December 10, 2015

Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Ostroff:

Public Citizen, a consumer advocacy organization with 400,000 members and supporters, writes to urge the Food and Drug Administration (FDA) to further investigate the potentially dangerous situation involving a drug approval and the role of FDA Commissioner nominee Dr. Robert Califf, then Co-Chairman of the industry Steering Committee advising Johnson and Johnson on the study, especially his role in choosing the poorly-performing measuring device that was central to interpreting the study.

Serious concerns have been raised about the possible impact of inaccurate measurements, by a device called INRatio, on subjects’ anticoagulation while on warfarin during the ROCKET AF trial, which sought to compare the most commonly prescribed standard anticoagulant (blood thinner) drug warfarin with the newer drug rivaroxaban (Xarelto). Public Citizen’s Health Research Group has now analyzed data from the FDA’s Manufacturer and User Facility Device Experience (MAUDE) database, which tracks adverse reports on medical devices, and found that between INRatio’s approval in 2002 and November of this year, there have been 9,469 malfunction reports and 1,445 injury reports to the FDA with the INRatio devices from people not in the study. This same device was also used for the study. Many of these reports were publicly available before the ROCKET AF study began.

Background

This important study, ROCKET AF, compared the safety and effectiveness of the blood thinner rivaroxaban in preventing strokes and heart attacks with that of the older, standard blood thinner, warfarin, in patients with a heart arrhythmia called atrial fibrillation. The FDA has always taken the position, for this and other studies, that patients in the warfarin group must be carefully monitored to ensure that their warfarin dose keeps their international normalized ratio (INR; a
measure of blood thinning status) in the effective therapeutic range (2 to 3) so there is a proper basis for comparison with the experimental drug, in this case rivaroxaban, for which INRs are not a useful measure the drug’s blood thinning status.¹ Time in therapeutic range (TTR) measures this control. It reflects how well the physicians have used the results from the INR-measuring devices to adjust patients’ doses to stay in the desired therapeutic range. At a September 8, 2011, meeting of the Cardiovascular and Renal Drugs Advisory Committee, the FDA criticized the relatively inadequate control in the warfarin-treated subjects in the ROCKET AF study,² but ROCKET AF Johnson & Johnson Steering Committee Co-Chairman Robert Califf vigorously defended this criticism at the meeting, including the statement that “we gave warfarin not only in an acceptable way, we gave it in a commendable way during this trial.”³ He also stated that “there’s increasing evidence that TTR has no effect on the benefit for novel anticoagulants versus warfarin.”⁴

Nothing could more adversely impact the validity of monitoring warfarin’s blood-thinning effectiveness in keeping patients in the desired therapeutic range than false readings — whether too high or too low — generated by the testing device used to monitor the degree of blood thinning (the INR). It first became clear 10 years ago that there were dangerous measuring inaccuracies in a widely used home INR-measuring device, known as INRatio (now manufactured by Alere), the same device used for all warfarin-treated subjects in the ROCKET AF study.

In 2005, more than a year before ROCKET AF began, FDA had warned the company that then manufactured the device, HemoSense Corporation, about this problem, stating, “Our review indicates that your firm had information indicating that INRatio devices were generating clinically significant erroneous values. … If the INR is too low, a patient will be prone to form blood clots or strokes. If the INR is too high, a patient will be prone to excessive bleeding. Therefore, both [erroneously] high and low test results have the potential to cause or contribute to a death or serious injury, because: they may result in erroneous [warfarin] dosing and thus improper control of coagulation” [emphasis added].⁵

² Ibid. PDF pages 13-15.
⁴ Ibid. PDF pages 89.
On December 5, 2014, Alere issued an urgent medical device correction acknowledging INRatio errors in measuring INR in patients with certain conditions. The FDA classified this as a Class I recall, defined as a recall that “involve[s] situations when it is likely that use of these devices will cause serious health problems or death.”

Despite the FDA’s criticism of the inadequacy of controlling the INR range of patients on warfarin in ROCKET AF, relative to comparable studies with other newer blood-thinning drugs, Dr. Califf’s defense at the advisory committee meeting against this criticism failed to include any mention of a serious underlying problem with the INR readings, namely the inaccuracy of many INRatio readings of patients on warfarin, incorrectly lower or higher than their actual INRs. This could certainly contribute to the difficulty of physicians being able to achieve adequate anticoagulation. The FDA also failed to discuss this problem either in its briefing materials or during its presentation at the September 8, 2011, meeting.

