Trends-in-Medicine

August 2004
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Quick Pulse

Trends-in-Medicine
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THE FDA, BIOEQUIVALENCY, AND 505(B)(2) APPLICATIONS

Bioequivalency is critical to generic drug approvals, but FDA regulations can be complicated and difficult to interpret. In order to better understand the FDA's requirements for 505(b)(2) and bioequivalency, ***Trends-in-Medicine*** interviewed two FDA experts in these areas.

The 505(b)(2) NDA application process can be confusing and a frustrating experience for many companies. Fewer than 100 applications have been filed under this Section of the FDCA since its enactment in 1984. Within the last few years, citizen petitions have challenged FDA's implementation of Section 505(b)(2) of the Act. In addition, the suitability of this type of application for biologically derived products, in particular, has also been challenged. The legal ramifications of these petitions and FDA's responses may impact the planning and execution of 505(b)(2) NDA application strategies.

The FDA says applicants can rely on this information in their 505(b)(2) application:

1. Published literature and/or
2. The FDA's finding of safety and effectiveness for an approved drug

The types of applications that can be submitted under 505(b)(2) include:

- ***New chemical entity*** *(NCE)/new molecular entity (NME)* – when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference.
- ***Changes to previously approved drugs*** – permit relying on the FDA's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information can be new studies conducted by the applicant or published data.

The types of changes to approved drugs for which the FDA says 505(b)(2) applications can be submitted include changes in:

- ***Dosage form*** – for example, from an oral to a transdermal patch. An FDA official offered this explanation: "If, for example, a dosage form is entirely targeted at children, and the drug dosage form already approved is adult-friendly –a big tablet which adults don't have trouble swallowing – and someone else wants to develop a cherry-flavored syrup and wants approval for a lower age group, the new age and new dosage form can still fall under 505(b)(2)."
- ***Route of administration*** – such as a change from an intravenous to an intrathecal route.
- ***Strength*** – to a lower or higher strength.

- ***Active ingredient*** – a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

- ***Active ingredient in a combination product*** – substitution of a new active ingredient for another active ingredient, whether that active ingredient has or has not been previously approved. There are situations where combination products can qualify for a 505(b)(2) application. However, there are several issues that must be addressed with combination products under 505(b)(2), including:

  - **Whether the AUC and C_{max} match.** An FDA official said, "Here, the AUC and C_{max} need to match." Another FDA expert said, "Both the C_{max} and the AUC have to match (within the 80%-125% range)…The clinical division may decide a very small difference in C_{max} is not clinically significant…If it is too much, they may say you have to go back and reformulate."

  - **No drug-drug interactions.** The official explained, "One of the things we look for in combination products is the theoretical possibility that when you take and mix them into a tablet, when they are binding they are not forming another product that doesn't have the time to occur when they are just thrown into the stomach together…so we can know they can be taken together and there are no drug interactions."

  - **Unexpected reactions.** An FDA expert said, "The question is whether pressing two drugs together closely in a single tablet will do anything unexpected. The binding or the physical proximity of the molecules may cause a breakdown of one that wouldn't ever form when they are separate…Part of that is a chemistry issue, and part of that is looking at whether together they might affect bioavailability."

  - **Whether both drugs make a contribution.** An FDA official said, "If all the information is well known and supported, then it comes down to taking the same drugs and packaging them together…Each has to make a contribution."

- ***Formulation*** – a different quality or quantity of an excipient(s) than the listed drug, where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.

- ***Dosing regimen*** – such as a change from BID to QD dosing.

- ***Indication*** – a new indication for an approved drug.

505(b)(2) applications also can sometimes be submitted for:

- ***Combination product*** – in which the active ingredients have been previously approved individually.

- ***New molecular entity*** *(NME)* – In some cases an NME may have been studied by parties other than the applicant and published information may be pertinent to the new application. This is particularly likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.

- ***Rx/OTC switch.***

- ***OTC monograph*** – a drug product that differs from a product described in an OTC monograph, such as a non-monograph indication or a new dosage form.

- ***Naturally derived or recombinant active ingredient*** – a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

- ***Bioinequivalence*** – Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j)…Applications for proposed drug products where the rate and/or extent of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence may be submitted under 505(b)(2). This may require additional clinical studies to document safety and efficacy. The proposed product does not need to be shown to be clinically *better* than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application.

Things that can't be submitted under 505(b)(2) include:

- A duplicate of a listed drug that is eligible for approval under 505(j).

- When the *only* difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is intentionally or unintentionally less than the listed drug.

BIOEQUIVALENCE AND 505(B)(2)

A new drug or new formulation of an existing drug, to be bioequivalent, is supposed to have an AUC and a C_{max} within the range of 80%-125% of the approved drug (with a 90% confidence interval). However, there are situations where the C_{max} can be outside this range and still meet the requirement for 505(b)(2) and bioequivalency. An FDA official said, "This is a very confusing area…People – even those who know something – assume (incorrectly) that the average AUC or C_{max} has to fall within the range of 80%-125%."

