Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
1st International Standard for Adalimumab
NIBSC code: 17/236
Instructions for use
(Version 2.01, Dated 05/11/2019)

1. INTENDED USE

The World Health Organization (WHO) Expert Committee on Biological standardization (ECBS) recognised the need for a reference standard to evaluate the performance of in vitro biological assays for adalimumab.

The International Standard 17/236 is intended to support the calibration, characterisation and validation of assays used for assessing adalimumab and to support the establishment of in-house standards.

The standard was assessed in an international collaborative study (described in section 3), for in vitro biological activities of adalimumab. The standard was also assessed for use in assays for therapeutic drug monitoring.

2. CAUTION

This preparation is not for administration to humans or animals in the human food chain

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. 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 should 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

Bioactivity: The preparation has been assigned the following arbitrary unitage per ampoule:

500 international units (IU)* of tumor necrosis factor-alpha (TNF-alpha) neutralising activity.
500 IU of TNF-alpha binding activity.
500 IU of ADCC activity.
500 IU of CDC activity.

*These units are independent of the amount of TNF-alpha used in various bioassays. For details regarding neutralising activity in terms of the 3rd IS for TNF-alpha (coded 12/154), see report referenced in section 9.

It should be noted that the neutralising activity may vary according to the assay format. Therefore, a relationship between the unitage of the WHO IS coded 17/236 and the activity assigned to in-house standards in the assay system in routine use should be established.

Users should also note that the biological activity of TNF-alpha is likely to vary between different suppliers and this should be controlled by use of an appropriate standard (e.g. WHO IS).

The adalimumab IS was tested in a multi-centre collaborative study involving 26 laboratories in 13 countries. Participants tested the IS using assays established in-house, and reported results for cytotoxicity, apoptosis, reporter gene, ADCC, CDC and binding assays (see reference in section 9).

Therapeutic drug monitoring: The use of an assumed mass content of 50 micrograms of adalimumab per ampoule is recommended only for therapeutic drug monitoring assays (see section 4).

The suitability of the adalimumab IS for therapeutic drug monitoring was assessed in a range of binding assays in a study involving 16 laboratories in 8 countries (see reference in section 9).

It should be noted that the unitage or mass content of the standard should not be used to define the specific activity of adalimumab products for regulatory purposes nor to describe product labelling or dosage requirements. Furthermore, the standard and its unitage is not intended to serve any regulatory role in defining biosimilarity, and should not be inferred as serving this purpose.

4. CONTENTS

Country of origin of biological material: United Kingdom.
Each ampoule contains the residue after freeze-drying of 1.0 ml of a solution containing:

Adalimumab, approximately 50 micrograms
25mM tri-sodium citrate dihydrate
150mM sodium chloride
1.0% human serum albumin

The adalimumab protein was expressed in CHO cells.

5. STORAGE

Unopened ampoules should be stored at -20ºC.
For economy of use, it is recommended that the solution be sub divided into aliquots and stored at -40ºC or below. Avoid repeated thawing/freezing.

Please note: because of the inherent stability of lyophilized material, NIBSC may ship these materials at ambient temperature.

6. DIRECTIONS FOR OPENING

DIN ampoules have an 'easy-open' coloured stress point, where the narrow ampoule stem joins the wider ampoule body. Various types of ampoule breaker are available commercially. To open the ampoule, tap the ampoule gently to collect material at the bottom (labelled) end and follow manufactures instructions provided with the ampoule breaker.

7. USE OF MATERIAL

No attempt should be made to weigh out any portion of the freeze-dried material prior to reconstitution

Dissolve the total contents of the ampoule in 1.0ml of sterile distilled water. Use carrier protein where extensive dilution is required.
Users should note that in rare instances interference due to excipients may occur if the IS is used at high concentrations ($\geq 10\mu g/ml$).

8. STABILITY

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities and they should be stored on receipt as indicated on the label. It is the policy of WHO not to assign an expiry date to their international reference materials. Accelerated degradation studies have indicated that this material is suitably stable, when stored at -20ºC or below, for the assigned values to remain valid until the material is withdrawn or replaced. These studies have also shown that the material is suitably stable for shipment at ambient temperature without any effect on the assigned values. Once reconstituted, diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use. Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

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

World Health Organization

9. REFERENCES

This standard was produced under WHO guidelines cited in the WHO Technical Reports Series, No. 932, 2006, Annex 2.

Report on a Collaborative Study for Proposed 1st International Standard for Adalimumab WHO/BS/2019.2365

10. ACKNOWLEDGEMENTS

We are thankful to Abbvie and Samsung for their generous donations of the adalimumab materials used in the collaborative study. We are grateful to all participants of the collaborative study for their contribution in evaluating the candidate preparations.

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

Physical and Chemical properties	
Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not Physical appearance: Freeze dried powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: No	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: 4.6g
Toxicity Statement: Toxicity not assessed
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.