Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
4th IS Chorionic Gonadotropin, Human
NIBSC code: 75/589
Instructions for use
(Version 3.0, Dated 30/11/2007)

1. INTENDED USE

The 3rd International Standard for Chorionic Gonadotrophin (3rd IS; in ampoules coded 75/537) was established by the WHO Expert Committee on Biological Standardization in 1986 (WHO ECBS, 1987). The same material had earlier been established as the International Reference Preparation of Human Chorionic Gonadotrophin for Immunoassay (WHO ECBS, 1975), and its unitage assigned in 1978 (WHO ECBS, 1978) on the basis of the results of a collaborative study (Storring et al., 1980). This Standard has been widely used for the calibration of assays to control the quality and potency of chorionic gonadotrophin (CG) used in the treatment of infertility in women and sometimes in men, and for the calibration of assays used in the diagnosis of pregnancy and a range of other clinical conditions. In 1999 it became apparent that stocks of the 3rd IS were becoming exhausted and that it needed to be replaced.

A second batch of ampoules (coded 75/589; CG 75/589), containing the same bulk preparation of CG as that in the 3rd IS, had been prepared at the same time as the 3rd IS using identical procedures, and was included in the collaborative study of this Standard (Storring et al., 1980). In the collaborative study, CG 75/589 did not differ significantly from the 3rd IS in any of the biological or immunological assay systems studied, and so appeared to be suitable to replace the 3rd IS, and with the same potency of 650 International Units of CG activity per ampoule.

Further studies of the activity and stability of CG 75/589 were carried out during 1999: The CG activity of ampoules of CG 75/589 kept at +4°C, +20°C and +37°C for 23.2 years were estimated by the seminal vesicle weight gain assay (Van Hell et al., 1964) as % of that in ampoules kept at -20°C. The mean estimates of activity (with 95% confidence limits) were 130 (107-157%) from two assays of ampoules kept at +4°C, 115 (83.8-158)% from two assays of ampoules kept at +20°C and 102 (69.7-174)% from one assay of CG 75/585 kept at +37°C. The CG activity of CG 75/589 kept at -20°C estimated in terms of the 3rd IS in a seminal vesicle weight gain assay was found to be 689 iu/ampoule, with 95% confidence limits of 482-997 iu/ampoule. The degradation rates of CG 75/589 were considered using the methods of Jerne & Perry (1956) and Kirkwood (1977), taking each of -20°C and +4°C as base line temperatures. The observed difference between the -20°C and the +4°C samples was not consistent with either of these predictions, and in particular, the activity of the sample kept at +4°C appeared to have increased relative to that of the sample kept at -20°C. Estimated activity relative to the -20°C sample for samples kept at +20°C and +37°C showed no decrease in activity and did not differ significantly from 100%. In the absence of any detectable loss in activity, prediction using an Arrhenius equation was not possible.

Comparison of CG 75/589 with the 3rd IS shows no change in their relative activities, although this could reflect similar losses of activity for each preparation during storage. These data did not suggest that there had been any significant loss of activity of CG 75/589 kept under normal storage conditions at -20°C.

2. CAUTION

<u>This preparation is not for administration to humans or animals in the human food chain</u>.

The preparation contains material of human origin, and either the final product or the source materials, from which it is derived, have been tested and found negative for HBsAg, anti-HIV and HCV RNA.
However, as with all preparations of human origin, this material cannot be assumed to be free from infectious agents. Suitable precautions should be taken in the use and disposal of the ampoule and its contents. 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.

3. UNITAGE

Each ampoule contains 650 INTERNATIONAL UNITS (by definition).

4. CONTENTS

Country of origin of biological material: United Kingdom.
Each ampoule contains the freeze-dried residue of 0.5 ml of a solution which contained:

Human chorionic gonadotrophin	approx	70µg
Human plasma albumin	"	5mg
sodium chloride	"	445µg
acetic acid	"	300µg

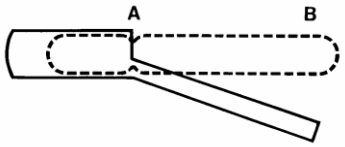
Nitrogen gas at slightly less than atmospheric pressure.

5. STORAGE

Unopened ampoules should be stored at -20°C
Please note: because of the inherent stability of lyophilized material, NIBSC may ship these materials at ambient temperature.

6. DIRECTIONS FOR OPENING

Tap the ampoule gently to collect the material at the bottom (labelled) end. Ensure ampoule is scored all round at the narrow part of the neck, with a diamond or tungsten carbide tipped glass knife file or other suitable implement before attempting to open. Place the ampoule in the ampoule opener, positioning the score at position 'A'; shown in the diagram below. Surround the ampoule with cloth or layers of tissue paper. Grip the ampoule and holder in the hand and squeeze at point 'B'. The ampoule will snap open. Take care to avoid cuts and projectile glass fragments that enter eyes. Take care that no material is lost from the ampoule and that no glass falls into the ampoule.



Side view of ampoule opening device containing an ampoule positioned ready to open. 'A' is the score mark and 'B' the point of applied pressure.

