Novartis Biopharmaceuticals

Reflection Paper – Examples from Industry

Heike Wöhling, Head Biostatistics Biopharmaceuticals
Franz Innerbichler, Statistical Process Expert

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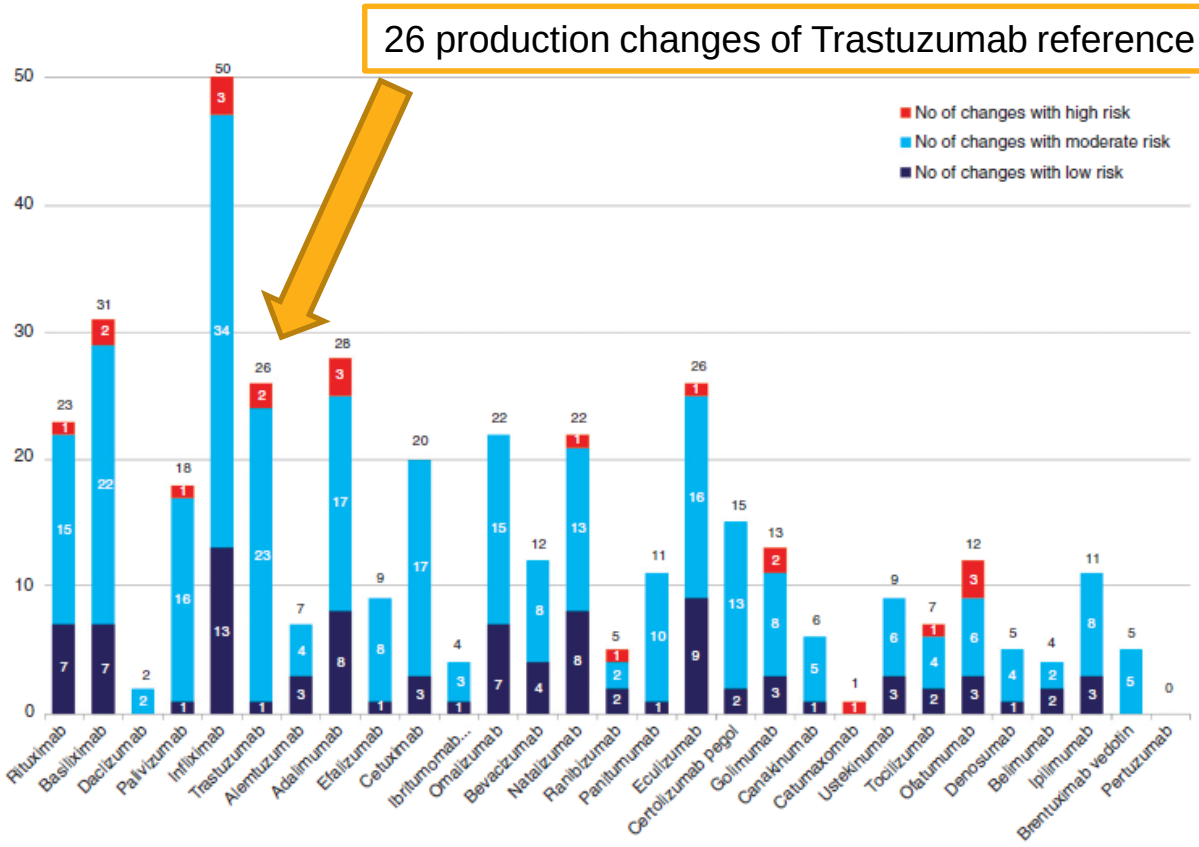
Originators have changed their manufacturing processes multiple times after approval



Changes include

- Change in the supplier of a cell culture media
- New purification methods
- New manufacturing sites and conditions
- Changes in batch size

