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**Assignment of Potency to the 1st International Standard for Protein C, Concentrate, Human  
(04/252)**

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## **SUMMARY**

Twenty laboratories from 10 countries took part in a collaborative study to assign potency values to 2 proposed World Health Organisation (WHO) international standards: the 2nd International Standard for Protein C, Plasma, Human (02/342) and the 1st International Standard for Protein C, Concentrate, Human (04/252) and also to calibrate the Scientific Standardisation Committee (SSC) secondary plasma standard Lot#3 for Protein C functional activity and antigen. The 2nd International Standard for Protein C, Plasma was established by the ECBS in October 2006 (WHO/BS/06.2045), however one of the participants in the study raised concern over the recommendation of the value assignment on the functional activity of the proposed concentrate standard. The decision to recommend the establishment of this concentrate standard was therefore deferred. Based on further discussion and the consensus opinion of the participants and experts from the SSC of the ISTH, it was decided that this proposed international standard should not be labeled with a functional clotting value as obtained by this collaborative study. A new proposal agreed by consensus was formulated to recommend that the candidate concentrate standard, 04/252 be assigned with potencies relative to the 2nd International Standard for Protein C, Plasma, Human, 02/342 with labeled values of 14.5 IU/ampoule for antigen and 15.0 IU/ampoule for functional chromogenic activity only (no protein C functional activity by clotting assay will be assigned).

## **INTRODUCTION**

In 2006, a collaborative study was carried out to value assign a replacement international standard for protein C, plasma and a new international standard for protein C, concentrate. The candidate plasma preparation, 02/342 was subsequently established by the Expert Committee on Biological Standardisation (ECBS) of the World Health Organisation (WHO) in October 2006 as the 2nd International Standard (IS) for Protein C, Plasma, Human. It was value assigned against the 1st International Standard for Protein C, Plasma, Human (86/622) and the labelled values are 0.85 and 0.84 IU/ampoule for function and antigen respectively<sup>1</sup>.

For the proposed concentrate standard, 04/252, all participants and the SSC subcommittee approved the proposed assigned antigenic value of 14.3 IU/ampoule against the 1st IS plasma. However, based on their in-house experience, one participant did not agree with assigning the candidate with an overall functional potency ie combining the values obtained for chromogenic and clotting assays. As this has implications for the comparability of the proposed candidate with clinical products, further consideration and study was required to clarify this issue and so the recommendation to establish the 1st IS for Protein C, Concentrate was deferred until more discussion and/or data were available.

NIBSC and the participant who raised this concern have now carried out a joint study involving assays of a number of their production batches by chromogenic and clotting methods and have found that there is a distinct discrepancy between the potencies obtained by chromogenic and clotting assays. Taking into consideration that 02/342 has been established as the 2nd IS, we have now come up with new proposals for 04/252, the proposed concentrate standard.

## SUMMARY OF RESULTS

Details of the collaborative study are described in the participants report (sent to all participants in May 2006) and in the WHO ECBS report WHO/BS/06.2045<sup>1</sup> (available upon request from David Wood, woodd@who.int). The following gives a summary of data from this collaborative study that relates to the calibration of the proposed concentrate standard against the 1st IS for Protein C, Plasma, Human, 86/622 (sample A in the collaborative study) and the 2nd IS for Protein C, Plasma, Human, 02/342 (sample B in the collaborative study).

Tables 1 – 3 show the individual laboratory geometric mean potencies and the % geometric coefficient of variation (GCV) of the proposed concentrate standard as estimated by functional chromogenic assay, functional clotting assay and antigen measurement relative to the 1st and 2nd IS for Protein C, Plasma. Table 4 shows a comparison of potencies of the proposed concentrate standard against the 1st and the 2nd IS for Protein C, Plasma. Statistical analysis shows that there is no significant difference between the potencies obtained against the 1st or the 2nd IS.

## STABILITY

Stability of the Proposed WHO 1st IS for Protein C, concentrate has been assessed in an accelerated degradation study which involves the potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at -150 °C. The study was carried out in one laboratory (NIBSC), using a chromogenic assay with Protac® activation. To date, 16 months storage data is available. The observed relative potencies (from 2 independent assays) was analysed using the Arrhenius equation in order to provide a prediction of loss per year for ampoules stored at various temperatures. Because of insufficient loss of activities at the various temperatures and time points, the Arrhenius equation was unable to give a prediction of loss of activity per year. The accelerated degradation study and real time monitoring will continue for the lifetime of the standard.

