Approval of Generic Fluticasone Propionate/Salmeterol Xinafoate Dry Powder Inhalers in the US: A Difficult Exercise in Regulatory Science

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Abstract In 2013, the US FDA published a draft guidance document for the development of generic dry powder inhalers containing fluticasone propionate and salmeterol xinafoate. This article discusses the requirements of the FDA's draft guidance and makes comparison to the general requirements of the EU. Getting US regulatory approval for a generic dry powder inhaler containing fluticasone propionate and salmeterol xinafoate will be very difficult due to the testing burden if the requirements given by the draft guidance are all implemented. It will involve a total of 50 tests (36 in vitro, 12 pharmacokinetic, 2 pharmacodynamic), which must all evaluate towards equivalence. This means each of the 50 individual tests must be highly powered in order to get an acceptable level of overall success. An ethical concern over the use of pivotal in vivo trials on the basis of in vitro data only is raised.

Summary Points

Conforming with the draft US requirements will be very difficult for most, if not all, companies because numerous in vivo and in vitro tests must all prove equivalence

Approval in the US requires in vitro equivalence and pharmacokinetic equivalence and pharmacodynamic equivalence, whereas approval in the EU requires in vitro equivalence or pharmacokinetic equivalence or pharmacodynamic equivalence

1 Introduction

In 2005, European regulators decided to update the guidelines pertaining to the approval of orally inhaled products (OIPs), mainly due to concerns over assay sensitivity [1]. The guideline was published in 2009 and came into force the same year. In the US, there has been much debate over the last decade about the general principles for generics, and in 2013 the US FDA published a draft guidance with specific recommendations for the work necessary to obtain approval for a generic combination of fluticasone propionate and salmeterol xinafoate in a dry powder inhaler [2]. This short review discusses the draft FDA guideline and makes a comparison of the US approval principles and the corresponding path to approval in the EU.

Fluticasone propionate and salmeterol xinafoate is available under the brand name AdvairTM in the US and SeretideTM in the EU. In the following, the term 'listed drug', 'reference listed drug' or just 'reference' refers to the brand.

This work does not address standard issues relating to chemistry, manufacture and controls (CMC), nor does it discuss pediatric investigations.

2 Approval in the US

Generics are defined by section 505(j) titled "Abbreviated New Drug Applications" (ANDAs) of the Food, Drug and Cosmetic Act [3]. The applicant must provide documentation to show that the abbreviated new drug:

- has the same label (prescribing information) as the listed drug;

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- “(...) that the active ingredients of the new drug are the same as those of the listed drug (...);”
- shares the listed drug’s route of administration, dosage form, and strength;
- is bioequivalent to the listed drug and can be expected to have the same therapeutic effect.

Section 505(j) lists other requirements which are not mentioned here as they have little or no practical significance for the topic discussed in this manuscript and are thus outside its scope.

Interestingly, the definition of bioequivalence is not completely clear; title 21 of the Code of Federal Regulations title 21 section 320.23 (21CFR320.23) defines [4]:

“Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.”

whereas section 320.1 (21CFR320.1) reads [5]:

“Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”

For drugs that are supposed to be absorbed into the general circulation, and from there delivered to the target organ, the two definitions are concordant; if the two drugs are absorbed into the systemic circulation with the same speed and at the same extent, it is credible that the two drugs will also become available at the site of action at equal speed and extent. However, for drugs that act locally and are not supposed to be absorbed into the systemic circulation in order to exert its effect the two definitions can be considered slightly discrepant as absorption and availability at the site of action is not necessarily one and the same thing.

With the 2013 draft, the FDA has introduced requirements that entails elements from both definitions; applicants must provide proof of similarity in terms of local delivery via a pharmacodynamic study and must also investigate absorption. In addition, the draft imposes requirements on both the inhalation devices and the in vitro performance of the new drug.

2.1 Device Requirements

The new drug must come in a device that is similar in size and shape to the brand’s inhaler. It must have a dose counter and must have comparable resistance. The device should be breath-actuated and contain 60 pre-metered doses. The operating instructions should be the same as for the reference. Finally, robustness should be demonstrated.

The terms similar and comparable are not defined and there are no instructions on how to investigate device robustness.

2.2 In Vitro Requirements

The in vitro endpoints suggested by the FDA are single actuator content (SAC) and impactor-sized mass (ISM) as measured via the particle size distribution sampled by means of pharmacopoeial impactors. Both ISM and SAC should be evaluated at flows of 90, 60 and 28.3 L/min (SAC) or 30 L/min (ISM). The statistical evaluation is based on population bioequivalence, and was introduced in a document for budesonide suspensions for nebulizers to which the draft guidance makes reference [6].

