



**WHO International Standard
Darbepoetin, 1st International Standard
NIBSC code: 17/204
Instructions for use
(Version 1.0, Dated 15/11/2019)**

1. INTENDED USE

The World Health Organisation (WHO) Expert Committee on Biological Standardisation (ECBS) has recognised the need for a reference standard for the calibration of in vitro potency assays to assess the biological activity of darbepoetin. A candidate standard, coded 17/204, was evaluated in an international collaborative study, based on which the preparation was formally adopted by WHO ECBS in October 2019 as the 1st International Standard for darbepoetin.

This standard is intended to support the performance of in vitro bioassays of darbepoetin, by definition of the International Unit (IU) of darbepoetin biological activity. It is not intended to serve any regulatory role in defining biosimilarity, nor is the assigned IU intended to define the specific activity (U/mg) of darbepoetin for regulatory purposes, or describe the dosage or labelling of darbepoetin products.

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

Each ampoule contains 100,000 IU of darbepoetin.

4. CONTENTS

Country of origin of biological material: USA .

Each ampoule contains the residue after freeze-drying of 0.5 ml of a solution that contained:

| | |
|---------------------|--------------------|
| Darbepoetin | approximately 5 µg |
| Human serum albumin | 0.2 % (w/v) |
| Trehalose | 1.0 % (w/v) |
| Sodium chloride | 0.12% (w/v) |

5. STORAGE

Unopened ampoules should be stored at -20oC.

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 manufacturers 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

For practical purposes, each ampoule contains the same quantity of recombinant darbepoetin. The material has not been sterilized and the ampoules contain no bacteriostat.

The entire content of each ampoule should be completely dissolved in an accurately measured amount of buffer solution. For example, dissolution in 1.0 mL sterile distilled water will result in a solution containing darbepoetin at a concentration of 100,000 IU/mL.

COLLABORATIVE STUDY

The preparation 17/204 was evaluated in a collaborative study in which ten laboratories in seven countries took part. 17/204 was analysed alongside a comparator preparation with lower darbepoetin content, using a variety of in-house in vitro (cell-based) bioassay procedures. The consistency of relative potency estimates of 17/204 and the comparator preparation was considered to be demonstrative of the suitability of the preparation 17/204 to serve as an International Standard.

The long-term stability of 17/204 was also predicted via an accelerated thermal degradation (ATD) study. Analysis of the 17/204 ATD samples (stored at +4, +20, +37 and +45oC) showed no detectable loss in potency compared with the reference storage temperature (-20oC). This suggests that 17/204 is likely to be highly stable under long-term storage at -20oC.

8. STABILITY

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

NIBSC follows the policy of WHO with respect to its reference materials. Thus, no expiring date is assigned to international reference materials. Accelerated degradation studies have indicated that this material is suitably stable when stored at the recommended -20 °C or below, for 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.

9. REFERENCES

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

Ben Cowper, Jason Hockley, Peter Rigsby, Chris Burns and Jackie Ferguson. WHO International Collaborative Study of the Proposed 1st International Standard for Darbepoetin, for bioassay (2019). https://www.who.int/biologicals/expert_committee/BS.2019.2356_Darbepoetin_ECBS_study_report_Initial.pdf

10. ACKNOWLEDGEMENTS

We gratefully acknowledge the important contributions of all the participants and the donor of the darbepoetin bulk material used to prepare the standard.

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: Freeze-dried power | 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: 6 mg

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_biol_efstandardsrev2004.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.