WHO 3rd International Standard for Thrombin

FXIII and Fibrinogen Subcommittee

**Project leader:** Matthew Locke, National Institute for Biological Standards and Control (NIBSC), UK.

**Description Abstract**

State the application’s broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Suggested length is 2-3 paragraphs.

The current WHO 2nd International Standard (IS) for Thrombin (01/580) was established in 2002 and unified the WHO/NIH standard with a common unit (Whitton C et al 2002). Annual sales of the standard have averaged approximately 290 ampoules in the past 10 years. Stocks are now running low, and a replacement is required. The aim of this project is to replace 01/580 through an international multicenter collaborative study.

The calibration of thrombin products worldwide rely on the thrombin IS, which defines the International Unit (IU) for thrombin potency. Many of these products have important therapeutic and diagnostic applications, such as in fibrin sealant (fibrin “glue”) kits, in clinical laboratory testing, and in the measurement of hirudin-based anticoagulant pharmaceutical products.

The current project will ensure the continuity of the thrombin IU and ensure supply of the IS for the next 15-20 years.

**Design and methodology (Data expected to collect, sample size and statistical analysis):**

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs.

A donation of human alpha-thrombin (the same material used for the 2nd IS) has been secured from a manufacturer to serve as the candidate 3rd IS. The material will be reformulated, filled, and freeze-dried at NIBSC into approximately 10,000 ampoules, with a target potency of 100 IU/ampoule. Formulations will be based on the 2nd IS, requiring minimal process development. A second material will be included, 01/578, which was a candidate sample from the 2002 study. We will evaluate the suitability of this material as a secondary standard, following recalibration in this exercise.

A multicenter collaborative study (20-25 laboratories) will determine the potency of the candidate IS against the 2nd IS, using chromogenic and/or clotting assays. Example protocols will be provided, but participants will be free to use their own in-house methods. Participants will comprise a mix of regulatory, academic, and research laboratories, spanning a wide geographical location. Raw data will be analysed at NIBSC using established biostatistical methods for potency determinations.

The current IS has an excellent stability profile, and we expect the 3rd IS to be similarly stable. Long-term stability monitoring will be carried out using accelerated degradation and Arrhenius
modelling, with ampoules stored at elevated temperatures for undefined periods, and potencies periodically determined relative to -20 °C samples.

**Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):**

Suggested length 2-3 paragraphs

N/A

**Expected timeline:**

Q3 2019 - obtain bulk material for 3rd IS  
Q4 2019 - freeze-dry material, recruit laboratories for study  
Q2 2020 - samples sent out to study participants  
Q3 2020 - results returned  
Q3/Q4 2020 - calculations, reports at NIBSC  
Q1 2021 - review by participants  
Q2 2021 - review by SSC  
Q3 2021 - presentation to SSC  
Q3 2021 - submission to WHO  
Q4 2021 - approval by WHO and establishment of 3rd IS

**Expected outcomes (ie. publications):**

WHO ECBS report published on WHO website following establishment of 3rd IS.  
SSC communication in Journal of Thrombosis and Haemostasis.

**Description of project set/up and management, needed infrastructure and resources (summary):**

The Project Leader will assemble a project team comprising other scientists and specialists at NIBSC, including personnel from standardization science (formulation and freeze-drying), standards processing (sample storage and dispatch), business development (MTA for candidate donation), and Biostatistics. The project leader will also liaise with WHO-ECBS for project approval, and write and compile reports for participants, SSC, and ECBS.

Source material (alpha-thrombin) for the project will be donated by a manufacturer for use as an IS. Study design and methodology will be based on the previous study to establish the 2nd IS. All other resources required for successful completion of the project are currently in place and in routine use at NIBSC.
References: