

CURATIO. QUO VADIS?

Where goes therapeutic development?

CV Safety Trials – A Cloud over Diabetes Drug Development

Some notes from Dr. Zan Fleming

As a member of the diabetes drug development community, I want to bring you a few impressions* in the wake of the DIA-FDA conference on CV safety evaluation of T2DM products held last month in Washington DC. This topic is of vital importance to the development of metabolic drugs.

Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

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The Latin word, *Curatio*, is an apt name for a forum intended to span a wide spectrum of issues related to maintaining health and treatment of disease. The word's meaning to the Romans included—healing, remedy, cure, caring for, public duty, administration, oversight, care, management, charge, office. The Romans were therefore comfortable with uses beyond those confined to physical health and disease. And, so too can we use *Curatio* to cover discourse around developing and evaluating therapies, tools, systems, and goals.

60 Second Top Line Summary

- ✓ FDA provided essentially no new clarifications on its CV general guidance.
- ✓ The most helpful FDA presentation was from Dr. Todd Sahlroot on specific examples of acceptable and unacceptable statistical approaches that various sponsors have proposed to FDA for yielding and analyzing CV safety data.
- ✓ The only new FDA offering was a presentation on the Agency's Post-marketing Risk Assessment tool—The Sentinel Effort—by Dr. Judith Racoosin, the project's scientific lead in the Office of the Commissioner. Sentinel is an FDA partnership with Boston-based healthcare providers to capture population-based drug-associated adverse event data. This is essentially an epidemiologic approach that will be of marginal utility in identifying signals for commonly occurring adverse reactions.
- ✓ The most startling talk was given by Dr. Anders Svensson of Roche, who mentioned that his company has cancelled 14 of its metabolic drug programs because of FDA's new CV safety requirements. He stated that, going forward, a viable product profile must contain more than just glucose lowering. It must add potential for one or more other substantial clinical benefits.
- ✓ The conference also suggested some clues in how the CV safety guidance will be applied by FDA and EMEA in the future. Dr. Kristina Dunder's presentation of the EMEA Draft Guidance clarified the difference between Europe and FDA. Essentially, EMEA will take each drug on a case by case basis while, for now, FDA will apply its CV safety requirement across the board.
- ✓ Even from FDA I sensed a certain surprise and defensiveness in reacting to the news from sponsors that the CV guidance is posing major challenges for developing diabetes drugs. Dr. Bob Temple himself specifically acknowledged the difficulties and the limitations. He even asked rhetorically if the relative risk upper bound for NDA submission be raised from 1.8 to 2.0.

*This is not meant as a complete report. For comprehensive coverage of this and other conferences in the metabolic drug space, I recommend the Close Concerns subscription newsletter (<http://www.closeconcerns.com>).

What can we reasonably expect from FDA related to safety evaluation of diabetes drugs going forward?

- No changes in the short run. We may be at the darkest point before the first rays of dawn. Since the DIA-FDA conference we have observed with some concern FDA's citing the need for a 'thorough QT study' before Bydureon, Amylin's extended release version of Byetta, can be approved. This 'deficiency' did not appear in the previous complete response letter to Amylin and its appearance now is baffling. Two anti-obesity therapies have received unfavorable FDA advisory panel and FDA responses and the third is not likely to fair much better. The advisory panel has raised the issue of CV safety data for obesity drugs and that raises an even more daunting challenge in the lower CV event rate population. It would be surprising if CV safety guidance does not appear for other chronic therapies. All this is evidence of the systemic risk aversion we find today in FDA and beyond.
- In the longer run, FDA will likely become closer to Europe in how it applies its CV guidance. The economics, and even the ethics, of requiring CV safety programs for every diabetes drug are just not sustainable and cannot be ignored by FDA. Third and fourth to-class agents may benefit from the efforts of their predecessors in providing reassuring safety data, but can a sponsor know far enough in advance about its NDA timing if it will get a pass on a CV program requirement?
- Eventually, the unintended impact of FDA's actions on costs, choice, and health outcomes to the consumer will result in a re-balancing of FDA's policies and practices.

In the meantime, what can we in the therapeutic development community do?

- Embrace the importance of demonstrating acceptable CV and other long-term outcomes for diabetes drugs but within the framework of stages based on reasonable benefit to risk assessments.
- Put forward positive proposals for improving drug safety evaluation
- Advocate changes in the regulatory approval system—such as putting needed drugs out sooner under restricted conditions.
- Support public discourse between FDA and all interested parties aimed at creating viable tools and approaches.

A proposal for consideration

As an example of that last suggestion, my colleagues and I made a novel proposition at the FDA-DIA conference (presentation can be found on our website: www.kinexum.com/home/info/#presentations)

The basic idea is to use modern technology, expanded patient and investigator recruitment, and focused

objectives to substantially reduce the time and costs involved in doing safety and efficacy CV outcome studies. We benefitted from the reactions provided by a diverse group of colleagues at a dinner symposium centered on this idea the week of the conference. We hope to engage in and foster similar meetings to collaborate and reason together in the future. I look forward to working with you in these 'interesting' times.

Best wishes, Zan

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