Evaluation of the Precision and Accuracy of the INRatio®2 Prothrombin Time (PT) Monitoring System

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The product performance claims in this white paper are pending 510(k) clearance. The product available for sale has been cleared based on the performance claims in the current product labeling.

Prothrombin Time (PT) monitoring systems must demonstrate precision and accuracy, including comparability to standardized lab methods. This paper summarizes the performance of the INRatio®2 system, consisting of a monitor and test strips with two levels of built-in quality control, across six test strip lots with over 350 duplicate INR measurements.

Precision was shown to be excellent across the entire therapeutic range (INR 2.0 to 4.5), with a mean INR of 3.0 and CV of 5.9%**.** Accuracy was also shown to be excellent with an overall correlation of 0.96 to the laboratory reference method.

INTRODUCTION

Patients on oral anticoagulation therapy (OAT) with warfarin require frequent monitoring using the prothrombin time (PT) test, reported in INR (International Normalized Ratio). The ACCP Consensus Guidelines recommends a therapeutic range between 2.0 to 3.0 INR[1]. Individuals requiring more intensive therapy, such as with prosthetic (mechanical) heart valves in the mitral position, often have a target therapeutic range from 2.5 to 3.5 INR.

Everyone metabolizes warfarin differently[1]. Too little warfarin results in under-anticoagulation, increasing the risk of forming clots; too much warfarin results in over-anticoagulation, increasing the risk of bleeding. Frequent monitoring is required since critical dosage decisions are largely based on the INR. PT test systems must give accurate and precise results, and must pass stringent quality control (QC). Accessibility and timeliness of the PT are also crucial.

The INRatio®2 system is a second-generation portable monitor for evaluating the PT test, in INR units, of patients taking warfarin. The test principle is the same as used in the original INRatio system (2002), and both systems utilize the same INRatio/INRatio2 test strip. INRatio2 system is intended for use by healthcare professionals at the point-of-care (POC) and by patients (or their caregivers) at home on the order of their physician for patient self-testing (PST).

The INRatio/INRatio2 systems enable a quick, easy and convenient way to confirm that an individual is within their target therapeutic range, or to determine if medication counseling or dose adjustment is needed. With a single drop of finger stick whole blood applied to the test strip, the monitor measures the PT as well as two integrated quality control PT tests at clinical decision points. The INR result is reported once these functional QC and additional electronic QC have passed strict requirements. If QC is ever out of range, the INRatio2 monitor behaves as would a laboratory, and does not report the patient's INR result, eliminating the possibility of an erroneous result.

The INRatio/INRatio2 test strips are manufactured with a human recombinant tissue factor, have an International Sensitivity Index (ISI) close to 1, and are core to both INRatio and INRatio2 systems. In production for over seven years, hundreds of lots and millions of test strips have delivered accurate, precise and timely INR results worldwide to healthcare professionals and patients at home. In the United States, the INRatio brand was the best selling point of care PT/INR monitoring system for the past four years*.

The purpose of this paper is to evaluate the performance, including precision and accuracy, of the INRatio2 system.

*GHX Data, 2005-2008 POC PT/INR Monitors Sold

METHOD COMPARISON

For OAT patients only, the PT test results are presented in INR units, a calculation adopted in 1983 by the World Health Organization (WHO) to enable comparison of results from PT tests performed using thromboplastins of different sensitivities and from different labs or systems.[2] The sensitivity of a thromboplastin is defined by its ISI. Thromboplastins with low ISI values are more sensitive to factor deficiencies. The manufacturer of a commercial thromboplastin assigns an ISI, following WHO guidelines[3], to each reagent lot, as well as the mean normal (MN) PT value (determined from non-anticoagulated healthy donors). The following equation calculates the INR based upon the patient's PT (seconds):

$$INR = (\text{Patient PT}/\text{MN PT})^{ISI}$$

Each patient's INR result is calculated automatically by the INRatio/INRatio2 monitor.

