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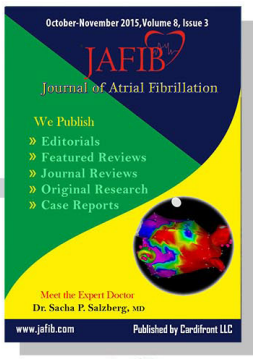

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Does the FDA Owe Us an Explanation?

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Abstract

The approval process for new medications sometimes appears to require pharmacokinetic data in some circumstances and clinical trial data in others. This editorial calls for more clarity and transparency in the process and uses three examples to raise the issue.

Introduction

In the U.S., approval of generic congeners of branded drugs requires bioequivalence.[1] Bioequivalence is determined by serum concentration parameters (e.g., area under the curve, peak concentrations) within a defined range of those obtained with the parent proprietary compound. No clinical testing of outcomes, tolerance, etc. are necessary.

Moreover, in the recent past, plasma concentration assessments were all that were apparently needed for the approval of dabigatran 75 mg bid in patients with significantly reduced creatinine clearance (15-30 ml/min) and for apixaban 5 mg bid in patients on dialysis. For these two agents in these two circumstances, large scale clinical outcomes trials were not required. Only pharmacokinetic (pk) studies in very small numbers of individuals were used.

Why, Then, Was A Similar Approach Not Taken In The Following Three Circumstances?

When approval of sustained-release propafenone was being sought in the U.S., and under circumstances where generic congeners of immediate-release propafenone had already been approved under the process noted above, the FDA mandated two, large-scale, prospective, placebo-controlled, double-blind outcomes trials in atrial fibrillation.[2, 3] Is there any reason to believe that if pk studies had shown plasma concentrations of the sustained-release compounds to fall within the same parameters as occur with the immediate-release proprietary and generic compounds that should not have been sufficient for approval? The requirement for the large prospective trials rather than just pk studies as are used for approval of generics added significant cost to the development of this drug and no doubt to its pricing in the marketplace.

When dabigatran was approved for the prevention of stroke and systemic embolism (SSE) in patients with non-valvular atrial fibrillation (NVAF) in the U.S., only one of the two doses studied in the pivotal RE-LY trial[4] was approved: 150 mg bid. This dose was superior to warfarin in reducing SSE while having similar rates of overall bleeding. Notably, fatal and intracranial bleeding were lower with dabigatran 150 mg bid than with warfarin. However, also studied but not approved by the FDA was a dose of 110 mg bid. This dose was non-inferior to warfarin for prevention of SSE but had a lower incidence of bleeding. The 110 mg bid dose has been approved in multiple other countries based upon this profile, but was turned down by the FDA largely because the 150 mg bid dose was superior not only to warfarin in preventing SSE but also to the 110 mg bid dose. Yet, rivaroxaban was subsequently approved after its pivotal trial against warfarin based upon non-inferiority to warfarin in both SSE prevention and bleeding.[5]

Notably, there are circumstances in clinical practice where there are bleeding concerns with the 150 mg bid dose, such as in patients with moderate renal impairment (e.g., creatinine clearance of 30-60 ml/min) who are also taking concomitant drugs that can modestly impair the clearance of dabigatran (e.g., amiodarone and others). It would seem prudent to have approved the 110 mg bid dose for such occasions and a pk study to define such circumstances could have been requested. At least with dabigatran, plasma concentrations correlate reasonably well with anticoagulant activity and a potentially useful target range is known.[6,7] This is the major role ex-U.S. If the FDA was concerned about physicians not using the more effective 150 mg bid dose in most patients, as was suggested in a report by some review committee members,[8] then a down-titration algorithm as is required for dofetilide could have been mandated, in which case,

Disclosures:
None.

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for most patients, the 150 mg bid dose would be the required starting dose with down titration to the 110 mg bid dose requiring specific parameters to be present (such as renal dysfunction plus concomitant p-gp inhibitory medications plus elevated plasma dabigatran concentration). It is not too late for the FDA to pursue such a path.

Finally, the HARMONY trial results were recently reported,[9] in which reduced doses of ranolazine combined with reduced doses of dronedarone were found to be more effective in suppressing paroxysmal atrial fibrillation than either of the drugs used individually in the same doses as were used in the combination. The combination was well tolerated and had no serious adverse safety signal. Notably, both ranolazine and dronedarone are available in the U.S. in higher doses than were used in HARMONY, and both had completed large-scale efficacy and mortality trials with their higher doses. The HARMONY results were sufficiently enticing that a larger-scale phase 3 trial was being planned. Reportedly, when discussions were held with the FDA about further development of this combination, the FDA requested that a substantial mortality trial also be performed – thus raising the development costs significantly. This raises memories of the sustained-release propafenone issue. Absent any pk data to suggest that the combination of drugs produces higher serum concentrations than does either drug alone, is there any reason to expect that the combination of reduced doses of these two agents would produce an additive adverse mortality outcome? I know of no evidence to suggest that would be the case. Moreover, could the FDA not have required a series of pk studies to determine if any such concern were realistically likely? Additionally, with both agents individually available for use in full dose now, physicians are already free to prescribe them together in doses that have not been tested in combination.

Importantly, I am not criticizing the FDA for its admirable attempt to protect the American public. They have an incredible responsibility and have done a remarkable job overall – especially considering their underfunding. However, I do believe that more consistency in approach and more transparency in the process should be considered, such that pharmaceutical manufactures and medication prescribers are better informed about the process and have clearer expectations during drug development, and such that cost containment may be better accomplished.

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