Source: Vezer B et al, Current Medical Research and Opinion, 2016,32(5): 829-834

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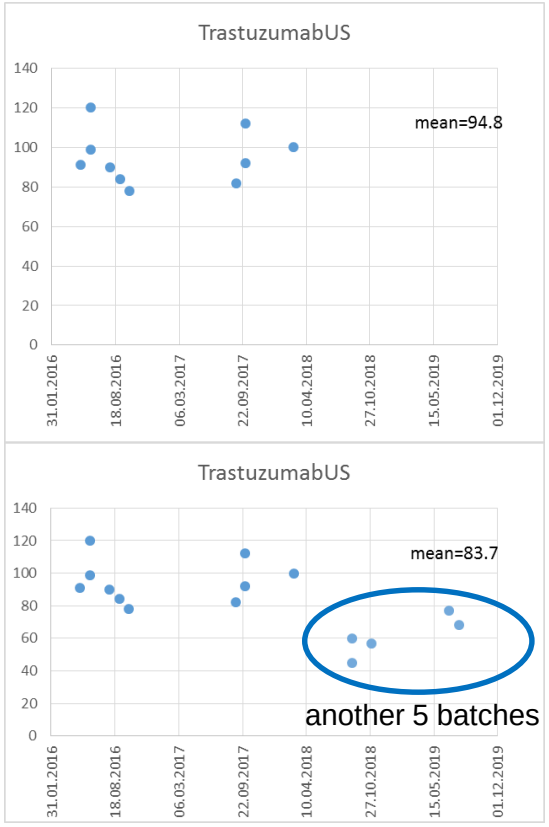
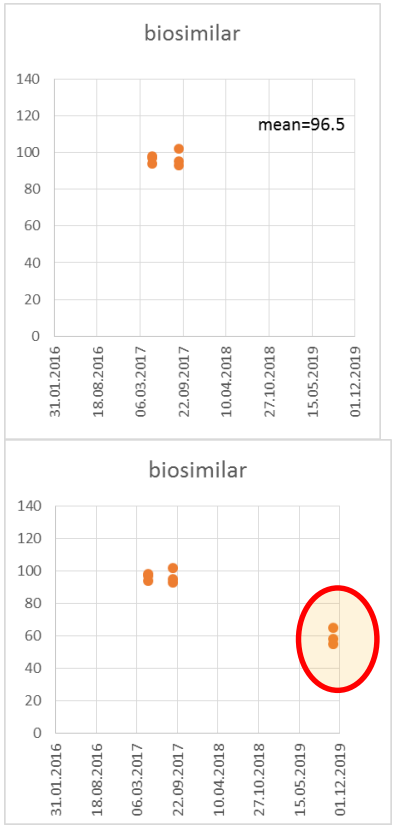
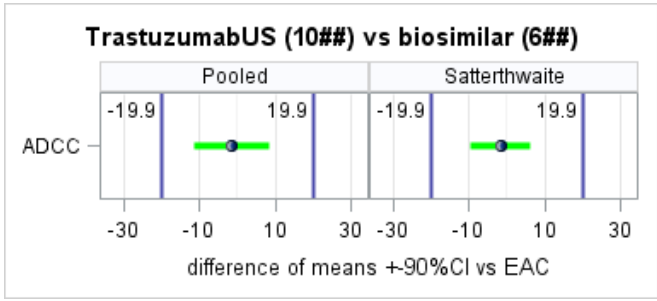
Implications of sampling reference biologic lots across many years

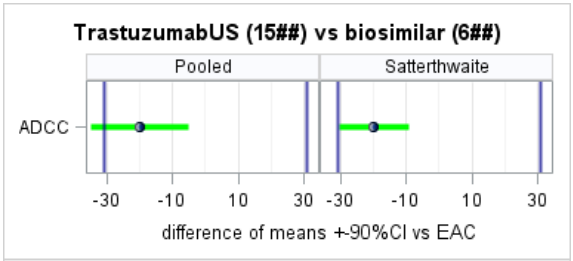
10 random batches

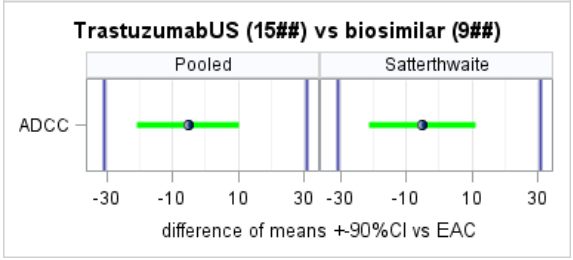


biosimilar ~same mean









The biosimilar applicant has to develop 2 different manufacturing processes to become equivalent

