. The FDA Adverse Event Reporting System (FAERS)[18] Drug Quality Reporting System (DQRS) is a subset of MedWatch reports related to quality or therapeutic failure. The CSSS evaluates approximately 500 MedWatch reports in DQRS per month. Of these, approximately 53% are related to unexpected therapeutic effect or failure, 34% are related to quality concerns, 11% are related to adverse events, and 2% are related to labeling issues. These reports may contain information from consumers, pharmacists, physicians or other stakeholders related to generic drug issues of concern. These areas of concern could include (but not be limited to):

- Tablets breaking apart
- Scored tablets breaking unevenly or crumbling into powder when split
- Tablets sticking in the throat
- Precipitates or foreign matter in oral liquids and injectables
- Patches not sticking
- Errors in packaging (wrong quantity)
- Container/closure issues
- Device issues
- Suspected contamination
- Dropper issues with ophthalmologic products
- Abnormal solubility
- Large size tablet/capsule

The CSSS utilizes literature searches and evaluates drug market share data to better understand post-marketing reports in the context of use in the marketplace and reported experience in clinical practice with an RLD and its generics.

The most common issue related to generic and RLD drugs reported to the FDA is perceived therapeutic failure. Given the expectation for “sameness” in therapeutic performance, reports of perceived therapeutic failure for a generic drug are important and need to be investigated. However, multiple factors make it challenging to determine whether reports of perceived therapeutic failure indicate a real difference in effectiveness between an RLD and one or more of its generics. The high number of perceived therapeutic failure reports combined with high rates of generic drug dispensing, general underreporting of post-marketing adverse events, and incomplete information provided in adverse event reports confound the calculations of adverse event rates and rate comparisons between the different generic drugs. These issues require the CSSS to approach the issue of perceived therapeutic failure based on a “level of concern” or “failure mode analysis” through the initiation of an internal investigation. All generic drugs that were approved referencing the same RLD are included in the investigation. Critical elements in the approval process are identified and evaluated for

their probability of contributing to the root cause of the report of perceived therapeutic failure.

Critical elements are identified by a CSSS-led multidisciplinary review team during the generic drug application review, and post-marketing when changes may occur in drug manufacturing or production. Each area of review is subject to scrutiny for critical elements that could be the root cause of the reported therapeutic failure. A chemist evaluates the drug substance, dosage form, specifications, impurities, and formulation. A bioequivalence reviewer focuses on the results of BA/BE studies, including elements of PK, PD, and in vitro drug release. A physician considers the intended clinical use of the generic drug, the target population, chronicity of use, and the specific circumstances in which the drug was used when the reported lack of therapeutic effect occurred. Review team members assess the complexity of the generic drug's physical, biochemical, and biopharmaceutical attributes and their potential clinical relevance with respect to the questions and concerns under review. Labeling reviewers ensure that the label, carton, and container for any generic drug under review are consistent with the RLD, following regulatory guidelines[19,2021]

When requested by the multidisciplinary review team, FDA's inspectors visit manufacturing sites, where they perform facility and bioanalytical assessments and evaluate study procedures, documentation, and data integrity from clinical BE studies. These inspections may reveal critical areas of concern. Regulatory and legal professionals check that the generic drug applicants are following the appropriate FDA regulations and other legal requirements. This multidisciplinary approach to identifying critical elements within the CSSS' safety investigation provides a broad consideration of the root cause of a generic drug perceived therapeutic failure or other safety concern.

Examples

Two real-life examples of the CSSS' multidisciplinary, collaborative safety and surveillance work led to improvements in the FDA review process for these particular generic drugs. In addition, both products were voluntarily withdrawn from the U.S. market.

Clonidine Transdermal System USP (0.1 mg/day, 0.2 mg/day or 0.3 mg/day), more commonly referred to as a medicated patch, is indicated in the treatment of hypertension.[22] In 2009, OGD identified 89 reports for this new-to-market generic drug, largely involving lack of adhesion and efficacy. FDA MedWatch report narratives related the large size of the generic patch as compared to the RLD. For example, the 0.3 mg/day generic patch measured 32.4 cm^2 compared to the RLD, which measured 10.5 cm^2. FDA inspected the generic company in December 2009, and identified significant problems in the manufacture of these generic clonidine transdermal systems, including residual generic drug in the discarded patch creating an unacceptable safety risk. Upon identification of a quality concern and safety risk, FDA issued a warning letter to the generic manufacturer on May 21, 2010.[23] Subsequently, the generic manufacturer voluntarily stopped making the generic clonidine patch in March 2011.

Lansoprazole is a proton pump inhibitor, a drug indicated for the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease, erosive esophagitis, and Zollinger-Ellison

Syndrome. Lansoprazole is available as an oral disintegrating tablet (ODT), and although the ODT dosage form is designed to dissolve in the mouth, RLD prescribing information included the potential for administration through nasogastric tubes.[24] In 2011, OGD received multiple reports about a generic lansoprazole ODT clogging oral syringes and feeding tubes. Some patients required surgical replacement of their obstructed permanent feeding tubes.

The CSSS' internal investigation revealed different clinical drug performance for this generic lansoprazole ODT and the RLD due to allowable differences in the drug formulation. The generic drug tablets were found to not fully disintegrate when water was added to them and after disintegration would later form clumps. These clumps would adhere to the inside walls of oral syringes and feeding tubes. In some cases, patients needed emergency medical assistance and their clogged feeding tubes had to be unclogged, removed, or replaced. The CSSS' efforts identified both the target population and the route of administration as significant factors that were not considered in the determination of PE. An FDA Drug Safety Alert was posted on the FDA website on April 15, 2011[25] and the manufacturer voluntarily withdrew their generic drug from the market. This post-marketing pharmacovigilance investigation also led to a widespread policy change in that all generic drugs that carry an indication in their labels for administration through a feeding tube are now subject to in vitro comparative testing to assure that the generic drug will perform in the same manner as the RLD.

Conclusion

Generic drugs provide considerable cost savings and greatly enhance the availability of quality medications to the American public. The safety and efficacy of generic drugs are presumed by their PE, BE, and TE to the RLD. However, unanticipated safety concerns or therapeutic failure of generic drugs based on allowable differences can arise at any point in the generic drug's lifecycle. OGD created the CSSS to monitor for these unique safety and surveillance issues related to generic drugs. Surveillance investigations by the CSSS are critical to promptly identifying unanticipated critical elements to performance and safety that may have been unanticipated during generic drug development. The CSSS' safety and surveillance efforts continue to enhance the quality of generic drugs on the U.S. market.

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