Precision (Repeatability):
The degree of agreement among a series of measurements of the same quantity is typically reported as coefficient of variation (CV), or how much a result deviates from the mean of all results. A smaller CV is a measure of greater precision.

$$\%CV = (SD/mean) \times 100\%$$

Accuracy
The accuracy of the INRatio® system is evaluated by performing a method comparison. The results of the INRatio systems are compared to the results from a standard laboratory reference. In this study the reference was the widely used laboratory plasma instrument, the Sysmex CA-560 (Kobe, Japan), with Dade Innovin® recombinant human tissue factor reagent (Marburg, Germany). The lab reference blood sample was obtained from the patient using a 3.2% sodium citrate Vacutainer® and processed as plasma according to manufacturer instructions. This reference method had been calibrated to the manual tilt tube method using reference thromboplastin rTF/95. [3]

Six representative INRatio test strip lots were evaluated with respect to precision and accuracy. Test strips were tested with capillary finger stick whole blood samples from each patient in duplicate analysis. Over 200 patients on OAT and over 100 non-anticoagulated (normal) volunteer donors were included in the study. The therapeutic donors on OAT were being treated for a variety of disorders, including atrial fibrillation, prior stroke, and coronary artery disease. Patients ranged in age from 27 to 91 years old. Data were analyzed in accordance with current ISO guidelines. [4]

One-way ANOVAs (analysis of variance) were performed to evaluate whether the INR values from any of the six lots were likely to have come from groups with different means. If a P-value indicated that the null hypothesis (all groups have the same mean) could not be rejected, the data were deemed poolable. Analyses were performed in Matlab® version 7.8.0.347 (R2009a). Data from all 6 lots were deemed poolable. In addition, while the data are not included here, data from the INRatio and INRatio2 systems were deemed poolable.

This study reports on the precision and accuracy of the INRatio2 system. Previous studies have illustrated that the INRatio and INRatio2 systems are substantially equivalent in performance.[5]

RESULTS / DISCUSSION

Precision

Six lots of strips were tested on the INRatio and INRatio2 systems using the same donors with duplicate measures. Precision of the INRatio2 system is reported here as having a CV of 5.9% for patients within the therapeutic interval of INR 2.0 to 4.5, and 7.6% for non-anticoagulated (normal) donors. Precision, based on pooled data from the six lots, is summarized in Table 1.