In addition, warfarin-treated subjects in the study with erroneously low INRatio INR readings who actually had high INRs would be at risk of serious bleeding because of the higher INR. Warfarin-treated subjects in the study whose INRs were incorrectly read as low could have been subjected to further risk of bleeding if they were given more warfarin to raise their INR. Beyond presenting serious harm to these subjects, extra bleeding in the warfarin-treated subjects also could have made the bleeding comparison with rivaroxaban more favorable to this newer drug in the ROCKET AF study. Erroneously high readings could, conversely, have led to reducing the warfarin dose or temporarily stopping the drug because of the mistaken belief that the INR exceeded the desired therapeutic range when, in fact, with a truly normal or low INR, warfarin needed to be continued or even increased. This also had attendant risks, such as an increased risk of embolic strokes.

Because of recent publicity about the problems with the INRatio devices, the European Medicines Agency (EMA), the European equivalent of the FDA, has very recently stated that it “is currently investigating whether the data generated from the INRatio device could have had any impact on the Rocket trial results and the extent of this impact, if applicable.” EMA spokeswoman Rebecca Harding told Regulatory Focus that the manufacturer of Xarelto, Bayer, recently informed the agency that the defect in the INR device could have an impact on the study results. “Due to the defect, it is now thought that the INR device has impacted the clotting results measured for the warfarin arm, which might affect the overall results for Xarelto as compared

---


with warfarin,” Harding said in an email. It should be noted that only months after ROCKET AF began, a paper was published raising concerns about the accuracy of the INRatio device. This study, published in 2007, meticulously assessed the INR results of five point-of-care devices and showed clearly that INRatio performed worst among those tested when compared with the gold-standard laboratory test for measuring the INR. In 10 percent of patients, the discrepancy was more than 1 INR unit, a difference which would almost always lead to different therapeutic actions and, possibly, to harm to patients. The study referred to earlier analyses also showing clinically significant discrepancies with gold-standard laboratory tests. A publication in 1996 by one of us (Dr. Frits Rosendaal) found that for every increase of just one unit of INR, the bleeding risk increases between 42 percent and 44 percent, emphasizing the importance of accurate INR measurement to avoid needless bleeding episodes.

Newly Analyzed FDA Data on Serious Injuries From Faulty INRatio Devices

Public Citizen’s Health Research Group has now analyzed data from the FDA’s MAUDE database, which tracks reports of adverse events associated with medical devices submitted to the FDA and found that between INRatio’s approval in 2002 and November of this year, there have been 9,469 malfunction reports and 1,445 injury reports to the FDA with the INRatio devices.

Injury reports include decisions to increase anticoagulation (warfarin) because of inaccurately low INR readings on the INRatio device, or, much less commonly, to decrease warfarin because of inaccurately high readings. Although many of these cases were not accompanied by bleeding due to previous over-anticoagulation, they were still listed as injury because they put patients needlessly at risk, often necessitating treatment with vitamin K (a warfarin antagonist) to prevent bleeding or plasma or blood transfusions, and often involving hospitalization. The injury cases chosen here and presented below are a sample of those in which bleeding occurred, limited to cases reported up to July 31, 2009.

Malfunction reports usually contain evidence that the INRatio INR reading turned out to be incorrectly low when compared with a standard laboratory INR reading. Just as often, the reverse was true, and the INRatio reading was confirmed to be actually higher than a standard laboratory

---

INR. The difference between malfunction and injury reports is that at least at the time the malfunction report was filed, bleeding had not occurred nor had patients been treated with any of the measures described in the injury section above. The INRatio malfunction reports described below are consistent with the FDA’s definition of “malfunction”: “A malfunction is reportable when it is likely to cause or contribute to a death or serious injury if it were to recur. The regulation assumes that a malfunction will recur” [emphasis added].

**Injury Reports**

The injury reports are divided into two groups. The first group consists of cases reported to the FDA before the initiation of the ROCKET AF study on December 21, 2006. There were a total of 63 such cases during this interval. The second group are those cases that occurred in the general population while the study was ongoing, until July 31, 2009, but not including any subjects in the study or patients with bleeding injuries after July 31, 2009. There were a total of 173 injury cases reported during this latter interval.

Summarized in the table below are FDA MAUDE injury reports from the first group for patients who experienced serious bleeding injuries.