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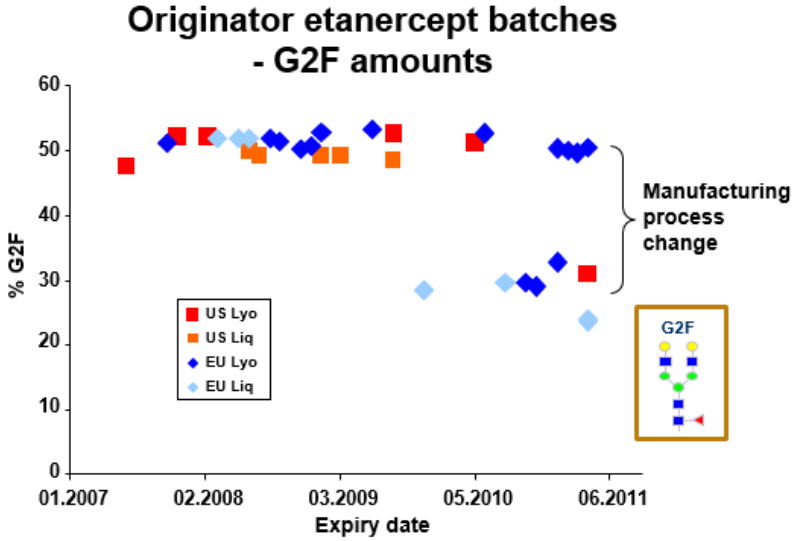
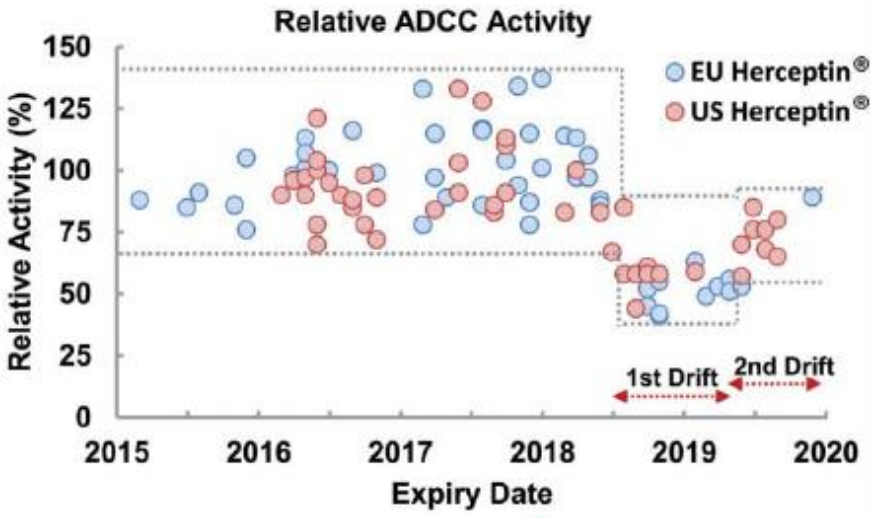
Process variation is in the nature of biologics

- Analytical data revealed manufacturing changes
- The processes before and after changes were evaluated and deemed to be highly similar / comparable by regulatory agencies
- The modified process was approved and the batches were administered to patients

