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EUROPEAN GENERIC MEDICINES ASSOCIATION



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Off-Target Toxicity

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Therapeutic antibodies are highly selective

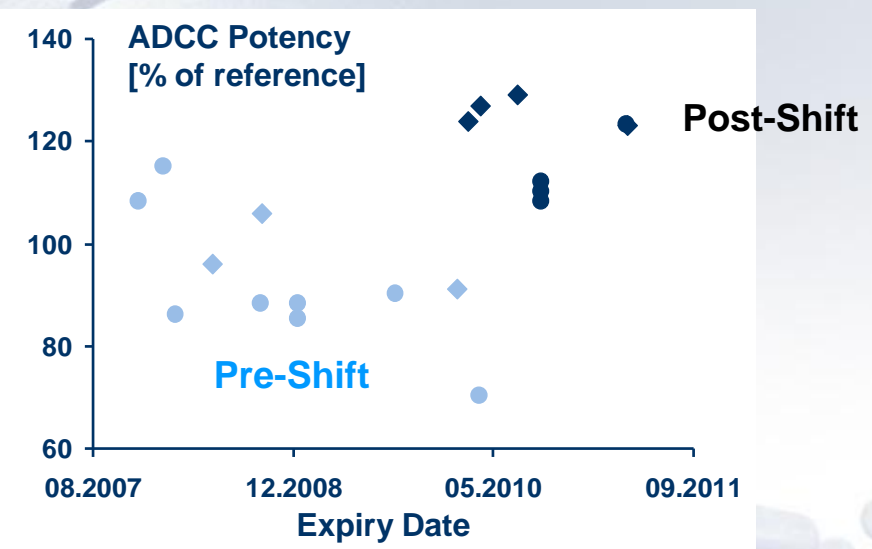
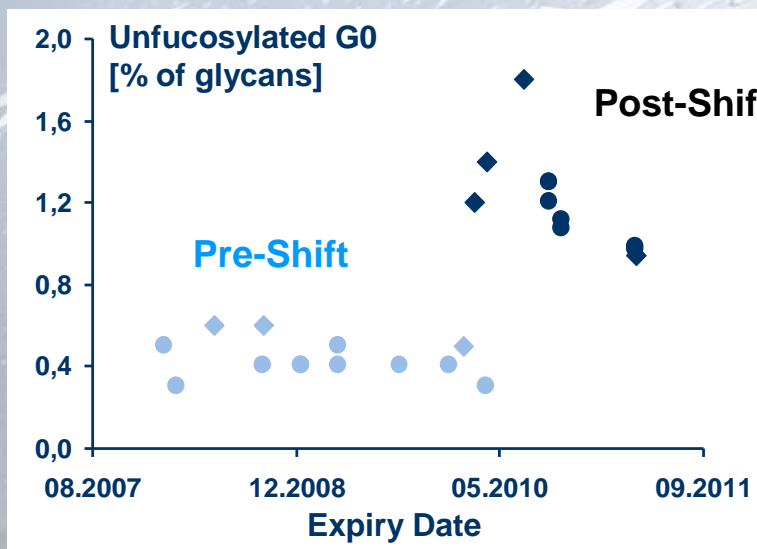
- Therapeutic antibodies intrinsically express a high degree of selectivity and specificity for the target, compared to small molecules
- Off-target binding, if present, is commonly triaged during initial novel discovery phase (e.g. via chip analysis, tissue cross reactivity) or during (pre)clinical assessment of the originator candidate compound
- Toxicity and clinical safety of approved, clinically validated therapeutic antibodies are therefore associated with the biological function of the target and binding by the antibody
- Biosimilars contain the same amino-acid sequence of the originator and are systematically engineered and tested to match the reference product regarding target binding and all relevant Fc functions

Clinical safety is related to MOA

- A total of 174 biologicals, 27 of which therapeutic antibodies, were approved between 1995-2007 in the EU and US:
 - 17 of the antibodies received safety-related regulatory actions
 - Common adverse events were injection site reactions, infections, immune system disorders and different forms of neoplasms
 - These events were generally attributed to mechanism-of-action
(Giezen et al 2008, JAMA 300:1887)
- None have been suspected to be related to off-target toxicity
- Despite common process changes during the life-cycle of biologicals, off-target activity has not been reported to be associated with any of the above clinical adverse events

Significant changes in originator mAbs - the MabThera[®]/Rituxan[®] case

- Monitoring batches of MabThera[®] and Rituxan[®] revealed a shift in glycosylation profile and ADCC potency
- Manufacturing changes have not led to any differences in off target toxicity - even when Fc functions were markedly changed



Schiestl, M. et al., *Nature Biotechnology* 29, 310-312, 2011)

EMA guidance requires extensive comparative in vitro characterization

- Very comprehensive range of attributes are assessed using state-of-the-art technologies, beyond what is typically requested of the originator:
 - Primary and higher order structures
 - Physicochemical characterization of post-translational attributes, such as glycosylation, glycation, deamination, aggregation, etc.
 - Binding affinity to target (receptor or soluble protein) as well as panel of FcγR and FcRn
 - In vitro biological characterization of target and Fc-mediated functions, even those that are not reported to be clinically relevant
=> ensures no unexpected alteration of function activity
 - Conclusion: current guidance ensures that off-target toxicity is not an issue for biosimilar antibody development
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