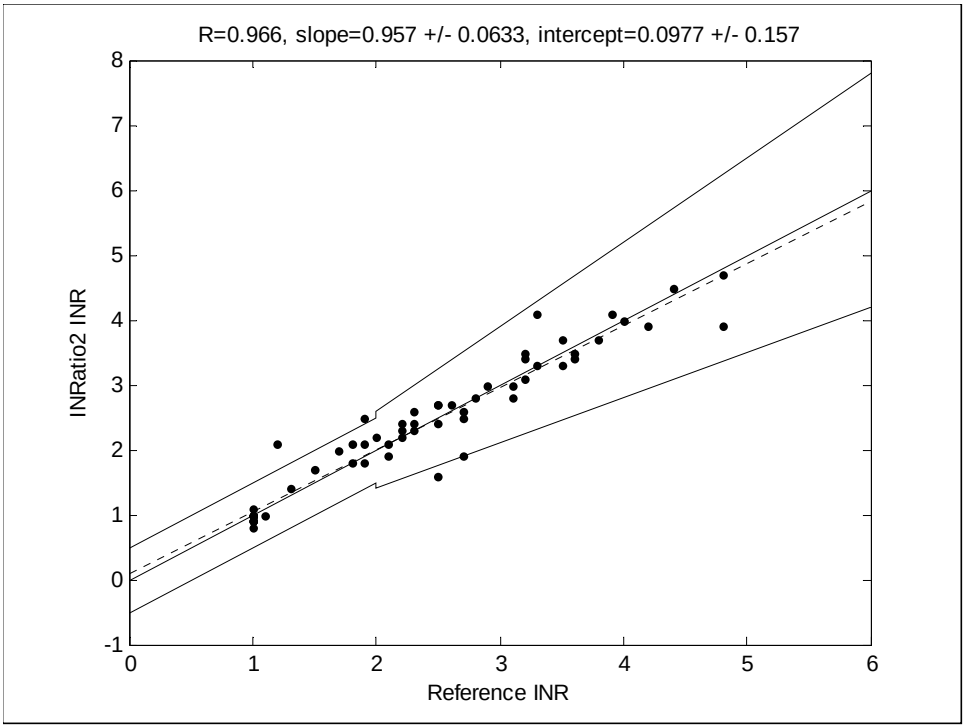
TABLE 1: Precision for INRatio®2 System

INR	N	Mean INR	STDEV	%CV
Normals	**119**	**0.98**	**0.07**	**7.6%**
>2.0 - 3.0	**136**	**2.50**	**0.15**	**5.9%**
>3.0 - 4.5	**97**	**3.60**	**0.21**	**5.8%**
2.0 - 4.5	**233**	**2.96**	**0.18**	**5.9%**

Accuracy (Method Comparison)

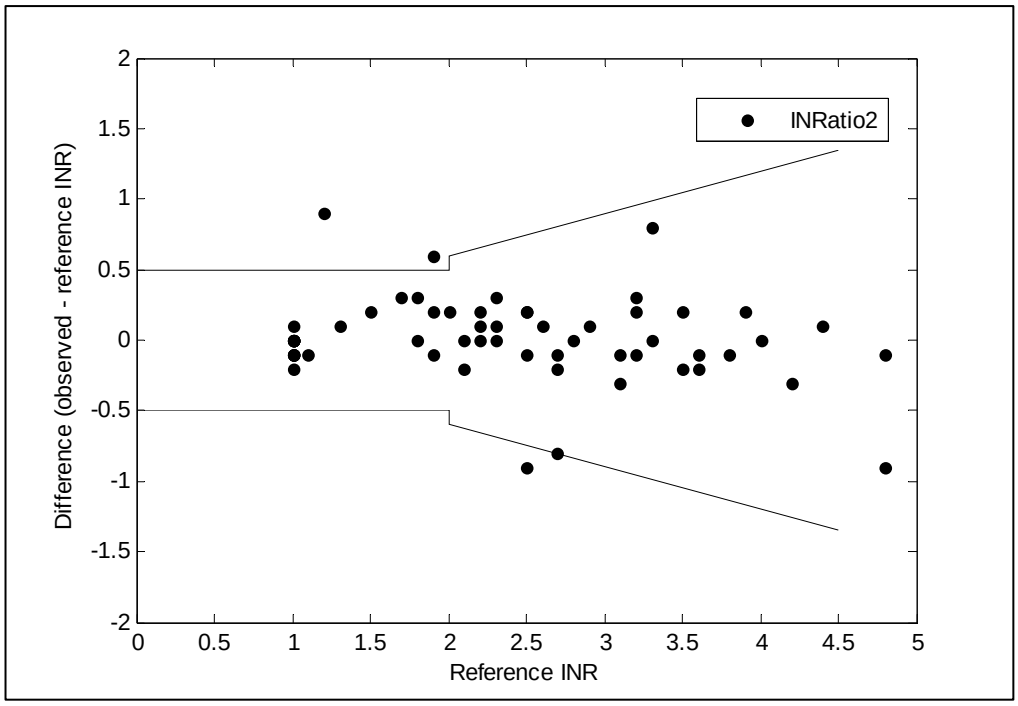
Accuracy is demonstrated by performing a method comparison between the finger stick whole blood test method, INRatio2 system and the venous plasma comparison method. Accuracy of each system is shown in the tables and depicted in the graphs, below.

FIGURE 1: ACCURACY Method comparison, INRatio®2 system Capillary Blood



The correlation of the INRatio2 system results (representative lot #3; capillary blood) to plasma results from the Sysmex CA-560 System (Dade Innovin) is shown in Figure 1. Linear regression (n=67) yielded a slope of 0.96 with an intercept of 0.1. The correlation coefficient is 0.97.

