Long-Term Stability Study of Prussian Blue: A Quality Assessment of Water Content and Cyanide Release
A. Mohammad, Y. Yang, M. A. Khan, P. J. Faustino
U.S. Food and Drug Administration

Purpose
To assess the long-term stability of Prussian Blue (PB), drug products (DPs) and active pharmaceutical ingredients (APIs) by evaluating bound water content and cyanide release. PB or ferric hexacyanoferrate is an approved oral dosage form for the treatment of internal radioactive contamination of cesium or thallium. Of particular concern is cyanide which makes up 35-40% of PB's molecular composition, thus cyanide may be released during transit through the digestive tract under physiological pH conditions.

Methods
Test samples of API and DP were stored at ambient conditions for 10 years. Water loss from PB was measured using thermogravimetric analysis (TGA). An in vitro physiological pH model that brackets gastric exposure and GI transit was utilized for cyanide release. PB was incubated in situ at pH 1.0, 5.0 and 7.0 @ 37°C for 1-24 hours. Cyanide was measured using a validated colorimetric method by UV-VIS spectroscopy.

Results
Although the water content of PB API and DP decreased by about 10.5% and 13.8%, respectively since 2003, the cyanide release remained comparable. At pH 7.0 for 24 hrs cyanide released from API-1 was 21.33 +/- 1.76 micro g/g in 2004, and 28.45 +/- 3.15 micro g/g in 2013; cyanide released from DP-1 was 21.89 +/- 0.56 micro g/g in 2004, and 27.31 +/- 0.78 micro g/g in 2013. At pH 5.0 for 24 hrs cyanide released from API-1 was 20.28 +/- 0.72 micro g/g in 2004, and 26.49 +/- 6.86 micro g/g in 2013; cyanide released from DP-1 was 20.71 +/- 0.77 micro g/g in 2004, and 20.01 +/- 3.11 micro g/g in 2013. At pH 1.0 for 24 hrs cyanide released from API-1 was 135.11 +/- 5.19 micro g/g in 2004, and 148.23 micro g/g in 2013; cyanide released from DP-1 was also comparable in 2013.

Conclusion
This is the first long-term stability study of PB that monitors product quality through the assessment of cyanide release and water loss. The 20% water loss had no significant impact on the amount and profile of cyanide released from PB at all GI relevant pH conditions. Therefore, the long-term stored PB does not present additional safety concerns for clinical use.