How can these process changes be detected?
By looking at the time scale

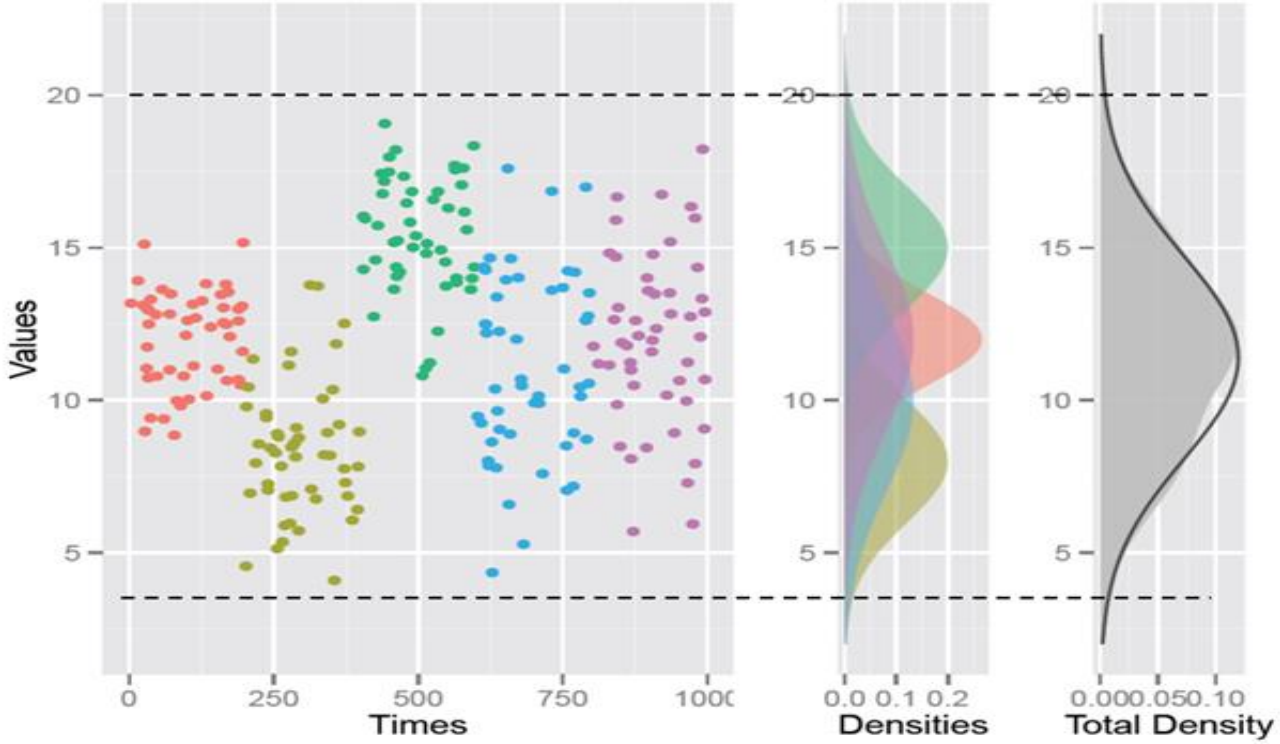




Schiestl M, et al. Nat Biotechnol. 2011;29(4):310-312.
McCamish M, et al. Clin Pharmaco Ther. 2012;91(3):405-417.
Kim S, et al. mAbs 2017;9(4):704-714

Process variation in reference biologics
Which distribution?

Process shifts can hide in an overall "normal" distribution



Data: simulated random normal data resulting in multiple means

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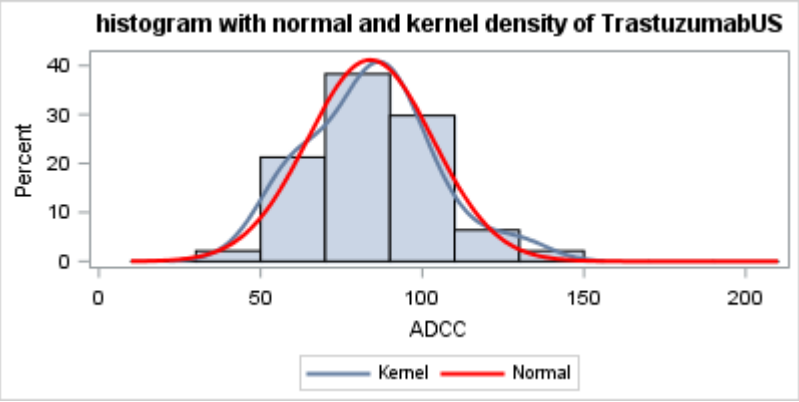
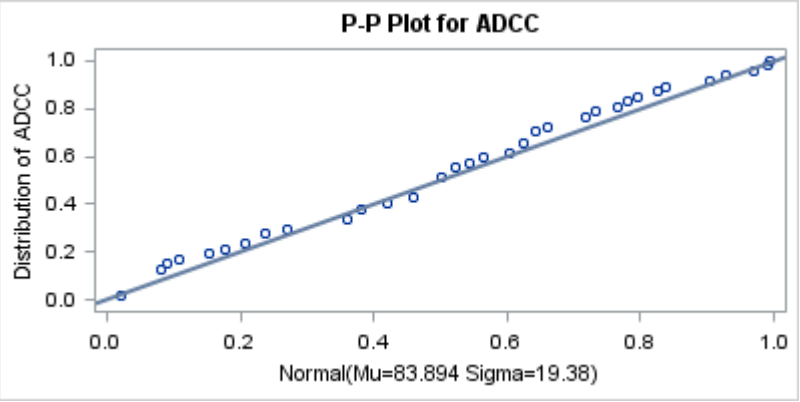
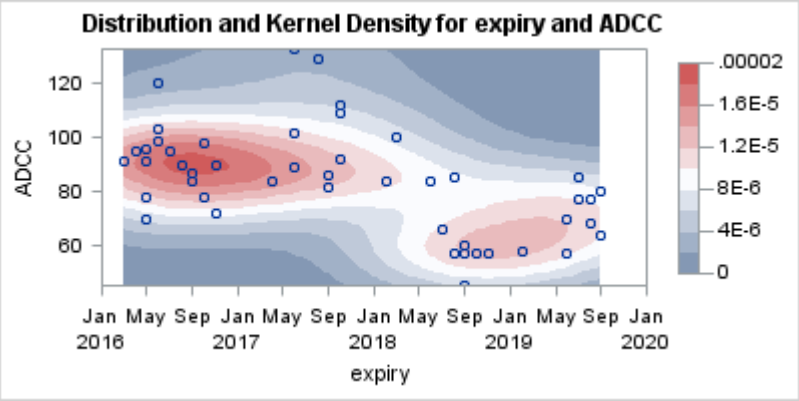
Variation in Trastuzumab US reference biologic
Major role of manufacturing/expiry date

Multimodality is hard to detect with traditional methods





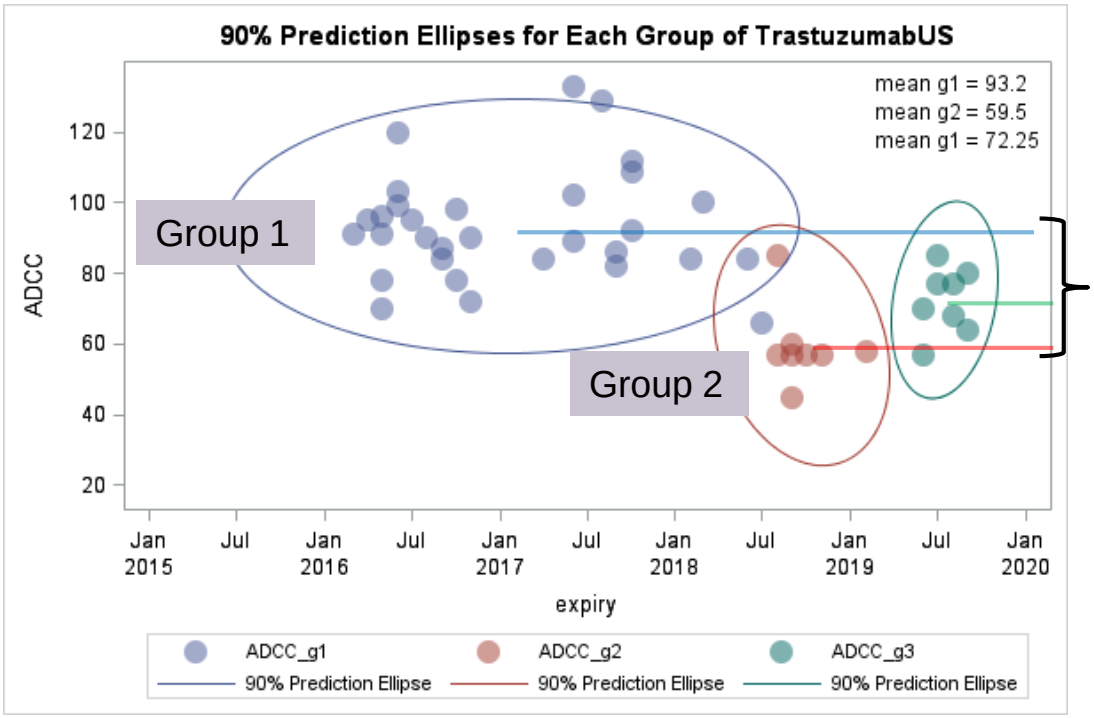
Time axis (manufacturing/expiry date) is crucial to detect mixture distribution



Data extracted from ADCC chart in
Kim S, et al. mAbs 2017;9(4):704-714

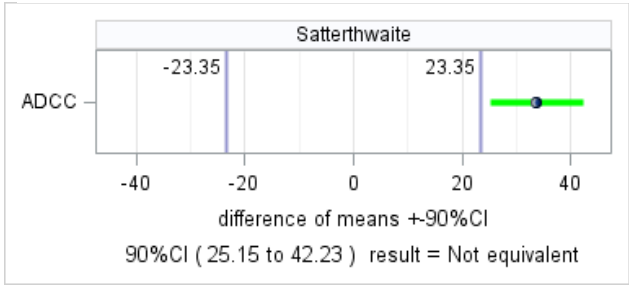
Variation in Trastuzumab US reference biologic