## DISCUSSION

The inter-laboratory variability for the proposed concentrate standard was higher than for other plasma samples (details shown in WHO/BS/06.2045). Despite pre-dilution with protein C deficient plasma, approximately 50% of the assays for the proposed concentrate standard against the 1st IS plasma were still non-parallel and therefore invalid. These assays were not included in the assignment of potencies. This supports the need to assay like against like and the use of a concentrate standard for concentrates may yield more valid assays.

It is clear from further discussion that assigning a functional potency by combining the chromogenic and clotting values will cause a problem with the therapeutic products as these have been calibrated against the plasma IS. In addition, the chromogenic value was found to be significantly different to the clotting value albeit that only 3 laboratories produced valid clotting results that were included in the value assignment. The options from this scenario are value assign only with chromogenic potency or separate chromogenic and clotting potencies.

In addition, as the 2nd IS has been established and there is no significant difference between the potencies against the 1st and the 2nd plasma IS, the value assigned should be against the 2nd IS rather than the 1st IS.

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We therefore suggested that the candidate concentrate standard, 04/252 be assigned with potencies relative to the 2nd International Standard for Protein C, Plasma, 02/342 and presented the following options to the participants of the study:

- a. Label with chromogenic and antigenic value:

Functional Chromogenic Activity: 15.0 IU/ampoule;

Antigen: 14.5 IU/ampoule

- b. Label with functional chromogenic and clotting potency and antigen value

Functional Chromogenic Activity: 15.0 IU/ampoule;

Functional Clotting Activity: 11.7 IU/ampoule

Antigen: 14.5 IU/ampoule

## **PARTICIPANTS RESPONSE**

All participants agreed with the proposed assigned value for antigen and the proposed assigned value for functional chromogenic activity. Five out of the 20 participants also agreed with labelling with functional clotting potency

## **SSC EXPERTS RESPONSES**

All nine experts who responded to the review request agreed with the assigned values for antigen and functional chromogenic activity. Three experts made the following comments:

### **Comment 1**

- I recall when the IU for FVIII was realigned arising out of the calibration of the 4th WHO IS and this did cause problems as manufacturers of commercial reference plasmas changed over. For this reason I strongly support the decision to maintain the IU and ignore the fact that the values against pooled normal plasma were slightly different
- I agree with the proposal to accept 04/252 as the 1st IS for PC concentrates
- I agree with the Antigen potency of 15.0 IU/ampoule ( against the 2nd IS for PC in plasma)
- I agree with the proposal to assign a chromogenic potency of 15.0 IU/ampoule.
- The clotting assays are more of a problem. There are several different clotting protein C assays and there is the possibility that different tests could give different results. The 3 centres who performed clotting assays on the proposed concentrate sample all used different methods (Stago, IL, in house) The 95% confidence intervals for the clotting PC results (10.4 -13.1 IU/ampoule) do not overlap with the chromogenic (14.1- 15.9) so this seems to be a real difference. On the other hand they are wider and since there are only 3 results , each by different methods (with means of 11.5, 13.4 and 10.8) I think it is safer not to assign a clotting value. Is it possible to include the data relating to clotting assays for information only in the supporting documentation when issuing the standard, which would prevent a manufacturer making the false assumption that the chromogenic functional assigned potency was suitable for use with clotting assays.

**Comment 2**

The chromogenic assays measured significantly higher protein C activity than the clotting assays. Without knowing definitively why the results of these two types of protein C activity assays differ significantly, it would be best to report only the chromogenic assay potency which is similar to the antigenic potency.

**Comment 3**

I would favor adopting as standard, with option 1 - just chromogenic and antigenic values. You may want to reference the issue with the clotting assay in the package insert.

**PROPOSAL AND RECOMMENDATION**

Taking into account the responses of the participants and the SSC experts, it is proposed to recommend that the candidate concentrate standard, 04/252 be assigned with potencies relative to the 2nd International Standard for Protein C, Plasma, Human, 02/342 with the following values for:

**Functional Chromogenic Activity: 15.0 IU/ampoule;**  
**Antigen: 14.5 IU/ampoule**

**PRODUCT SUMMARY FOR 04/252**

The candidate 1st IS for Protein C, Concentrate, Human was prepared from a batch of plasma derived protein C clinical concentrate. The bulk material was diluted to approximately 15 U/mL with 50mM Tris, 150 mM NaCl, 5mg/mL human albumin, 2mg/mL trehalose, pH 7.3. The final ampouled material was produced as described by Campbell, 1974<sup>2</sup> and the finished product summary is as follows:

<b>Code number</b>	04/252
<b>Presentation</b>	Sealed, glass 5 ml DIN ampoules
<b>Number of ampoules available</b>	3000
<b>Date filled</b>	19 May 2005
<b>Precision of fill – CV of fill mass (% , n = 44)</b>	0.32
<b>Residual moisture after lyophilisation and secondary desiccation (% , n = 6)</b>	0.09
<b>Mean dry weight (g, n=6)</b>	0.03
<b>Storage conditions</b>	-20 °C
<b>Address of processing facility</b>	NIBSC, Potters Bar, EN6 3QG, UK
<b>Address of present custodian</b>	NIBSC, Potters Bar, EN6 3QG, UK

A proposed Instruction For Use and Material Safety Data is shown in appendix 2.

**ACKNOWLEDGEMENT**

We would like to acknowledge the donation of the protein C concentrate by Baxter AG (Vienna, Austria), the participants of the study (Appendix 1), the SSC experts (Trevor Barrowcliffe, Eric Preston, Herb Whinna, Francesco Bernardi, Fred Ofori, John Brandt, Mark Weinstein, Craig Jackson and Steve Kitchen) for reviewing the study report, the support of the Plasma Coagulation Inhibitors Subcommittee of the SSC of the ISTH, Paul Matejtschuk (TDI, NIBSC) for formulation and trial fills of the candidates and the staff of the CBRM, NIBSC for filling the candidates.

**REFERENCES**

1. WHO/BS/06.2045
2. Campbell PJ. International biological standards and reference preparations. 1. Preparation and presentation of materials to serve as standards and reference preparations. *J Biol Standardisation* 1974; 2; 249-67

Table 1: Potencies of sample C, the proposed 1st IS for Protein C, Concentrate in chromogenic assays

Lab	Potency relative to A (0.82 IU/amp)		Potency relative to B (0.85 IU/amp)	
	Geometric Mean	GCV	Geometric Mean	GCV
5	13.38	5.9	13.98	1.2
6	13.97	5.9	14.12	.
7	14.18	2.0	14.07	5.0
9	14.49	.	14.68	.
10	14.03	8.0	14.42	7.7
11	15.80	0.8	15.97	1.0
17	17.24	.	17.71	.
20	15.97	2.0	16.18	1.1
21	14.99	3.1	15.17	2.3
22	14.30	0.4	14.35	2.3
23	14.61	4.2	14.43	3.5

Table 2: Potencies of sample C, the proposed 1st IS for Protein C, Concentrate in clotting assays

Lab	Potency relative to A (0.82 IU/amp)		Potency relative to B (0.85 IU/amp)	
	Geometric Mean	GCV	Geometric Mean	GCV
5	11.50	4.2	11.48	3.4
6	13.37	4.2	12.27	.
9	10.83	.	11.25	.

Table 3: Potencies of sample C, the proposed 1st IS for Protein C, Concentrate in antigen assays

Lab	Potency relative to A (0.82 IU/amp)		Potency relative to B (0.84 IU/amp)	
	Geometric Mean	GCV	Geometric Mean	GCV
5	13.48	.	13.60	.
6	11.64	19.6	11.82	5.8
7	14.81	.	15.58	.
10	14.15	12.6	14.03	7.5
17	15.69	.	16.21	.
23	16.54	3.7	16.07	0.6

Table 4: Potencies of sample C, the proposed 1st IS for Protein C, Concentrate

Standard	Geometric mean potency (IU/amp), 95% confidence interval and between-lab GCV			
	Chromogenic:	Clotting:	Combined:	Antigen:
1st IS plasma 0.82 IU/amp	14.77 (14.07–15.52) 7.6% n=11	11.86 (9.05–15.52) 11.5% n=3	14.10* (13.14–15.12) 12.9% n=14	14.29 (12.55 – 16.28) 13.2% n=6
2nd IS plasma 0.85 IU/amp (func); 0.84 IU/amp (antigen)	14.98 (14.14 – 15.86) 8.9% n=11	11.67 (10.37 – 13.12) 4.9% n=3	14.20* (13.16 – 15.32) 13.2% n=14	14.45 (12.68 – 16.46) 14.1% n=6

\* Chromogenic assay results significantly higher than clotting ( $p < 0.01$ )

No significant differences between results obtained using different standards

**Appendix 1: List of Participants.**

Dr Jean Amiral, HYPHEN BioMed, Neuville-sur-Oise, France

Dr Eugenia Biguzzi & Ms Daniela Asti, A. Biauchi Bonomi Hemophilia and Thrombosis Center, University of Milan and Department of Medicine and Medical Specialties, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy

Dr Peter Baker, John Radcliffe Hospital, Oxford, UK

Dr Paul Braun, bioMérieux Inc, Durham, USA

Dr S Berrier & Ms C Bisson, Diagnostica Stago, Quality Control, Franconville Cedex, France

Dr Peter Gärtner, Baxter Bioscience, Vienna, Austria

Ms Marilyn Johnston & Mrs Joanne McGrath, Hemostasis Reference Laboratory, Hamilton, Canada

Dr Barbara Kerbl, Technoclone GmbH, Vienna, Austria

Dr Steven Kitchen & Mr Peter Cooper, Royal Hallamshire Hospital, Sheffield, UK

Dr Chong Loh & Mr Matt Harvey, Therapeutic Goods Administration, Symonston, Australia

Dr Catherine Michalski, LFB, Lille, France

Sandy Morrison, Precision BioLogic Inc, Dartmouth, Canada

Dr Ingrid Pabinger-Fasching, University Hospital, Vienna, Austria

Dr William Pickering, NIBSC, South Mimms, UK

Dr Miriam Ramondetta & Mr Luigi Leo, DMCO-University of Milan, Hematology and Thrombosis Unit and Transfusion Center, S. Paolo Hospital, Milan, Italy

Mrs Jeannette Rentenaar, Sanquin Blood Supply Foundation, Amsterdam, The Netherlands

Dr Cheng-Hock Toh & Mr Alan Smith, Royal Liverpool University Hospital, Liverpool, UK

Dr Kathleen Trumbull & Dr Barbara Phillips, Instrumentation Laboratory, Lexington, USA

Dr Barry Woodhams, Diagnostica Stago, Research and Development, Gennevilliers, France

Dr Renata Zadro, Clinical Hospital Center Zagreb University School of Medicine, Zagreb, Croatia

## Appendix 2: Proposed Instruction for Use and Material Safety Data

### The 1st International Standard for Protein C, Concentrate, Human 04/252 (established 2007) Instructions for Use (Version 1 July 2007)

#### 1. INTRODUCTION

The 1st International Standard for Protein C, Concentrate, Human, consists of ampoules, coded 04/252, containing aliquots of a freeze-dried concentrate prepared from human plasma. This preparation was established as the 1st International Standard for Protein C, Concentrate, Human, by the Expert Committee on Biological Standardisation of the World Health Organisation in 2007.

The ECBS report is available from the WHO ([www.who.int/biologicals](http://www.who.int/biologicals)). Document number: WHO/BS/07.....

#### 2. UNITAGE

The standard was value assigned in an international collaborative study involving 20 laboratories from 10 countries against the 2nd International Standard for Protein C, Plasma, Human, 02/342. The following potency was assigned based on the geometric mean of all the valid assay results:

**Functional (chromogenic assay only) : 15.0 IU/ampoule**

**Antigenic: 14.5 IU/ampoule**

**NOTE: This standard has not been assigned with a functional activity by clotting assays and therefore should not be used for calibration of protein C activity by clot based methods.**

**Uncertainty:** the assigned unitage does not carry an uncertainty associated with its calibration. The uncertainty may therefore be considered to be the variance of the ampoule content and was determined to be +/- 0.32 %.

#### 3. CONTENTS

One vial (50,000 U/vial, ~100 ml) of plasma derived human protein C concentrate was thawed at 37°C and was further diluted with approximately 3.5 litres of 0.05M Tris, 0.15M NaCl, pH 7.4 containing 2 mg/ml trehalose and 5 mg/ml human albumin. The solution was distributed at 4°C into 3500 ampoules, coded 04/252. The mean weight of liquid content of 44 check weight ampoules was 1.0081g, with limits of 1.0037 - 1.0273g (coefficient of variation 0.32%). The contents of the ampoules were then freeze-dried under the conditions normally used for international biological standards<sup>1</sup>.

#### 4. CAUTION

**THIS PREPARATION IS NOT FOR ADMINISTRATION TO HUMANS.**

The preparation contains material of human origin, which has been tested and found negative for HBsAg, HIV antibody, HCV antibody and HCV RNA by PCR.

As with all materials of biological origin, this preparation should be regarded as potentially hazardous to health. It should be used and discarded according to your own laboratory's safety procedures. Such safety procedures probably will include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts.

## **5. DIRECTIONS FOR OPENING THE DIN AMPOULE**

DIN ampoules have an 'easy-open' coloured stress point, where the narrow ampoule stem joins the wider ampoule body.

