June 2022

Package insert, version 01, deks@deks.dk

Koagulationskalibrator Normal
(Coagulation Calibrator Normal)

Product code 2004 DK

LOT **21-06** **2029** IVD CE

Assigned Values

P—Coagulation, tissue factor-induced; rel.time (actual/norm; INR[1]; IRP 67/40; proc.)	**1,00 INR**	U = 0,042 INR
P-Coagulation, tissue factor-induced; arb.subst.c.	**1 arb.unit/L**	
P-Fibrinogen (340 000); sust.c.	***8,99 µmol/L***	U = 0,12 µmol/L

Please note: *The values mentioned above are not adjusted for dilution at sampling and should only be used if you do not use citrate-dilution, or if you do not want to include the correction in the calibrating function. If you use citrate tubes when sampling with the dilution proportion of 9 parts full blood to 1 part natrium citrate and want this included in the calibration, the following fibrinogen concentration must be used:*

10,78 µmol/L

P-Antithrombin; arb.subst.c.	**1,03 · 10^3 IU/L**	U = 0,038 · 10^3 IU/L
P-Protein S; arb.subst.c.	**1,05 · 10^3 IU/L**	U = 0,031 · 10^3 IU/L
P-Protein C; arb.subst.c.	**1,12 · 10^3 IU/L**	U = 0,013 · 10^3 IU/L

Expected Use

The material can be used for calibrating of the following quantities:

- P-Coagulation, tissue factor-induced; rel.time (actual/norm; INR; 67/40)
  Calibration hereof also takes the use of DEKS's INR Calibrator Therapeutic and INR Calibrator High
- P-Coagulation, tissue factor-induced; arb.sust.c. (coag.; proc.)
- P-Fibrinogen
- P-Antithrombin
- P-Protein C
- P-Protein S

The calibrator can furthermore be used for the determination of:

- Normal coagulation time for the test P-Coagulation, surface-induced; time.

Receipt

Upon receipt it is checked that the calibrators are frozen.
Are the calibrators *not* frozen, the validity can be reduced, or the calibrators can be totally useless – please contact DEKS.

[1] INR is short for International Normalized Ratio.

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Safety

The used donor plasmas have individually been tested negative for hepatitis B, hepatitis C and HIV.
The calibrator and waste products should be handled as potentially infectious patient samples according to the laboratory's internal instructions and good laboratory practice.
The calibrators may only be handled by educated persons qualified to perform calibration.
The calibrators may not be used for calibration:

- if they were thawed at receipt
- if they have exceeded the shelf-life
- if they have exceeded the maximum in-use stability after thawing
- if they have been thawed-frozen-and-thawed again

as the assigned values may be altered.

Material

The calibrator is produced from plasma from 30 healthy persons.
Whole blood is at collection diluted with natrium citrate 0,109 M in the proportion 9-parts blood plus 1-part citrate.
The plasma is separated by double centrifugation and frozen at -80 °C. The separate portions are thawed and mixed in a pool, which is then aliquoted in vials of 0,5 ml (filling volume).
The material is frozen and kept at -80 °C.

Shelf-life

The calibrator is at -80 °C valid until the end of 2029 and at –20 °C it is valid for 2 weeks.

In-use Stability

After thawing the calibrator can be used for a maximum of 4 hours.

Calibration of Analytical Equipment

Calibration must be performed with equipment and with a reagent intended for the relevant tests and according to manufacturer's procedure. The equipment must be maintained regularly and adequately suited for the examination of the chosen components.
The analytical equipment should as minimum be calibrated following the change of reagent batch, following equipment adjustments or when service has been made on the equipment.
Calibration must always be carried out when the internal controls show a need.

Handling and Use

Thawing and preparation of the calibrator

1. The calibrator is thawed at a water bath at 37 °C in exactly 5 minutes, mixed in a turning device at ambient temperature for 5-10 minutes.
   Mixing without a turning device is possible by holding the calibrator between thumb and index finger and tilting it carefully 180° approx. 20 times.
   The calibrator must have room temperature before use.

Further steps when calibrating INR

2. Coagulation times for *INR Calibrator Therapeutic*, *Coagulation calibrator Normal* and *INR Calibrator High* is decided with the laboratory's routine method[2].
   At least five measurements are made on each set of material. Mean values of the results are calculated.
   If one result deviates more than 5% from the mean value, the result should be omitted.

[2] 3-point calibration follows the WHO recommendations [4] for the use of plasma pools and ensures a calibration of the assay over a wide range

3. Find the spreadsheet: *Beregning af ISI og MNPT (normalkoagulationstid)*: www.deks.dk/laboratorier/pakningsvedlaeg and fill in the measurement results[3].
   USE ONLY THE LATEST VERSION OF THE SPREADSHEET AND CHECK THAT THE VALUES ARE CONSISTENT WITH THE USED LOT OF CALIBRATORS.
   The spreadsheet calculates *Mean Normal Prothrombin Time (MNPT)* and *International Sensitivity Index* (ISI) and follows the principle from van den Besselaar, et al. [1].