The above cases, publicly available before ROCKET AF began, illustrate the clinical importance of large differences between the INRatio results and the actual INRs as determined in a standard clinical laboratory assay.

For the three patients in the October 12, 2005, entry, all of the laboratory determinations were made within an hour of the INRatio readings. The INRatio readings averaged 1.7, below the therapeutic range for most patients, but the laboratory readings averaged over 3.5, more than twice as high and above the therapeutic range for many patients. Their clinical picture “rectal bleeding and bruising” also reflected overcoagulation, not undercoagulation as implied by the low INRatio results.

The first and last patients on the above chart were both treated with warfarin because of lower (1.8 and 2.8, respectively) INRatio readings. Their hospital readings, after this mistaken additional warfarin treatment, were 8.0 and 15.0. The first patient subsequently had a “spinal bleed” and suffered lower-body paralysis, and the second patient died.

Summarized in the table below are FDA MAUDE injury reports from the second group for patients who experienced serious bleeding injuries.
In the table below are the URLs for all of the cases presented in the tables above for the first and second groups for patients who experienced serious bleeding injuries.

<table>
<thead>
<tr>
<th>Date of event</th>
<th>URL of FDA record of 20 selected bleeding events up through July 31, 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/12/05</td>
<td><a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=645722">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=645722</a></td>
</tr>
<tr>
<td>2/24/06</td>
<td><a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=691866">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=691866</a></td>
</tr>
<tr>
<td>5/18/06</td>
<td><a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=721891">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=721891</a></td>
</tr>
<tr>
<td>7/6/06</td>
<td><a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=732853">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=732853</a></td>
</tr>
</tbody>
</table>
Malfunction Reports

There were 652 MAUDE malfunction reports for INRatio devices posted before ROCKET AF began, all, according to the FDA definition on page 4 (above), “likely to cause or contribute to a death or serious injury if it were to recur.”

For the majority of these reports, most of which had both INRatio and comparable laboratory results for the same patient, the difference between the INRatio and the laboratory result was at least 1 INR unit. Discrepancies of this magnitude can lead to inappropriate adjustments in
anticoagulation therapy if one value is in the therapeutic range and the other is not. In many cases the INRatio reading was higher than the gold-standard laboratory reading, suggesting that the patient might be overcoagulated. In many other malfunction cases, as was the case in all of the bleeding cases above, the INRatio reading was significantly lower than the gold-standard laboratory reading, leading to falsely derived concerns that the patient might not be getting enough warfarin.

**Conclusion**

The findings from these 1,445 FDA INRatio injury reports and almost 10,000 malfunction reports in patients not in the study raise serious questions about both the validity of the findings from ROCKET AF in the face of the inaccuracies of the INRatio INR measurements in the study and whether this device should be allowed to stay on the market in view of the ongoing harm to patients using it.

Because INRatio was determined to be substantially equivalent to similar earlier FDA-cleared devices under the 510(k) provision of the device law, there was no requirement to prove that its results were equivalent to those obtained in standard laboratory INR assays before allowing it to be sold. The injury data in this report show that INRatio is dangerously different in too many instances from this gold-standard laboratory test for INR measurement, but this fact was only discovered after the FDA allowed the device on the market in 2002. The MAUDE report information included here is not from patients in the ROCKET AF study but in patients being monitored with the same INRatio device both before the study began and while it was ongoing.

The information in this letter also is being sent to Dr. Guido Rasi, Executive Director of the European Medicines Agency. The former has opened an investigation into the possible implications of this faulty medical device on its interpretation of the ROCKET AF results, and the FDA has recently acknowledged some kind of review of the matter. We urge the FDA to initiate a thorough investigation to answer the question posed by the EMA. For obvious reasons of conflict of interest, Dr. Califf, the current nominee for Commissioner of the FDA, should recuse himself from any FDA review of this matter. He should, however, be prepared to answer relevant questions and provide evidence about the basis of the decision of the ROCKET AF Steering Committee, which he co-chaired, to use the INRatio device in the ROCKET AF study.

---

Public Citizen

December 10, 2015, Letter to the FDA Regarding INRatio

despite multiple injury and malfunction cases that had been reported to the FDA prior to the initiation of ROCKET AF.

Sincerely,

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen Health Research Group

F.R. Rosendaal, M.D., Ph.D.
Professor and Chair, Department of Clinical Epidemiology
Leiden University Medical Center, Leiden University
Leiden, The Netherlands