

INR Control Plasma (Human) Levels 1, 2, 3, 4 and 5

I. Intended Use

Pacific Hemostasis® INR Controls, Levels 1 through 5, are intended for use as controls to check the performance of PT testing.

II. Summary and Principles

The most common method used for monitoring coumarin therapy has been the Prothrombin Time (PT), expressed either as a PT clot time in seconds or as a ratio of the patient PT to the mean normal PT (obtained from a reference population of healthy, normal donors). However, neither method takes into account variation in thromboplastin reagents or instrumentation.¹

The inherent variability of thromboplastin reagents was addressed in 1977 when the World Health Organization (WHO) recommended a system of reagent normalization.² By calibrating against a WHO reference thromboplastin, an International Sensitivity Index (ISI)³ can be assigned to each lot of thromboplastin. Furthermore, since the ISI can vary with the clot detection method,⁴ the WHO has recommended the following relationship for reporting patients on stabilized oral anticoagulant therapy:

$$\text{INR} = \left(\frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{\text{ISI}}$$

WHERE: INR is the International Normalized Ratio; ISI is the International Sensitivity Index of the thromboplastin/instrument combination (provided by manufacturer); **Patient PT** is the PT clot time for the patient on stabilized oral anticoagulant therapy; and **Mean Normal PT** is the average of PT times established by the individual laboratory by testing a reference population of donors with no known coagulation abnormalities. The **Mean Normal PT** is specific for each reagent lot/instrument combination.

In effect, the INR represents the PT ratio which would have been obtained had the WHO reference PT reagent been utilized. PT reagents with low ISI values are more responsive and generate more prolonged PT values at a given level of anticoagulation. The ISI/INR system for reporting patient results is designed to make the results independent of the reagent and test method used. However, it is important to recognize the variability in the ISI assignment and that it is inappropriate to use a normal control PT in place of a mean normal PT.^{5,6}

III. Reagent

For *in vitro* diagnostic use.

INR Controls 1 through 5 are manufactured from human plasma collected with sodium citrate anticoagulant. Each level is adjusted to produce appropriate INR values. Stabilizers and buffers are added prior to lyophilization. After lyophilization, the INR values are determined on three different classes of coagulation instruments using two different Pacific Hemostasis thromboplastins. The mean normal PT for each reagent/instrument combination is determined from 20 or more normal donors and each thromboplastin ISI is directly traceable to the WHO international

Reference Thromboplastin. The INR value of each control is an average of these determinations and can be found on the vial label.

Caution: Each unit of source material used in preparation of this product has been tested by FDA licensed method and found non-reactive for HBsAg and negative for antibodies to HIV and HCV. However, no known test method can offer complete assurance that products derived from human blood will not transmit hepatitis, AIDS or other infectious diseases. This product should be handled as potentially infectious biological material.

Store unopened vials at 2-8°C. Reconstitute with 1.0 mL of distilled water. Swirl gently and let stand undisturbed for 15 minutes at room temperature. Do not invert vial or mix vigorously. After proper reconstitution, controls are stable for 8 hours when stored in a capped vial at 2-8°C. Do not freeze reconstituted controls. Gently mix contents prior to each use.

Erratic values, product color variations, or lack of vacuum in the vials could indicate product deterioration. However, poor control performance could also be due to other factors within the test system.

IV. Procedure

Materials provided:

Pacific Hemostasis® INR Controls, Levels 1,2, 3, 4 and 5

Materials required but not provided:

Distilled water, pipette capable of accurately delivering 1.0 mL

Using instructions provided by instrument and reagent manufacturers, determine the PT for Pacific Hemostasis® INR Control plasmas following methods established for patient samples. Calculate the INR for each control by dividing the laboratory mean normal PT into each clot time and raising that result to the lot-specific ISI for the instrument. Each laboratory must establish its own mean normal PT for each lot of thromboplastin and instrument used. The mean normal PT should be determined with at least 20 healthy, non-medicated normal donors with no coagulation abnormalities.⁸

For example: a control with a PT of 27 seconds would have an INR of $(27/12)^{1.13} = 2.5$ for a lab with a mean normal PT of 12 and an ISI of 1.13. In another lab, this same control would have a PT of 18 seconds and an INR of $(18/11)^{1.86} = 2.5$ with a mean normal PT of 11 seconds and an ISI of 1.86.

V. Expected Results

Level	Description	Assigned INR	Expected Value
1	very low	See vial Label	± 10%
2	low	See vial Label	± 10%
3	moderate	See vial Label	± 10%
4	high	See vial Label	± 10%
5	extreme	See vial Label	± 10%

The INR is dependent on both the ISI and mean normal. A valid mean normal PT is absolutely critical to recovering the correct INR. If the average recovery for all 5 controls is not within 10% of the labeled value, check to ensure that the correct ISI has been used and review the values used to determine the laboratory mean normal PT. Each of the assigned INR values is the average of 6 reagent/instrument combinations, each of which has an ISI and a unique mean normal PT.

VI. Limitations

Pacific Hemostasis warrants the INR values of Control Plasma only for use with Pacific Hemostasis-brand Thromboplastins. These controls should not be used as calibrators or reference plasmas or for determining the local ISI of commercial thromboplastins. All controls are subject to the limitations of the test system. Variables such as temperature, reagent stability, instrument performance, and individual technique can influence final results. Always follow instrument and reagent manufacturer guidelines. A valid mean normal PT is critical to recovering appropriate INR results.

VII. Performance Characteristics

The five Pacific Hemostasis INR Control Plasmas, are designed to span the therapeutic range for oral anticoagulant therapy as described by Hirsh et al, (INR 2.0-3.0 for regular therapy, 2.5-3.5 for mechanical prosthetic heart valve and 3.0-4.5 for high intensity warfarin therapy.)¹

VIII. References

- Hirsh, J., Dalen, J.E., Deykin, D., Poller, L.: Oral Anticoagulants Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range, 1992, Chest 102:312S-326S.
- Biggs, R., Denson, K.W.E.: Standardization of the one stage prothrombin time for control of anticoagulant therapy. 1967. Brit. Med. J. 1:84-88.
- van den Besselaar, A.M.H.P., van der Velde, E.A.: The manufacturer's Calibration Study in Thromboplastin Calibration and Oral Anticoagulant Control (van den Besselaar, A.M.H.P., Gralnick, H.R., Lewis, S.M., eds) 1984, pp127 - 149, Martinus Nijhoff Publishers, Boston, MA.

4. Poggio, M., van den Besselaar, A.M.H.P. van der Velde, E. Bertina R., The Effect of Some Instruments for Prothrombin Time Testing on the International Sensitivity Index of Two Rabbit Tissue Thromboplastin Reagents, 1989, Thromb Haemost 62:868-874.

5. Loeliger, E.A. , van den Besselaar, Lewis, S.M.: Reliability and Clinical Impact of the Normalization of the Prothrombin Times in Oral anticoagulant Control 1985. Thrombosis and Hemostasis 53: 148-154.

6. Hirsh, J., Poller, L.: The International Normalized Ratio, 1994. Arch Intern Med 154:282-288.

7. Tomenson, J. A. In Thromboplastin Calibration and Oral Anticoagulant Control (van den Besselaar, A.M.H.P., Gralnick, H.R., Lewis, S.M., eds) 1984, pp. 87 - 108, Martinus Nijhoff Publishers, Boston, MA.

8. National Committee for Clinical Laboratory Standards. Collection, transport and processing of blood specimens for coagulation testing and performance of coagulation assays. 2nd ed. Approved guideline. NCCLS Publication H21-A2. Villanova, PA 1991.

Ordering Information

Cat. No.	Description	Contents
100560	INR Control Plasmas	2 x 1 mL x 5 Levels
100356	Thromboplastin D, 200 Det.	10 x 4 mL
100357	Thromboplastin D, 500 Det.	10 x 10 mL
100360	Thromboplastin D, 1000 Det.	10 x 20 mL
100355	Thromboplastin DL, 200 Det.	10 x 4 mL
100359	Thromboplastin DL, 500 Det.	10 x 10 mL
100354	Thromboplastin DS, 200 Det.	10 x 4 mL
100362	Thromboplastin DS, 500 Det.	10 x 10 mL
100244	Reconstitution Fluid.	10 x 10 mL

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