Value Assignment and Traceability

- *Coagulation, tissue factor-induced; rel.time, (actual/norm; INR; IRP 67/40)* is determined with the manual reference method with use of the international reference preparations WHO 5th International Standard Thromboplastin, Human, Recombinant, Plain (rTF/16) and WHO International Standard Thromboplastin, Rabbit, Plain (RBT/16) [2, 3].
  The assignment was performed by 3 Nordic expert laboratories, Zealand University Hospital, Roskilde; Southwest Jutland Hospital, Esbjerg and University Hospital, Linköping. The measurements are performed by each expert laboratory in relation to a protocol, that complies with the WHO guidelines [4]. The expanded uncertainty, U, that indicates the 95%-confidence interval of the value (1,00 INR), is determined to 0,042 INR with the expansion factor k=2,0.

- *P-Coagulation, tissue factor-induced; arb.subst.c.* The value is per definition 1 arb.unit./L solely defined from the production procedure which is a pool of plasma from at least 30 healthy, non-medicated persons. As there are large inter-individual differences of the coagulation factors, there can be lot to lot differences, even with the stated amount of plasmas in the pool. By measuring with a routine reagent (Roskilde Sygehus, 2022), the following activity proportions between the produced lots of normal calibrators is found:
  4th national normal plasma 2014: 101 % and 5th national normal plasma: 100 %.
  This implies that when you change from LOT 13-05 to LOT 21-06 you can expect a change of level of up to 1 %.

- *P-Antitrombin; arb subst.c*. is assigned using the to 3rd International Standard for Antithrombin, Plasma (08/258) [5] and with use of a absorptionsfotometric method. The measurements were performed Slagelse Hospital. The assigned value is not adjusted for any potential dilution with anti-coagulants. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.

- *P-Fibrinogen; subst.c.* The value is assigned using the 3rd Internationale Reference Preparation (WHO 09/264) [6] using methods based on von Clauss´s method [De Maat MPM *et al*. 1999]. The measurements were performed at Zealand University Hospital, Roskilde and at Slagelse Hospital. The assigned value 8,99 µmol/L does not take into consideration that patient samples are usually diluted with anti-coagulants. Therefore, an adjusted value of 10,78 µmol/L is used, if compensation is necessary for the average dilution of patient samples when 9-parts whole blood is stabilized with 1-part citrate solution and the plasma therefore is diluted appr. 20%. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.
  When changing from LOT 13-05 to LOT 21-06, you can expect a change of level of up to 2%.

- *P-Protein C; arb subst.c.* is assigned using the 2nd International Standard for Protein C (02/342) [7].
  The measurements were performed at Næstved Hospital. The value is not adjusted for any potential dilution with anti-coagulants. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.

[3] The spreadsheet performs an orthogonal regression as described by van den Besselaar, AMHP [1].

- *P-Protein S; arb subst.c.* is assigned using the 2nd International Standard for Protein S (03/228) [8].
  The measurements were performed at Næstved Hospital. The value is not adjusted for any potential dilution with anti-coagulants. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.

Reference

In addition to Coagulation Calibrator *Normal* DEKS also offers INR Calibrator *Therapeutic* (product code 3346 DK) og INR Calibrator *High* (product code 3252 DK) for calibrating the INR.

Ordering and Shipment of the Calibrator

Coagulation Calibrator Normal is found in packages of 2 vials or in a tripple pack (product code 3457 DK) with the *INR Calibrator High* and *INR Calibrator Therapeutic* and can be ordered via DEKS.
The order is placed via the on-line ordering system at www.deksonline.dk (requires login).
DEKS can be reached at ☎ +45 3863 4400 or deks@deks.dk.
The materials are shipped as dry-ice shipment.

Literature references

[1] van den Besselaar, AMHP. et al. Journal of Thrombosis and Haemostasis. 1946-1953, 2, 2004.

[2] National Institute for Biological Standards and Control (NIBSC), WHO 5th International Standard Thromboplastin, Human, Recombinant, Plain, NIBSC code: rTF/16, Instructions for use (Version 2.0). 1-3. 2021-02-03.

[3] National Institute for Biological Standards and Control (NIBSC), WHO 5th International Standard Thromboplastin, Rabbit, Plain, NIBSC code: RBT/16, Instructions for use (Version 4.0). 1-3. 2021-02-03.

[4] WHO, WHO Expert Committee Biological Standardization, Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy with vitamin K antagonists. 271-303. 2013. Genova. WHO Technical Report Series no. 979.

[5] National Institute for Biological Standards and Control (NIBSC), WHO 3rd International Standard for Antithrombin, Plasma, NIBSC code: 08/258, Instructions for use (Version 4.0), 1-2. 2014-03-31.

[6] National Institute for Biological Standards and Control (NIBSC), WHO 3rd International Standard Fibrinogen plasma, NIBSC code: 09/264, Instructions for use (Version 1.0), 1-2, 2011-11-25.

[7] National Institute for Biological Standards and Control (NIBSC), WHO 2nd International Standard for Protein C, Plasma, Human, NIBSC code: 02/342, Instructions for use (Version 5.0), 1-2, 2016-08-05.

[8] National Institute for Biological Standards and Control (NIBSC), WHO 2nd International Standard for protein S, Plasma, Human, NIBSC code: 03/228, Instructions for use (Version 3.0), 1-2, 2014-02-10.

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Revision History

Version	Date	
01	2022-06	Packing insert created