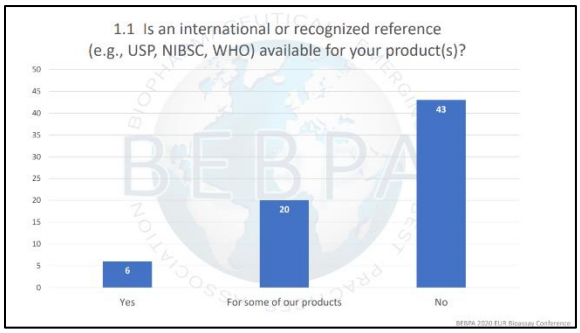
Survey Results for Bioassay Reference Standards

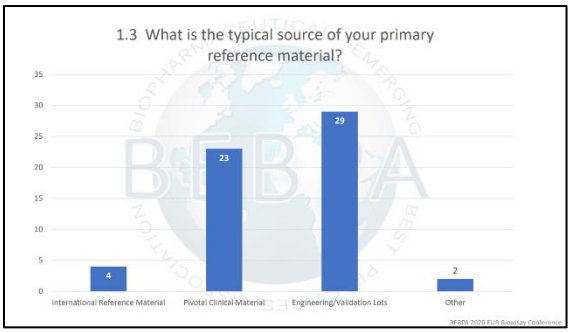
BEBPA Technical Note

February 2021

Product reference materials are critical for nearly all analytical assays used to release commercial biotech products However, for potency assays, which are usually relative potency assays (that is test material is compared to a known product reference), it is especially important and simultaneously difficult to maintain.

At our more recent BEBPA Bioassay Conference, we polled the audience to find out our current practices for laying down and establishing product reference material for bioassays. We found that most of us do not have available international references, and therefore use either an engineering lot or a pivotal clinical batch for our first reference. See our poll results below.

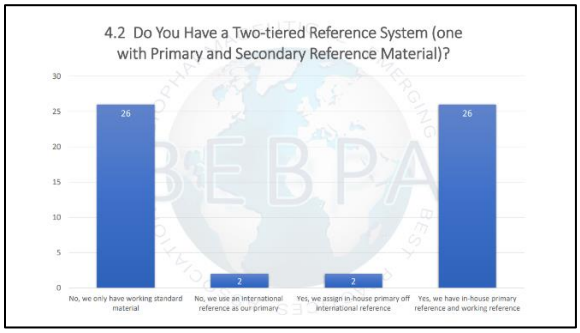




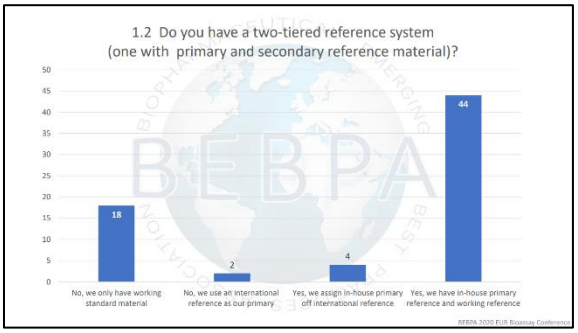
However, probably the most interesting result from our more recent poll is when we asked about using a two-tiered reference program. A two-tiered system consists of a primary (aka gold standard) reference and a secondary (aka working) product reference. The working reference typically comes from the standard manufacturing stream and is qualified against the master reference material. It is used on a daily basis to release product. The primary reference material is that material which comes from the pivotal clinical or engineering batch and is used to qualify secondary (working) references and/or for comparability studies when changing the manufacturing process. Several papers have been published in the past several years extolling the virtues of such a two-tiered reference programs. (See the reference list below).

In 2019, we asked bioassay conferences attendees if they use a two-tier reference system and found that 50% of the audience had only a working reference material – compare this to last year (2020) in which 30% stated they only had one-tier systems. Perhaps practices are changing? We will be polling the audience again this year – join us at our upcoming 2021 US Bioassay Conference to find out if this is a trend – or just an example of small sample size statistics.

September 2019



March 2020



Reference Materials Reading list:

General Guidance

1. **Recommendations and Best Practices for Reference Standards and Reagents Used in Bioanalytical Method Validation**. Joseph F. Bower, Jennifer B. McClung, Carl Watson, Takahiko Osumi, and Kátia Pastre. The AAPS Journal 2014 Mar, 16(2): 352-356 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3933579/
2. **Reference Standards for Therapeutic Proteins: Current Regulatory and Scientific Best Practices (Part 1)**. Mire-Sluis A, Ritter N., Cherney, B., Schmalzing, D., and Blumel M. BioProcess Intl., March 1, 2014 https://bioprocessintl.com/upstream-processing/assays/reference-standards-for-therapeutic-proteins-350518/
3. **Reference Standards for Therapeutic Proteins (Part 2)**. Mire-Sluis, A. BioProcess Intl. May 1, 2014 https://bioprocessintl.com/2014/reference-standards-for-therapeutic-proteins-351584/
4. **World Health Organization, Expert Committee on Biological Standardization. Sixty sixth report.** Report of a WHO informal consultation on international standards for biotherapeutic products. WHO Technical Report series 999:13–15, 2016. http://apps.who.int/iris/bitstream/10665/208900/1/9789240695634-eng.pdf

Stability of Reference Material:

1. **Rapid optimization of protein freeze-drying formulations using ultra scale-down and factorial design of experiment in microplates.** Grant Y, Matejtschuk P, Dalby PA. Biotechnol Bioeng. 2009 Dec 1;104(5):957-64. https://www.ncbi.nlm.nih.gov/pubmed/19530082
2. **The International Reference Preparation of Tetracosactide for Bioassay: characterization and estimation of its (1-24)corticotrophin-tetracosapeptide content by physicochemical and biological methods.** Storring PL, Witthaus G, Gaines Das RE, Stamm W. J Endocrinol. 1984 Jan;100(1):51-60. *"Bioassay estimates of samples … which had undergone significant degradation were higher than estimates by HPLC."* https://www.ncbi.nlm.nih.gov/pubmed/6317783