Multimodality: groups not equivalent to each other



Different means → Mixture distribution
→ autocorrelation;

Equivalence test: group1 vs group2

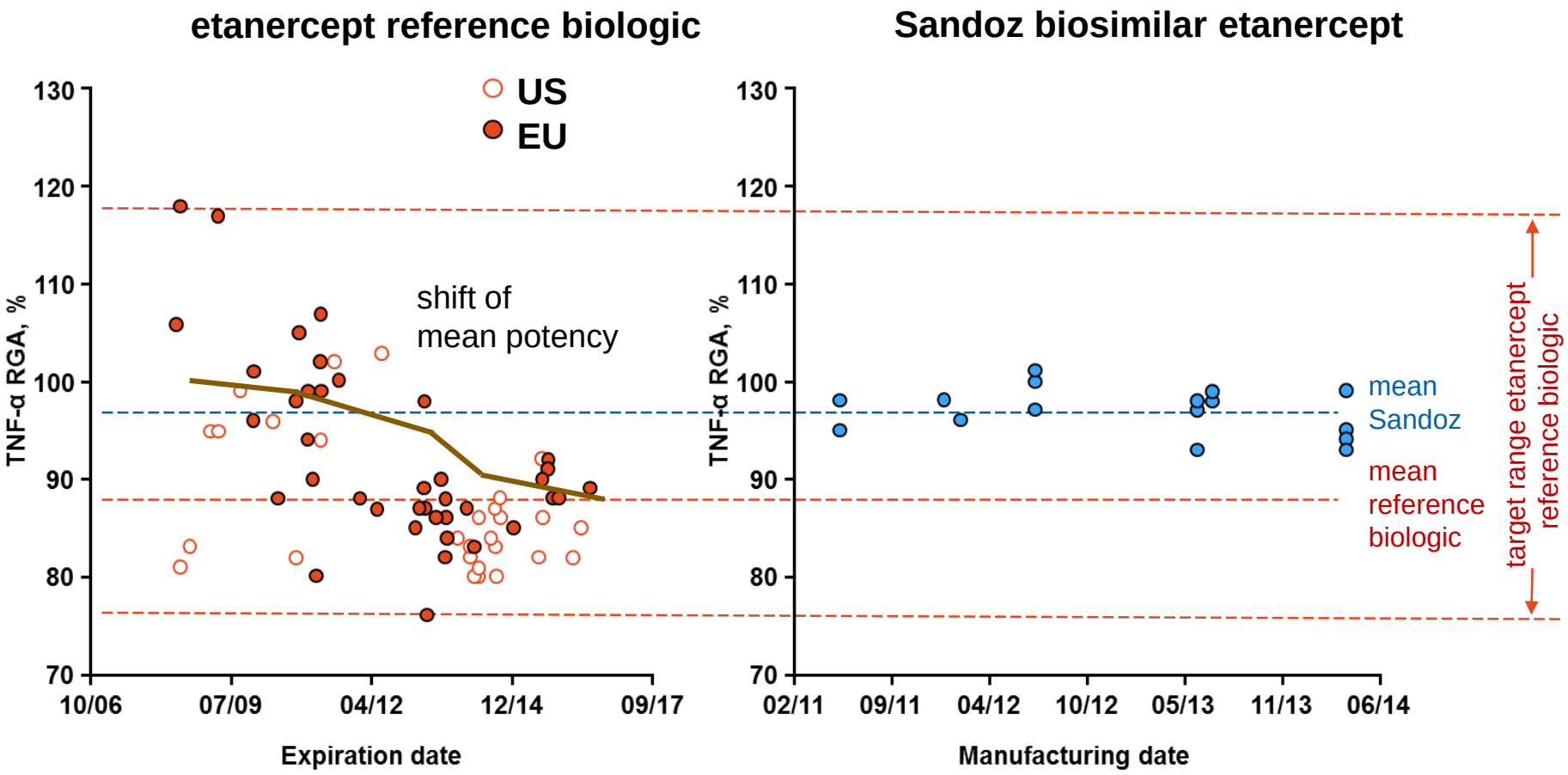


Equivalence between group 1 and 2 can not be detected, although all the batches were released and administered to patients.