Tap the ampoule gently to collect the material at the bottom (labelled) end. Ensure that the disposable ampoule safety breaker provided is pushed down on the stem of the ampoule and against the shoulder of the ampoule body. Hold the body of the ampoule in one hand and the disposable ampoule breaker covering the ampoule stem between the thumb and first finger of the other hand. Apply a bending force to open the ampoule at the coloured stress point, primarily using the hand holding the plastic collar.

Care should be taken to avoid cuts and projectile glass fragments that might enter the eyes, for example, by the use of suitable gloves and an eye shield. Take care that no material is lost from the ampoule and no glass falls into the ampoule. Within the ampoule is dry nitrogen gas at slightly less than atmospheric pressure. A new disposable ampoule breaker is provided with each DIN ampoule.

## **6. USE OF AMPOULED MATERIAL**

Unopened ampoules should be stored in the dark at or below  $-20^{\circ}\text{C}$ .

Allow ampoules to warm to room temperature. Open ampoule, taking care to ensure that all material is in the lower part, and reconstitute with 1.0 ml distilled water. Stand for 10 minutes at room temperature to allow complete dissolution of the material before use. The reconstituted Standard should be used as soon as possible.

## **7. STABILITY**

It is the policy of WHO not to assign an expiry date to their international reference materials. They remain valid with the assigned potency and status until withdrawn or amended.

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities and should be stored on receipt as indicated on the label. Once reconstituted,

diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use.

NIBSC follows the policy of WHO with respect to its reference materials. A preliminary accelerated degradation study, involving the potency estimation of ampoules stored at elevated temperatures (4, 20, 37, 45 °C) relative to ampoules stored at -150 °C was carried out in one laboratory (NIBSC), using the heparin co-factor chromogenic thrombin based assay. The observed relative loss of potency was analysed using the Arrhenius equation in order to provide a prediction of loss per year for ampoules stored at various temperatures. Estimates of % predicted loss of activity per year based on activities assessed at 3 different time points over a period of 9 months storage showed that there was no predicted loss of activity for samples stored at -20°C, the storage temperature of the proposed IS, thus indicating that the preparation is exceedingly stable and suitable for long term use as an International Standard. The accelerated degradation study and real time monitoring will continue for the lifetime of the standard.

Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

Stability of the Proposed WHO 1st IS for Protein C, concentrate has been assessed in an accelerated degradation study which involves the potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at -150 °C. The study was carried out in one laboratory (NIBSC), using a chromogenic assay with Protac® activation. To date, 16 months storage data is available. The observed relative potencies (from 2 independent assays) was analysed using the Arrhenius equation in order to provide a prediction of loss per year for ampoules stored at various temperatures. Because of insufficient loss of activities at the various temperatures and time points, the Arrhenius equation was unable to give a prediction of loss of activity per year. The accelerated degradation study and real time monitoring will continue for the lifetime of the standard.

## **8. CITATION**

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## 10. References

1. Campbell PJ. Procedures used for the production of biological standards and reference preparations. *J Biol Standardisation*. 1974, 2, 259-267.

For further information, please contact:

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**11.MATERIAL SAFETY SHEET**

**The 1st International Standard for Protein C, Concentrate, Human 04/252**

**Version 1, 17 July 2007**

Is the material infectious or toxic (delete as necessary)?	NO
If yes, which containment level?	_____
If no,	
Does the formulation contain material of human origin?	YES
Does the formulation contain material of animal origin?	NO
Does the formulation contain azide?	NO

<b>Chemical properties:</b>	
Stable	✓
Hygroscopic	✓
Flammable	
Corrosive:	
Oxidising:	
Irritant:	
Other (specify) contains material of human origin	
Handling: see safety compendium for handling material of human origin	

<b>Toxicological properties:</b>	
Effects of inhalation:	No adverse effects have been reported for this material
Effects of ingestion:	No adverse effects have been reported for this material
Effects of skin absorption:	No adverse effects have been reported for this material

<b>Suggested First Aid:</b>	
Inhalation:	Seek medical advice
Ingestion:	Seek medical advice
Contact with eyes:	Wash with copious amounts of water. Seek medical advice
Contact with skin:	Wash with copious amounts of water. Seek medical advice

<b>Action on Spillage and Method of Disposal:</b>	
Spillage of material should be taken up with absorbent material wetted with a virucidal agent. Rinse area with a virucidal agent followed by water.	
Absorbent materials used to treat spillage should be treated as biologically hazardous waste.	

Complied by E Gray, Haemostasis Section, Biotherapeutics

Signature : \_\_\_\_\_ Date: \_\_\_\_\_

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