It should also be noted that it is quite difficult to calculate power and thus to identify an adequate sample size. To derive sample sizes, applicants may need to first study the data distribution in pilot studies, then use bootstrapping of the observed data to derive an appropriate sample size for the desired level of power.

2.3 In Vivo Requirements

For evaluation of safety, and in line with 21CFR 320.23, all three strengths of SeretideTM DiskusTM (50/100, 50/250, 50/500 µg salmeterol xinafoate/µg fluticasone propionate) must be evaluated in single-dose, crossover, comparative pharmacokinetic studies in fasting healthy volunteers from the general population. The actual dose given to each subject should reflect the limit of quantification. The endpoints are area under the plasma concentration-time curve up to the last blood sampling time point (AUC_t) and maximum observed plasma concentration (C_{max}). The data is used to construct 90 % confidence intervals (CIs) for the geometric mean ratios of both endpoints for both analytes. To pass bioequivalence, the 90 % CI must be contained within 80.00–125.00 %.

For evaluation of efficacy, and in line with 21CFR320.1, the applicant should conduct a multiple-dose, placebo-controlled, parallel group study in adolescent or adult asthmatics. Treatment duration is 4 weeks plus 2 weeks

run-in. The common asthma endpoint, forced expiratory volume in 1 s (FEV_1), is used. Area under the FEV_1 -time curve from 0 to 12 h following the first dose is used to qualify equivalence for salmeterol. FEV_1 measured prior to the last inhalation after 4 weeks is used to qualify equivalence for fluticasone propionate. Ninety percent CIs for the test:reference ratios of these endpoints are constructed. Bioequivalence is concluded when the 90 % CIs are contained within 80.00–125.00 %.

3 Approval in the EU

In 2008, regulators in the EU made it clear that abbreviated dossiers for inhaled products did not meet the definitions for generics and thus had to be approved as hybrids [7]. Generics are defined by community directive 2001/83 article 10.1/10.2, while hybrids are defined by article 10.3, which reads [8]:

“In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.”

In a sense, the purpose of the 2009 guideline update was therefore to introduce ‘appropriate pre-clinical tests or clinical trials’.

This was done by proposing a stepwise approach to the development. Approvals can be based on in vitro testing, pharmacokinetic testing, or by pharmacodynamic testing.

If two products are sufficiently similar in vitro (device similarity, resistance, particle size distributions and more), approvals can be granted. The regulators do not impose a specific statistical model for particle size distribution comparison, but it is suggested to define at least four stages or relevant stage groups. The equivalence margin is given as 15 %.

If in vitro similarity cannot be demonstrated (for example if the devices are too dissimilar or if particle size distributions are too different) applicants are suggested to investigate safety and efficacy by means of pharmacokinetic comparisons, i.e. by traditional average bioequivalence studies. Efficacy is studied in the presence of co-administered charcoal which is intended to block gastrointestinal absorption, thus giving rise to plasma quantifications which reflect the amount of drug deposited in the lung and absorbed from there. Safety is studied in a similar fashion but in the absence of charcoal. Acceptance criteria

for the pharmacokinetic studies are the traditional ones, i.e. the 90 % CIs for AUC_t and C_{max} must generally be within 80.00–125.00 %. The EU guideline makes reference to a guideline on general proof of bioequivalence and which opens up the option to apply reference scaled designs if the reference product is highly variable (coefficient of variation >30 %) or to use a two-stage design. If a drug is not widely absorbed from the gastrointestinal tract, i.e. if the measurable plasma levels mainly reflect the amount of drug absorbed from the lung, then the guideline opens up the opportunity to skip one of the pharmacokinetic trials.

In case equivalence cannot be proven with in vitro testing or by pharmacokinetics (if, for example, pharmacokinetic comparisons indicate that the two products are bioinequivalent with no overlap of the CI with the acceptance range), the last option is pharmacodynamics. Here, EU regulators are asking for proof of sensitivity, which implies that the applicant must show a rudimentary dose-response relationship (often called assay sensitivity) by applying test and reference at two non-placebo dose levels. A bioassay approach is then used to establish a CI for the similarity of the two products. Acceptance criteria are 67.00–150.00 %. The proof of assay sensitivity is typically very difficult for locally-acting inhalation products when standard endpoints such as FEV_1 or peak expiratory flow are used since they tend to give a near-maximal response in the majority of the relevant populations.

As noted above, in vitro approvals require quite similar devices, but approval by pharmacokinetics or pharmacodynamics do not. This means that a reservoir device or capsule-based device being completely dissimilar to the device of the reference product is approvable. However, since these approvals are for hybrid products, and since generic inhalation products should not be approved, substitution (which is regulated nationally in very heterogeneous ways and separately from product approval) is not automatic and perhaps even impossible in some territories.

4 Discussion

The US draft guideline introduces the need for a total of 50 tests, all of which must show equivalence:

- 36 in vitro tests (two active ingredients tested at three flow rates, with two endpoints for all three strengths);
- 12 pharmacokinetic tests (two active ingredients that must each pass equivalence testing for two endpoints for all three strengths);
- 2 pharmacodynamic tests (two endpoints for one strength).

If we assume that the applicant is interested in an overall probability of success being 80 % then each of the 50

individual tests must, on average, have 99.55 % power (power is the chance of showing bioequivalence if the assumptions are correct). Some of the individual study powers could be correlated, but there is no published model for these correlations.

A numerical example with realistic figures for pharmacokinetic studies:

If the similarity of test and reference is 90 %, meaning the true geometric mean ratio is 0.90 for all metrics, and if the within-subject coefficient of variation is 25 %, then the corresponding pharmacokinetic study must involve 162 volunteers to achieve a power of 99.55 %. The applicant will, under such assumptions, be planning three pharmacokinetic trials, each having at least 162 evaluable volunteers.

A further complication is that assuring a geometric mean ratio of, for example, 0.90, as in the previous example, is extremely difficult. The in vitro–in vivo correlations (IVIVCs) for inhalation drugs are still not characterised to an extent that allows an applicant to control in vivo performance in bioequivalence in vivo trials by means of in vitro testing. There is no doubt that particle size is a key element for the IVIVCs (see, for example, the brilliant paper by Olsson et al. [9]). In this work, an anatomical modification of impactors allowed the authors to observe a quite linear relationship between an in vitro metric and lung deposition in humans. In spite of this very promising result, the lung deposition (and the in vitro metric itself) is associated with a level of uncertainty that makes it impossible, even with a seemingly perfect in vitro match, to be reasonably certain that the in vivo match is anywhere near the optimal value of 1.0 for the geometric mean ratio. The required sample size for any desired level of power goes towards untenable magnitudes as the true in vivo performance approaches either of the bioequivalence limits (0.8 and 1.25). Thus, there is a dire need for better IVIVC models that allow applicants to get much tighter control over the in vivo performances. A further complication is that particle size distributions tend to change over time. There is no literature available which describes what this implies for the demonstration of bioequivalence.

When the approval principles in the EU and the US are compared, it is obvious that the US path to approval is somewhat more comprehensive. In the EU, approval as per guideline requirements requires pivotal proof by either in vitro testing or pharmacokinetics or pharmacodynamics, and approval can be granted to products with devices that are dissimilar; in the US, approval requires proof of equivalence both in vitro and by pharmacokinetics and by pharmacodynamics for devices that are similar.

On a more personal note: It is my experience that in the US and the EU, 80–90 % of all pivotal pharmacokinetic or pharmacodynamic trials are currently failing; this does not mean they show bioinequivalence but just that they do not

show bioequivalence. They tend to fail on the point estimate and not on the variability (width of the CI), meaning that inhalation training is not the problem but it is the actual product performance that deviates from the expectation. This has to do with the lack of useful IVIVCs for ratios—as indicated above, a good match in vitro does not, with currently available techniques, assure a match in vivo even though clear IVIVCs have been established and even if the in vitro match is considerable. In other words, power (chance of approval if the assumptions are correct) is often overestimated and the true power is lower since the true in vivo performances of the two products are often more different from each other than expected. For this reason, I am beginning to consider that pivotal trials initiated on the basis of in vitro data only are largely futile and thus not really ethical. The issue with failed trials is not well-documented in the public domain since companies tend not to publish trial results unless the trials are successful.

5 Conclusions

In the absence of a relaxation of the requirements introduced by the FDA in their draft guidance, getting a generic dry powder inhaler approved in the US will be extremely difficult because of the testing burden. The individual tests are all relatively easy to conduct as they rely on well-known techniques, but passing the 50 tests without a single failure will be very difficult unless applicants are willing to work with very high sample sizes (thus accepting extreme costs) both in vitro and in vivo. Furthermore, the presently known IVIVCs do not allow applicants to predict in vivo performance very well, and this may negatively affect actual sample size calculations and, ultimately, chances of approval. On the basis of personal experience with trials in the US and the EU, I question the ethics behind pivotal trials initiated only on the basis of in vitro data.

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