Proposal to initiate a project to evaluate a candidate International Standard for Human Recombinant Insulin

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A. Background

Insulin is a medicine that is manufactured and administered worldwide, making the issue of standardization a global one. WHO International Standards (IS), established by the Expert Committee on Biological Standards (ECBS), play an important role in the worldwide regulation of biological medicines. They are widely accepted as primary standards for the measurement of biological potency. For purposes of assay, potency assignment, and dosing, insulin was transitioned from biological potency units to a mass balance assigned value in the late 1980s and has since been treated like a chemical. The widely accepted assay is an HPLC assay. The bioassay has been eliminated from insulin almost entirely worldwide, with the exception of the bioidentity test (rabbit blood glucose test) required by the USFDA as described in USP General Chapter Insulin Bioassay.<sup>121</sup> Correlation between potency units and mass is based on the well-established correlation: 1 Unit of human insulin (EP/USP/IU) corresponds to 0.0347 mg of insulin human. Since the decision to treat insulin as a chemical, major stakeholder pharmacopoeias have been independently establishing their own standards. Because each pharmacopoeial standard is assayed against that pharmacopeia’s previous lot, discontinuity of standards has been observed, as discussed below.

The current WHO standards for insulin (human – coded 83/500, bovine – coded 83/511, porcine – coded 83/515, Mol Wt 5,800) were established in the mid 1980’s. The potency is defined in IU/mg. Assignment of values to the current standard was based on a multi method collaborative study by in vivo bioassay, hence the need for an updated standard(s) to reflect the transition of insulin internationally to a well-characterized, mass-balance assigned molecule. The ECBS have discussed principles about transitioning well-characterized molecules to mass-assigned values (WHO/BS/07.2070). In fact several existing, ECBS standards are based on mass balance assignments, among them the IS for somatropin. These standards, and the discussion by ECBS, have set precedent for transitioning standards from activity- to mass-based assignments.

B. Standardization issue

The current approach regarding standardization of insulin is depicted in Figure 1 and demonstrates (in an exaggerated way) a potential for variability between reference standards. This variability cannot be determined nor addressed in a metrological sense, due to the lack of a common (primary) reference standard, as well as the differences in the methods or procedures used to assign potency values. This experience shows that the assigned potency values for different pharmacopoeial reference standards and also for different manufacturer’s reference standards can differ and there can be shifts in the relative assignments between batches of reference standard from the same agency. While these variations are typically small, they can be significant from the standpoint of process control (Figure 2). Even small differences may raise compliance questions from regulatory auditors. For the patient, these issues could potentially result in differences in the dose of this lifesaving medication in different regions of the world.
CURRENT APPROACH

![Graph showing variability in mg/mg between different reference standards]

This approach leads to variability between different documentary standards (procedures) and associated reference materials, resulting in an inability to determine compatibility or comparability of data.

Figure 1: The current approach for insulin standardization demonstrating the potential for variability between different reference standards.
C. Proposal

It is proposed to develop an International Standard for recombinant human insulin for which the assay/purity value is assigned in mass units of milligrams. Figure 3 demonstrates the benefit in the establishment of a single International Standard to be used for the value-assignment of pharmacopoeial and manufacturer’s reference standards. Using this approach, validated reference methods (e.g., HPLC) permit the assignment of potency to pharmacopoeial, regional, or manufacturer’s standards relative to a single international standard, thereby reducing the variation among the potency assigned to these different standards.

Figure 2: Example data from a manufacturer: potency shifts associated with the lot-to-lot transitions of Pharmacopoeial Reference Standards
D. Scientific considerations and impact:

Human insulin is considered a very well characterized small peptide so full physicochemical characterization is possible. There is also a well agreed upon conversion factor between potency units and milligrams, which can be stated in the documentation associated with the standard. This conversion factor is the same in the EP and the USP. The JP (SJP) assigns their insulin reference standard in a national unit, the conversion factor to mg differs from the one used in Europe and US and is 0.036 mg per 1 unit.

- **Assay**

The assay for human insulin is performed by HPLC analysis according to USP, Ph Eur and JP. The only significant difference in the three compendia HPLC procedures is sample concentration, which is 1.5 mg/ml (USP, JP) or 4.0 mg/ml (Ph Eur). No new method needs to be developed to implement a new International Reference Standard.

- **Conversion factor**

1 IU = 0.0347 mg insulin human (Ph Eur) or 1 USP unit = 0.0347 mg (USP). This will not have to change when implementing a new International Standard.
Due to a well defined conversion factor between International Units and mg, there will be no consequence for implementing a new International Reference Standard.

- Clinical consequences
  
  Due to a well defined conversion factor between unit and mg there are no expected clinical consequences.

- Consequences for labeling of products
  
  Manufacturers may continue to label products in units due to a defined conversion factor between unit and mg. This means labeling can remain unchanged.

- Transition period for implementation
  
  Not needed due to conversion factor is already known 1 IU = 0.0347 mg insulin human = 1 USP unit.

E. Logistical Aspects and Implementation

It is proposed to identify a candidate material that can be fully characterized by primary reference methods. USP and NIBSC have offered to collaborate on this and agreed to include this project as part of their Memorandum of Understanding (MOU) implementation plan. Since the project is supported by international industry stakeholders, the procurement of candidate materials is not considered to be an obstacle. In order to fully characterize the material and assign a final value to the standard, a collaborative study should be conducted. It is proposed to present the results of the collaborative study to ECBS for endorsement in the same way as other international standards are evaluated and endorsed.

F. Summary Recommendation

The WHO ECBS is requested to endorse a new project to evaluate the suitability of a primary standard for recombinant human insulin, with an assignment of mass of insulin content in mg/mg. The units of recombinant human insulin can be calculated using the well established conversion factor of 1 Unit (USP/EP/IU) = 0.0347 mg of insulin human. This material is intended to be used for the purpose of establishing traceability for regional and pharmacopoeial reference materials for insulin.