PT-Multi Calibrator
PT-Multi CALIBRATOR

Revision bar indicates update to previous version.

CE 0197

Intended Use

Calibrator set for the direct calibration of the prothrombin time (PT) by Dade® Innovin® and Thromborel® S in INR and % of Norm. For the determination of a local ISI value.

Principles of the Procedure

The prothrombin time (PT) is generally used for monitoring oral anti-coagulation therapy. It is recommended by the World Health Organization (WHO) to report PT values in "International Normalized Ratio" (INR). The INR is calculated via the ISI (International Sensitivity Index) and the MNPT (mean normal prothrombin time) using below equation:

$$INR = \left[\frac{PT}{MNPT} \right]^{ISI}$$

The manufacturer provides the corresponding ISI value for each lot of thromboplastin. However, the ISI value may be influenced by local, laboratory specific conditions and the particular instrument used. Therefore the use of a locally determined ISI is recommended[1,3,4].

The MNPT is in accordance with the ISTH (International Society on Thrombosis and Haemostasis) the geometric mean of the PT of at least 20 healthy adults[2,4].

The calibrant plasmas 1 through 6 of the PT-Multi CALIBRATOR allow establishing reference curves for reporting PT values in INR and % of Norm, using Sysmex Thromboplastin reagents. The reference curves allow for the direct interpolation of an INR for a patient sample (local INR calibration, calibrant plasma procedure).

Reagents

Note: PT-Multi CALIBRATOR can be used manually or on automated coagulation analyzers. Sysmex provides Reference Guides (Application Sheets) for several coagulation analyzers. The Reference Guides (Application Sheets) contain analyzer/assay specific handling and performance information which may differ from that provided in these Instructions for Use. In this case, the information contained in the Reference Guides (Application Sheets) supersedes the information in these Instructions for Use. Please also consult the instruction manual of the instrument manufacturer!

Reagent	Description	Storage	Stability
PT-Multi Calibrator PT-Multi CALIBRATOR			
PT-Multi CALIBRATOR 1	Lyophilized reagent containing: • human plasma[a] • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 8 hours[b]; 15–25 °C: reconstituted, 4 hours[b]; ≤ –18 °C: reconstituted, 4 weeks[b]
PT-Multi CALIBRATOR 2	Lyophilized reagent containing: • human plasma[a] • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 8 hours[b]; 15–25 °C: reconstituted, 4 hours[b]; ≤ –18 °C: reconstituted, 4 weeks[b]
PT-Multi CALIBRATOR 3	Lyophilized reagent containing: • human plasma[a] • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 8 hours[b]; 15–25 °C: reconstituted, 4 hours[b]; ≤ –18 °C: reconstituted, 4 weeks[b]
PT-Multi CALIBRATOR 4	Lyophilized reagent containing: • human plasma[a] • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 8 hours[b]; 15–25 °C: reconstituted, 4 hours[b]; ≤ –18 °C: reconstituted, 4 weeks[b]

Reagent	Description	Storage	Stability
PT-Multi CALIBRATOR 5	Lyophilized reagent containing: • human plasma[a] • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 8 hours[b]; 15–25 °C: reconstituted, 4 hours[b]; ≤ –18 °C: reconstituted, 4 weeks[b]
PT-Multi CALIBRATOR 6	Lyophilized reagent containing: • human plasma[a] • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 8 hours[b]; 15–25 °C: reconstituted, 4 hours[b]; ≤ –18 °C: reconstituted, 4 weeks[b]

[a] pooled
[b] closed original vial

PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 6 may be frozen (see stability after reconstitution) and thawed again once after reconstitution. The calibrant plasmas must be frozen as quickly as possible in the original vials, well sealed. Thaw in a water bath at 37 °C for a maximum of 10 minutes. The calibrant plasmas must be used for calibration within 2 hours at 15 to 25 °C.

Contamination by microorganisms must be avoided.

