FDA Workshop on Point of Care Prothrombin Time/International Normalized Ratio Devices for Monitoring Warfarin Therapy
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I have no conflict of interest

Two overarching problems highlighted by the INRatio/ROCKET AF case

● Inadequacy of the low FDA legal standard of substantial equivalence [510(k)] for devices needed to monitor life-threatening conditions.

"(i) any differences in technological characteristics do not raise different questions of safety and effectiveness and (ii) information submitted demonstrates that the new device is as safe and effective as the predicate device."

● Dangerous failure of parties involved---CDRH, CDER, Rocket AF investigators, Janssen/Bayer, INRatio manufacturers---to promptly investigate, communicate serious device warnings to all other parties and take appropriate, necessary actions

14 months before ROCKET AF began, FDA (CDRH) October 2005 warning to INRatio's manufacturer

"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"

Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: HemoSense Corporation. October 4, 2005.
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2005/ucm075594.htm.

FDA Cases of Serious Injuries with Faulty INRatio Devices (pre-ROCKET)

Event Date	INRatio INR	Lab INR	Treatment	Injury
03/04/05	1.8	8.0 (after Hosp'n*)	Increased warfarin (after 1.8 INR)	Hospitalized* 2 days later; 3 days after this, in hospital with spinal bleed and lower body paralysis 1
10/12/05 Three pts	1.7 1.9 1.5	2.6 4.8 3.3		Rectal bleeding and bruising Lab INRs measured < 1hour after INRatio
2/24/06	1.9	9.0 (next day)		Bruises and a swollen arm
3/1/06	1.3	6.0 in hospital	Hospitalized	Coughing blood and nosebleed
3/27/06	2.6	6.3		Lost vision in one eye for 5 minutes
4/4/06	1.6	8.0	Hospitalized	

From FDA Maude Reports

2007 study comparing INRatio with four other POC devices

- "Direct comparison of POCT results against the standard method using linear regression analysis suggested that correlation increased with increasing INR with all but the INRatio"
- "only the INRatio had more than 10% of results greater than 1.0 INR units difference"
- The Hemochron Junior Signature, ProTime and CoaguChek S demonstrated strong correlation with the laboratory method ($R2>0.94$)…percentages of paired results within 0.5 INR units (81.5, 92.0 and 74.0%, respectively); the INRatio and TAS demonstrated 54.2 and 62.2%, respectively.

Moore GW, Henley A, Cotton SS. Clinically significant differences between point-of-care analysers and a standard analyser for monitoring the INR in oral anticoagulant therapy. Blood *Coagul Fibrinolysis.* 2007:18:287-292.

February 5, 2016 EMA report* based on Janssen/Bayer analyses of ROCKET AF paired INRatio/lab INR: 6+ years after ROCKET AF was finished, 4+ years after Xarelto AF approval

- "the ROCKET AF trial was not designed to validate the performance of the POC device or to calibrate it against a Lab based INR." (quote from Janssen/Bayer p. 36)
- "When analysing the MAH [company] data, it appears that 64 INR values were excluded in these analyses as the device INR were ≥ 6.1." (p. 26)
- "the proportion of measurements with a lower Device INR values compared with Lab INRs values are reduced from 34% to 29% according to the rapporteur's calculation, **a number which still could be of some concern in relation for the possibilities of inappropriate dosing**." (p. 28)
- "(273 out of 5766) of the measurements for Device INR were lower by two categories compared to the Lab INRs, **meaning the dose would have been increased or maintained when should have been decreased** (according to the INR categories)" (p. 28)

* 2/10/16 EMA report on INRatio/ROCKET AF data (page of report after each quote above)

Conclusions

- **Five parties---FDA CDER, FDA CDRH, Janssen/Bayer, ROCKET AF investigators and INRatio makers---were not responsibly or promptly communicating with each other more than 10 years ago, when serious problems with INRatio reliability were first known, but, unacceptably, neither shared nor seriously acted upon.**

- **FDA's CDER should continue its investigation of INRatio device failure to provide accurate readings, including but not limited to companies' exclusion from its analysis for the EMA of 64 ROCKET AF readings in which the INRatio INR reading was 6.1 or higher.**

- **The failure of FDA to require pre-market evidence of acceptable comparability of these POC (point of care) devices to standard lab determinations argues strongly for CDRH reclassification to require such premarket studies.**

- **CDRH should consider removing the INRatio device from the market**