Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
2nd International Standard for insulin, human
NIBSC code: 11/212
Instructions for use
(Version 1.0, Dated 20/11/2019)

1. INTENDED USE

The 2nd International Standard for insulin, human (coded 11/212) is intended for use as a calibrator for diagnostic measurements of insulin. It was established at the 70th Meeting of the WHO ECBS (2019).

This standard replaces the 1st International Reference Preparation for insulin, human (coded 66/304), stocks of which are exhausted, and the WHO International Standard for insulin, human, (coded 83/500) for calibration of diagnostic measurements of human insulin. Both standards were assigned in IU, which no longer reflects the international transition to a mass assigned molecule. Consequently the 2nd International Standard for insulin, human, 11/212, has been assigned a content of 9.19 mg per ampoule by mass balance methods.

2. CAUTION

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

The material is not of human or bovine origin. 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 9.19 mg/ampoule (with expanded uncertainty of 9.14 - 9.24 mg/ampoule, k=2) of lyophilized human insulin.
This value can be converted to IU using the internationally recognized specific activity of pure insulin (1 IU=0.0347 mg).

4. CONTENTS

Country of origin of biological material: Denmark.
Each ampoule contains the residue after freeze-drying of 1 g of a solution containing highly purified, recombinant insulin.

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 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

For all practical purposes, each ampoule contains the same quantity of the substance listed above. The material has not been sterilized and the ampoules contain no bacteriostat.
Depending on the intended use, the entire content of each ampoule should be dissolved in an accurately measured amount of buffer solution. Users should make their own investigations into the type of diluent suitable for their use. If extensive dilutions are prepared, a carrier protein should be added.

COLLABORATIVE STUDY
The ampouled preparation, coded 11/212, was evaluated in a two-phase collaborative study to 1) value assign the standard by mass balance methods, and 2) to assess its immunoreactivity and suitability to serve as an International Standard by immunoassay in comparison with the 1st IRP 66/304 and a panel of human serum and plasma samples.

The results of the Phase 1 study gave an assigned content for 11/212 of 9.19 mg/ampoule (with expanded uncertainty 9.14 - 9.24 mg/ampoule) by mass balance methods, with good agreement from HPLC estimates of 9.19 mg/amp (9.07 - 9.31 mg/amp) and total nitrogen analysis of 9.14 mg/amp (8.97 - 9.30 mg/amp).

In Phase 2, the laboratory geometric mean immunoassay estimates for 11/212 of 267.1 IU/amp were in very good agreement with the assigned content of 9.19 mg/amp to 11/212, after application of the activity conversion factor for pure insulin of 1IU = 0.0347 mg insulin to give 264.8 IU/amp. Both 11/212 and 1st IRP 66/304 had acceptable GCVs and behaved in a similar manner in the immunoassays used.

A thermally accelerated degradation (ATD) study was also performed. The data from HPLC and immunoassay estimates of ATD samples of 11/212 indicate that the candidate is sufficiently stable when stored at -20ºC to serve as an International Standard.

The commutability of 11/212 with patient samples in the immunoassay methods performed in Phase 2 of the collaborative study was assessed using a difference in bias approach. In the 14 laboratories that demonstrated constant patient sample bias, the 1st IRP 66/304 was commutable in 7 laboratories and the candidate standard 11/212 was commutable in 8 laboratories. It is important to note that the commutability criteria for the difference in bias approach have been derived statistically, rather than based on clinical relevance. It is not possible, within the confines of a collaborative study to fully assess commutability of the standard 11/212 in all immunoassay methods. It is therefore recommended that manufacturers make their own assessment of commutability of the reference standard 11/212 with their assay method.

In conclusion, the candidate standard 11/212 was deemed to represent a well characterised, mass assigned standard for pure human insulin, that was shown to behave in a very similar manner to the 1st IRP 66/304 in immunoassays of human insulin in terms of immunoreactivity and commutability, and is therefore suitable as a replacement for 66/304 for the continued calibration of these immunoassays.

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 -20ºC or below. 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 characteristics of any reference preparation are encouraged to contact NIBSC.

9. REFERENCES

[1] WHO Tech Rep Ser No 800, 1990, 181-214

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

World Health Organization

10. ACKNOWLEDGEMENTS

We gratefully acknowledge the important contributions of all participants of the collaborative study phases, Novo Nordisk who kindly donated the human insulin material, the Standardisation Science Group at NIBSC for preparation of the trial materials and sub-portions, the Standards Processing Division at NIBSC for the preparation and dispatch of ampouled materials and the Biostatistics Group at NIBSC for analysis of the collaborative study data.

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: White powder		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	No	Irritant:	No
Flammable:	No	Handling:	See caution, Section 2
Other (specify):	N/A		

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: 10mg
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.

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