PT-Multi CALIBRATOR contains 6 calibrant plasmas for the calibration of the PT. The calibrant plasmas contain human pool plasma stabilized with buffer.

Certain calibrant plasmas may contain added portions of preprocessed human plasma. The calibrant plasmas are lyophilized and calibrated.

The PT-Multi CALIBRATOR kit is free of preservatives.

Warnings and Precautions

For *in-vitro* diagnostic use only.

For laboratory professional use.

According to EU regulation 2017/746, any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the EU Member State through your local distribution representative in which the user and/or patient is established.

Safety data sheets (MSDS/SDS) available upon request.

CAUTION! POTENTIAL BIOHAZARD
PT-Multi CALIBRATOR 1, PT-Multi CALIBRATOR 2, PT-Multi CALIBRATOR 3, PT-Multi CALIBRATOR 4, PT-Multi CALIBRATOR 5, PT-Multi CALIBRATOR 6
Each donor or donor unit was tested and found to be negative for human immunodeficiency virus (HIV) 1 and 2, hepatitis B virus (HBV) and hepatitis C virus (HCV) using either tests that are CE marked or FDA approved for this purpose. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with all government requirements.

Summary of Safety and Performance (SSP) is available in the European database on medical devices (see Eudamed public website: https://ec.europa.eu/tools/eudamed). In case Eudamed is not available, SSP can be delivered by the manufacturer on request.

Preparing Reagents

1. Reconstitute the PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 6 with the amount of distilled water indicated on the label.
2. Allow to stand at 15 to 25 °C for at least 30 minutes.
3. Shake carefully to dissolve (without foam formation).

Procedure

Materials Provided

REF	Contents	
OPAT03	PT-Multi Calibrator PT-Multi CALIBRATOR	
	PT-Multi Calibrator Level 1 PT-Multi CALIBRATOR 1	1 × → 1 mL
	PT-Multi Calibrator Level 2 PT-Multi CALIBRATOR 2	1 × → 1 mL
	PT-Multi Calibrator Level 3 PT-Multi CALIBRATOR 3	1 × → 1 mL
	PT-Multi Calibrator Level 4 PT-Multi CALIBRATOR 4	1 × → 1 mL
	PT-Multi Calibrator Level 5 PT-Multi CALIBRATOR 5	1 × → 1 mL
	PT-Multi Calibrator Level 6 PT-Multi CALIBRATOR 6	1 × → 1 mL

Materials Required but not Provided

Item	Description
REF OUHP29, OUHP49 REF B4212-40, B4212-50, B4212-100	*Thromboplastins*: Thromborel® S, or Dade® Innovin®
Coagulation analyzers[c], such as:	• Automated Blood Coagulation Analyzer CA-600 series (CA-600 series) • AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System) • AUTOMATED BLOOD COAGULATION ANALYZER CS-5100 (CS-5100 System)

[c] Availability of analyzers may vary by country.

Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified.

Depending on the thromboplastin used a different number of calibrant plasmas has to be used for calibration. PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 6 are used with Dade® Innovin®. PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 5 are used with Thromborel® S.

Performing Calibration

The primary calibration (value assignment) of PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 6 in INR is carried out by the manufacturer. The analytical values of the calibrant plasmas are

directly linked to the international reference preparation (IRP) of the respective thromboplastin in accordance with WHO guideline[2].

Internal Quality Control

The accuracy of the reference curve should be assessed by running appropriate controls. Controls are listed in each related reagent Instructions for Use. If controls repeatedly exhibit systematic deviations from the declared interval of the lot-dependent Table of Assigned Values, a new reference curve must be established.