He gave two examples:

- Study 1: with 6 C_{max} readings: 9-10-11-11-10-9. The mean would be 10.

- Study 2: with 6 C_{max} readings: 5-10-10-15-15-5. The mean would be 10.

The FDA official explained, "These seem the same, but they are not the same at all. Once you look beyond the average, it may not look the same. A group that is clustered around the average is different from one that is all over the place and the average is just a measure of the center. This is why we use confidence intervals, and we don't depend on the average or mean as the sole determinant…How variable a drug is has meaning because certainly part of the variability is just the difference between people. You and I taking the same dose of the same medication probably would not have the same absorption, which might lead to a difference in response or side effects. And there is variability within a person. A person can respond differently to the same medication and dose at different times of day…Physicians treat one patient at a time, and they need to know what the best prediction is of how a new patient will respond to a medication, what dosing to use because of their experience and that of their colleagues…Using an 80%-125% range for AUC and C_{max} says that we are controlling not only the average but the variability of it, too…If it is a very variable drug, there is less room to let it stray from 1 over the reference product…So, we are not just taking the average of the study and saying it has to be in the same boundaries…When there is tight variability, we can allow the ratio to vary a little more because there is a great deal of certainty."

Are there ever situations where the C_{max} could exceed 125% of the reference drug?

- **Not for a generic, under 505(j) (an ANDA).** The FDA official said, "Never…In 505(j) we are ***very*** strict. You always have to meet the range…In generics, they have to pass (meet it)…I don't ever remember a time or case that didn't meet (the range) and got approved."

- **Possibly for a 505(b)(2) application.** The FDA official said, "Yes and no…A lot of active ingredients are in different forms – like free base instead of a salt – where the chemical form and dosage form are different, so you can't apply for a generic status because the two active ingredients aren't the same…With 505(b)(2), there is no real regulatory requirement that you have to pass some pre-set criteria…It is really up to the discretion of the medical officer and the professionals reviewing whether the results of the study are acceptable to prove the point they are trying to prove or to get some labeling claim…So, it is up to the discretion of the reviewers whether the study supports the case…Not all cases pass the strict criteria…In 505 (b)(2), the object is not the same (as with generics)."

In fact, different release formulations actually should have a C_{max} that is outside the range – or they are *unlikely* to get approved. An official explained, "Take the case of a sponsor who comes in with a modified release delivery system for a reference drug with an immediate release delivery system – a drug that is now in tablet form which releases much more slowly with the new formulation – so instead of taking it four times a day, patients can take it one or two times a day. The new product has more drug and releases very slowly…It is very common for a new sponsor to compare an extended release (ER) product to an immediate release (IR) reference product. The characteristics of the extended release product are different because it releases slower…We don't expect it to match completely on absorption…You might have a reference product that is given 100 mg BID, but the new ER formulation is only QD, so the sponsor puts in 200 mg (of active drug). If we look at the actual measurement in a bioequivalence trial, we would hope to see that the material is absorbed the same. The AUC the same is ideal, but because it is released differently, the C_{max} probably wouldn't match if working properly…Usually, there are spikes with IR and a more gradual release with ER…If the product is working correctly, you wouldn't match the C_{max}, but the AUC should match. That is the expected outcome: for AUC but not C_{max} to match."

Other comments by FDA officials on this point included:

- "I've reviewed things where the sponsor brought in a supposedly new controlled release (CR) dosage, and the C_{max} matched, and that was a bad thing. The implication was that the company did not do a very good job in formulating the CR…How could you match the C_{max} if you did a good job…In that case, matching C_{max} is a negative."

- "For a 505(b)(2), it isn't a case by case situation, but it is a situation where it doesn't really have to match…The FDA has a whole lot of knowledge about the drug with the original NDA, and the new drug sponsor is just using the original as an index of expectations…and the (b)(2) is saying the sponsor wants to do something a little different – a different indication, a different formulation – on purpose, and has claims about what that will accomplish…The sponsor is bringing in a set of studies to say, 'I accomplished this…I don't have to repeat everything the sponsor did…We know the drug works because of PK, bioavailability, and the toxicity of the reference drug. All the sponsor is doing with the 505(b)(2) is building on that knowledge…We just need to figure out how the differences affect our knowledge…For example, with a different salt form, you don't have to do massive tox studies, but we need some small studies to show the change in the salt doesn't affect toxicity – maybe not a full program but maybe there are enough differences that we need some data."

- "Our approach is that if a company can demonstrate safety and that the C_{max} magnitude is not critical to the efficacy, then all they have to do is a bioequivalence study. If they couldn't convince us of that, then they would also have to do a clinical trial…A 505(b)(2) is reviewed by the same people who review a 505(b)(1) [NOTE: a 505(b)(1) is an NDA], not the folks who review generic drugs…And the 505(b)(2) reviewers have a lot of discretion." ♦