FIGURE 2: Difference PLOT, INRatio®2 System Capillary Blood correlation



The difference plot shown in Figure 2 compares the INRatio2 system capillary results to Dade Innovin/ Sysmex results. This graph shows that 97% of the results in the therapeutic interval of 2.0 to 4.5 are within the ±30% interval compared to 90% requirement per ISO guideline.

CONCLUSION

Point-of-care and patient self-testing of the PT test have become widely adopted in the clinical management of patients on chronic warfarin therapy. Compelling evidence supports PST in the context of a comprehensive anticoagulation management plan[6-8], and portable PT monitors are considered enabling technologies that facilitate high-quality management of patients receiving long-term OAT[8]. Unique from other POC/PST monitoring tests, such as blood glucose, PT is an activity test based on a series of enzymatic reactions and is not standardized across methods, so there is no “gold” standard for either whole blood or plasma, whether tested in the lab, POC or PST.

Expanded insurance coverage for PST by Medicare and private insurers enables more patients (MHV, Atrial Fibrillation, venous thromboembolism) to access PST[6-7]. The unique integrated on-board quality controls on INRatio/INRatio2 test strips ensure professional and patient compliance with proper quality assurance of each measurement, reportable at two clinical decision points, and offer QC “lock-out” to significantly reduce the likelihood of erroneous results being reported.

It is equally important that POC/PST systems offer high accuracy and precision. The INRatio®2 system demonstrates excellent performance when compared to both the INRatio system and to a plasma-based central laboratory system, the Sysmex CA 560 using Dade Innovin. Accuracy of the INRatio2 system was excellent with an overall correlation of 0.97 to the laboratory reference method for all comparisons. Precision was excellent across the 2.0 to 4.5 INR therapeutic ranges (2.0 – 3.0 and 3.0 – 4.5), with 5.9%CV, (mean INR of 3.0) across six strip lots for capillary whole blood samples**.**

The results of several years of internal and independent studies on INRatio/INRatio2 test strips also support the fact that capillary whole blood real-time PT/INR testing with the INRatio systems offer many advantages over venous testing on central lab equipment, which usually involves the treating health care professional basing clinical decisions on a delayed or “stale” INR result rather than a real-time or current result. Timely and accurate availability of INR translates to better patient outcomes and more effective patient and therapy management.[8-10] The consistency demonstrated by these results makes the INRatio brands an excellent choice for POC and PST testing, showing strong precision and accuracy.

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REFERENCES

1. CHEST 2008; Vol. 133, Number 6 (SUPPL): Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition): 67S – 970S

2. Loeliger EA, van den Besselaar AMHP, Lewis SM. Reliability and Clinical Impact of the Normalization of the Prothrombin Times in Oral Anticoagulant Control. *Thrombosis and Haemostasis* 1985;53:148-154.

3. Guidelines for Thromboplastins and Plasma Used to Control Anticoagulant Therapy. WHO Technical Report Series #889, Annex 3, World Health Organization (1999).

4. ISO 2007: 17593, Clinical laboratory testing and *in vitro* medical devices - Requirements for *in vitro* monitoring systems for self-testing of oral anticoagulant therapy.

5. HemoSense® INRatio®2 system 510(k) K072727 and K021923; Data on file at Inverness Medical.

6. Medicare coverage 2008 Centers for Medicare & Medicaid Services (CMS), Pub 100-03 Medicare National Coverage Determinations, Transmittal 90, Effective March 19, 2008; Implementation Date: August 25, 2008, Change Request 6138

7. National Coverage Decision, # CAG-00087N, Centers for Medicare and Medicaid Services, September 18, 2001.

8. Supplement to Managed Care. Volume 17, No. 10, Supplement 9, October 2008**:** Oral Anticoagulation Patient Self-Testing: Consensus Guidelines For Practical Implementation

9. THINRS Trial: Late Breaking Clinical Trials IV News Conference (Nov. 12, 2008), American Heart Association Scientific Sessions.

   Jacobson, AK and D. Matchar. Cooperative Studies Program #481 Palo Alto Cooperative Studies Program Coordinating Center (CSPCC): The Home INR Study (THINRS): Primary Results.

10. Heneghan, C et al. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis, The Lancet, 2006; 367:404-11