7. USE OF MATERIAL

For practical purposes each ampoule contains the same amount of the same materials. Dissolve all the contents in a known amount of buffer solution. No attempt should be made to weigh portions of the freeze-dried powder.
For economy of use the solution can be kept for several months if an anti-bacterial preservative is added and the solution is subdivided into several small containers, which are frozen rapidly to below -70°C and then stored below -30°C in the dark; repeated freezing and thawing should be avoided. If extensive dilutions are prepared, a carrier protein (0.1% w/v) should be added, which is free of peptidase. The material has not been sterilized and contains no bacteriostat.

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WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

World Health Organization

8. STABILITY

NIBSC follows the policy of WHO with respect to its reference materials.

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. Unopened ampoules should be stored on receipt as indicated on the label. In addition, once reconstituted, diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use.

9. REFERENCES

Jerne NK & Perry WLM (1956). Bulletin of the World Health Organization 14: 167-182.

Kirkwood TBL (1977). Biometrics 33: 736-742.

Storring P L, Gaines Das R E & Bangham D R (1980). Journal of Endocrinology 84:295-310.

Van Hell H, Matthijsen R & Overbeek GA (1964). Acta Endocrinologica (Copenhagen) 47: 409-418.

WHO Expert Committee on Biological Standardization (1975). WHO Technical Report Series No. 565.

WHO Expert Committee on Biological Standardization (1979). WHO Technical Report Series No. 638.

WHO Expert Committee on Biological Standardization (1987). WHO Technical Report Series No. 760.

8. ACKNOWLEDGEMENTS

Grateful acknowledgements are due to the Center for Population Research, USA and Reproduction Research Branch of the National Institute of Child Health and Human Development, USA for providing the hormone preparation; Drs R E Canfield and G T Ross and their colleagues for its purification and characterization; the participants in the collaborative study; and Dr P J Campbell for ampouling.

11. FURTHER INFORMATION

Further information can be obtained as follows;
This material: enquiries@nibsc.org
WHO Biological Standards:
http://www.who.int/biologicals/en/
JCTLM Higher order reference materials:
http://www.bipm.org/en/committees/jc/jctlm/
Derivation of International Units:
http://www.nibsc.org/standardisation/international_standards.aspx
Ordering standards from NIBSC:
http://www.nibsc.org/products/ordering.aspx
NIBSC Terms & Conditions:
http://www.nibsc.org/terms_and_conditions.aspx

12. CUSTOMER FEEDBACK

Customers are encouraged to provide feedback on the suitability or use of the material provided or other aspects of our service. Please send any comments to enquiries@nibsc.org

13. CITATION

In all publications, including data sheets, in which this material is referenced, it is important that the preparation's title, its status, the NIBSC code number, and the name and address of NIBSC are cited and cited correctly.

14. MATERIAL SAFETY SHEET

Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not classified

Physical and Chemical properties	
Physical appearance: Freezed dried powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: Yes	Irritant: No
Flammable: No	Handling: See caution, Section 2
Other (specify):	Contains material of human origin
Toxicological properties	
Effects of inhalation:	Not established, avoid inhalation
Effects of ingestion:	Not established, avoid ingestion
Effects of skin absorption:	Not established, avoid contact with skin
Suggested First Aid	
Inhalation:	Seek medical advice
Ingestion:	Seek medical advice
Contact with eyes:	Wash with copious amounts of water. Seek medical advice
Contact with skin:	Wash thoroughly with water.
Action on Spillage and Method of Disposal	
Spillage of ampoule contents should be taken up with absorbent material wetted with an appropriate disinfectant. Rinse area with an appropriate disinfectant followed by water. Absorbent materials used to treat spillage should be treated as biological waste.	

15. LIABILITY AND LOSS

In the event that this document is translated into another language, the English language version shall prevail in the event of any inconsistencies between the documents.

Unless expressly stated otherwise by NIBSC, NIBSC's Standard Terms and Conditions for the Supply of Materials (available at http://www.nibsc.org/About_Us/Terms_and_Conditions.aspx or upon request by the Recipient) ("Conditions") apply to the exclusion of all other terms and are hereby incorporated into this document by reference. The Recipient's attention is drawn in particular to the provisions of clause 11 of the Conditions.

16. INFORMATION FOR CUSTOMS USE ONLY

Country of origin for customs purposes*: United Kingdom * Defined as the country where the goods have been produced and/or sufficiently processed to be classed as originating from the country of supply, for example a change of state such as freeze-drying.
Net weight: 6mg
Toxicity Statement: Non-toxic
Veterinary certificate or other statement if applicable**.** **Attached:** No

17. CERTIFICATE OF ANALYSIS

NIBSC does not provide a Certificate of Analysis for WHO Biological Reference Materials because they are internationally recognised primary reference materials fully described in the instructions for use. The reference materials are established according to the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards http://www.who.int/bloodproducts/publications/TRS932Annex2_Inter_biolefstandardsrev2004.pdf (revised 2004). They are officially endorsed by the WHO Expert Committee on Biological Standardization (ECBS) based on the report of the international collaborative study which established their suitability for the intended use.