A reference medicine before and after a manufacturing change may not be equivalent. But, they are comparable and therefore highly similar.

Data extracted from ADCC chart in
Kim S, et al. mAbs 2017;9(4):704-714

Variation in Etanercept reference biologic: Moving mean



Reference: Sandoz presentations for the July 13, 2016 Meeting of the Arthritis Advisory Committee (FDA)

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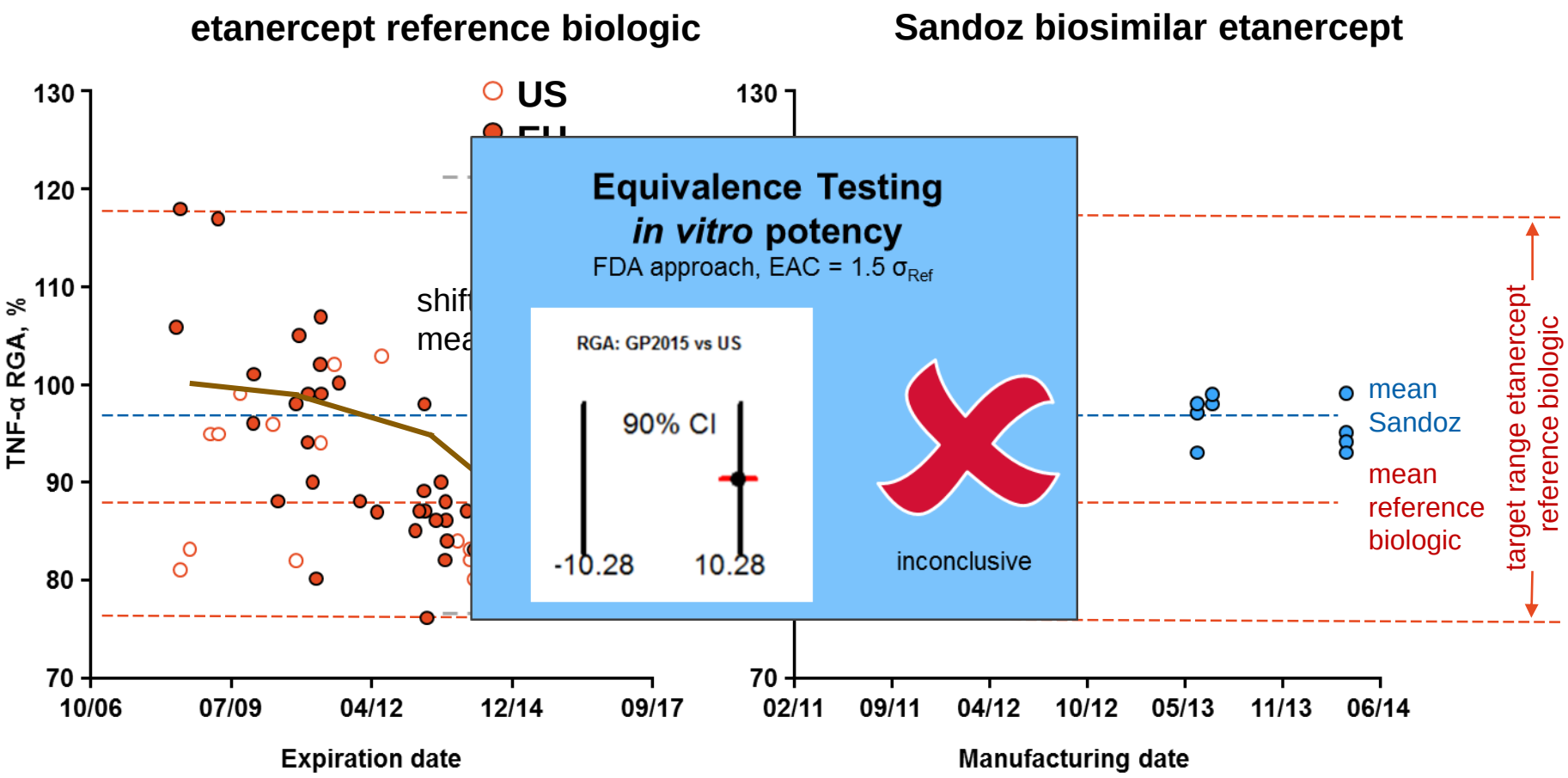
Variation in Etanercept reference: Moving mean



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