Manual Evaluation

1. Calculating an INR reference curve

The prothrombin times of PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 6(PT-Multi CALIBRATOR 1 through PT-Multi CALIBRATOR 5 using Thromborel® S) are measured in duplicate determinations. The mean values are plotted double-logarithmically (x-axis: INR values; y-axis: prothrombin times in seconds). The calibration points are connected by the best possible straight line. The INR value of patient plasmas can be directly read off the double-logarithmic representation of this reference curve.

$$[\log (s) = 1/ISI \cdot \log (INR) + \log (MNPT)]$$

$$y = m \cdot x + b$$

Note: Only when using the double-logarithmic scaling may the numeric values for m and b be read off the graph directly.

2. Calculation of the laboratory-specific, local ISI and MNPT value

The determination of the laboratory-specific, local ISI is based on above equation. The ISI can thus be determined graphically or can be calculated.

Graphical determination of the local ISI and MNPT

Calculate the slope of the INR reference curve generated under "1. Calculating an INR reference curve", page 5.

The laboratory-specific ISI corresponds to the reciprocal of the slope (m) of this straight line, i.e. ISI = 1/m.

The MNPT [s] corresponds to the y-axis intercept of the reference curve.

Calculation of the local ISI and MNPT

The local ISI and the MNPT can be calculated on the basis of the linear equation (y = log (s); x = log (INR); m = slope of the straight line; b = y-axis intercept). To determine the parameters of the linear equation refer to standard mathematical procedures.

Local ISI = 1/m

MNPT = 10^b

Example

Calibrant plasma	s	INR	log (INR)	log (s)
L1	9.0	1.00	0.00	0.950
L2	11.1	1.21	0.08	1.05
L3	14.8	1.60	0.20	1.17
L4	23.5	2.46	0.39	1.37
L5	42.0	4.25	0.63	1.62
L6	53.5	5.34	0.73	1.73
	Slope m **local ISI**			1.06 **0.94**
	Y-axis intercept **MNPT**			0.96 **9.12 s**

Note: It is not necessary to determine the local ISI and MNPT when using the INR reference curve. The INR of any PT value in seconds is directly read off the INR reference curve. This direct INR determination has been shown to improve accuracy of INR reporting, compared to INR calculation using ISI and MNPT values provided by the manufacturer[1].

Limitations

The reference curve is valid only for the particular PT-Multi CALIBRATOR lot and lot of Sysmex thromboplastin reagent. The calibration is instrument and reagent specific. For every new lot of thromboplastin reagent a new calibration is required. A new calibration is further required with change in experimental conditions, software, and after maintenance and repairs of the instrument.

Technical Assistance

For customer support, contact your local technical support provider or distributor.

References

1. Adcock DM, Johnston M. Evaluation of Frozen Plasma Calibrants for enhanced Standardization of the International Normalized Ratio (INR):A Multi-Center Study. Thromb Haemost. 2002;87:74-9.
2. Poller L. The Prothrombin Time. Prepared on behalf of the World Health Organization. WHO/LAB/98.3. 1998.
3. Van den Besselaar AMHP. Precision and Accuracy of the International Normalized Ratio in Oral Anticoagulant Control. Haemostasis. 1996;26:248-65.
4. Fairweather RB, Ansell J, van den Besselaar AMHP, et al. College of American Pathologists Conference XXXI on Laboratory Monitoring of Oral Anticoagulant Therapy. Laboratory Monitoring of Oral Anticoagulant Therapy. Arch Pathol Lab Med. 1998,122:768-81.

Definition of Symbols

The following symbols may appear on the product labeling:

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution		Manufacturer
EC REP	Authorized representative in the European Community	CH REP	Authorized representative in Switzerland
	Contains sufficient for <n> tests		Biological Risks
IVD	*In Vitro* Diagnostic Medical Device		Temperature Limitation
	Consult instruction for Use		Non-sterile
CE	CE marking of conformity	CE 0197	CE marking of conformity with notified body ID number. Notified body ID number can vary.
CONTENTS	Contents		Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat
WARNING	Warning	DANGER	Danger
RxOnly	Prescription device (US only)	UDI	Device Identification (UDI) barcode
REACH xx/xx/xx	REACH Authorization Number		

Legal Information

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