PP-027

LONG-TERM STABILITY OF DILUTED SOLUTIONS OF THE MONOCLONAL ANTIBODY CETUXIMAB

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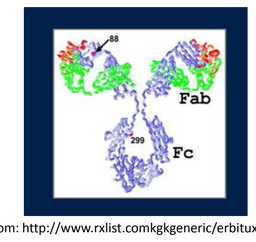
Objective:

To assess the long term stability of the therapeutic monoclonal antibody **Cetuximamb (Erbitux®)** once the single-dose vial was open (5.0 mg/ml) and diluted with 0.9 % NaCl to a final concentration of 2.0 mg/ml. The solutions were stored in dark glass vials refrigerated at 4 ° C and frozen at -20 ° C.

Background:

Cetuximab (CTX) (Erbitux®) is a chimeric mouse-human monoclonal antibody IgG1 targeting **epidermal growth factor receptor (EGFR)**. It is approved for use as treatment for metastatic colorectal cancer and squamous cell carcinoma of the head and neck.



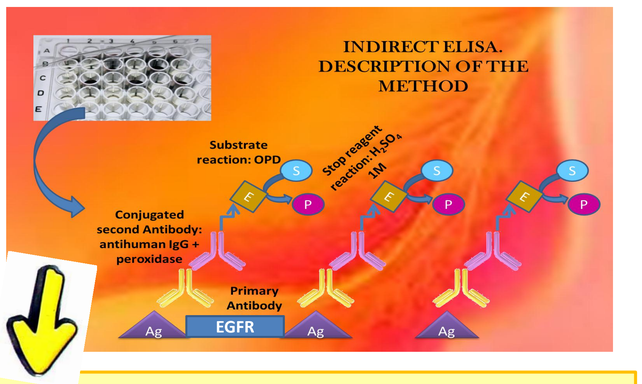
From: http://www.rxlist.comkgkgeneric/erbitux_ids.htm

Materials and methods:

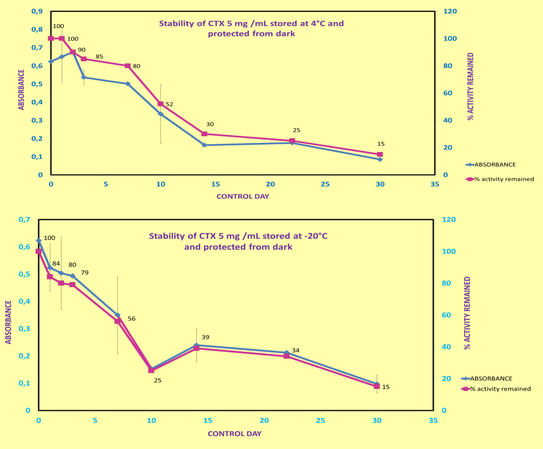
Ad hoc methods for assessing the **physicochemical properties** of cetuximab were developed and ICH validated: reverse phase high performance liquid chromatography with diode array detector ***[(RP)HPLC-DAD]*** for *quantification*; weak cation exchange high performance liquid chromatography ***[(WCX)HPLC-DAD]*** to track changes in the *isoforms profile*; size exclusion chromatography high performance liquid chromatography with diode array detector ***[(SEC)HPLC-DAD]*** for *aggregates* detection; and electrospray quadrupole/time of flight mass spectrometry ***(ESI qTOF-MS)*** to obtain molecular weight in order to detected *changes in the chemical structure*. **Biological activity** was assessed using a specific immunoassay based on the ***ELISA*** technique using plates sensitized with the **Epidermal Growth Factor Receptor (EFGR).**

Biological Activity

Specific Immunoassay ELISA based on EGFR



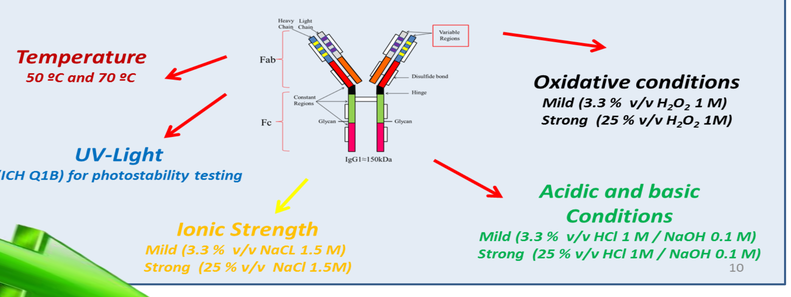
Biological activity was assessed using solutions CTX of 5.0 mg/ml stored refrigerated at 4°C and frozen at -20°C, protected from daylight up to 30 days.



Cetuximab Stability Study

ICH harmonisation for better heal

Accelerated degradation study ICHQ2(R1)
by ELISA - (RP)HPLC/DAD – (SE)HPLC/DAD – (WCE)HPLC/DAD



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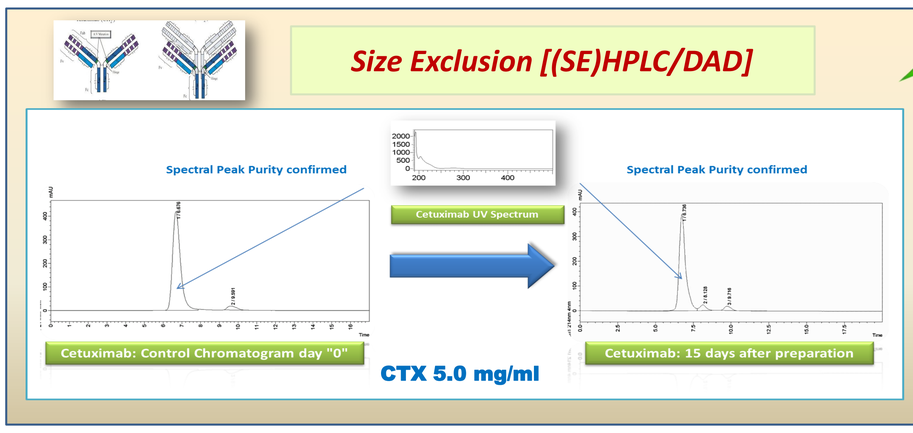
ESI-qTOF/Mass spectrometry Molecular Weight CTX 1 mg/ml ; 0.5 mg/ml

Molecular weight 145782.7 g/mol
No significant changes

Physicochemical properties

Liquid Chromatography HPLC/DAD

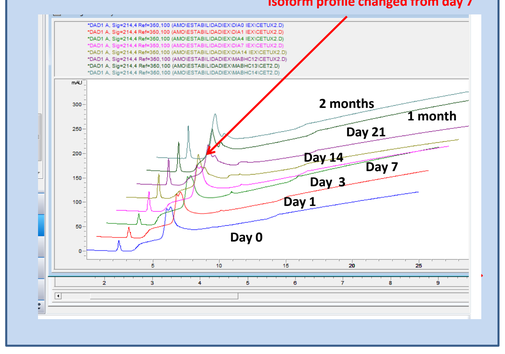
Size Exclusion [(SE)HPLC/DAD]

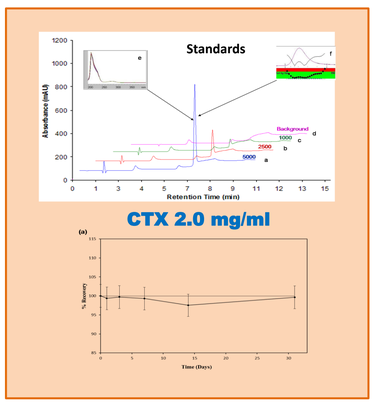


Weak Cation Exchange (WCE)HPLC/DAD

Reverse Phase (RP)HPLC/DAD Quantification

CTX 2.0 mg/ml in 0.9 % NaCl refrigerated at 4ºC





Results:

The decrease of biological activity was only 5 % after 24 hours the vial was open (5 mg/ml), raising 14% at day 3, 20% after a week, with a final decrease of 85% for the last control day (30 days). The overall quantity of CTX was unchanged for the month assessed. No aggregates formation was detected in the two weeks tested. Changes in the chromatographic isoforms profile (2 mg/ml) were detected after a week, with important isoforms variations from week 2 up to the end of the study (two months). Molecular weight indicated not major changes in the CTX structure (one month).

Conclusion:

Both the physicochemical and the biological properties assessed indicated good stability of the CTX within 24 hours after the vial was open. Even there was not an important decrease of the biological activity after a week of the opening of the medicine (20% decreased) with unchanged physicochemical properties for six days.

Authors declare no conflict of interest

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