TECHNOTE – STABILITY STUDIES

Shipment of CellGenix® Preclinical and GMP Cytokines at Ambient Temperatures

As we strive to provide our customers with the highest quality products suitable for clinical *ex vivo* processing of cells, we care greatly about safety and product reliability.

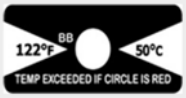
To ensure that the product quality of our CellGenix® cytokines is not compromised during shipment at ambient temperatures we have put a validated shipment procedure in place. As part of this procedure we implemented special temperature control measures and performed shipment stability studies.

Temperature Control Measures

In order to prevent extreme temperature peaks we include gel-packs in our standard packaging during the summer months (April to September) in Europe and throughout the year for overseas shipments. This gel-pack is not frozen and is not intended to keep the product cool. Instead, it serves as a temperature buffer to prevent extreme temperature peaks of more than +50°C which might arise in very rare occasions. **For this reason there is no quality defect when the gel-pack arrives at ambient temperature.**

For additional product safety, High Temperature Ascending (HTA) indicators are added to each cytokine package. The HTA indicator is an irreversible color-change label which helps to eliminate the risks of undetected exposure to critical temperatures[1] during shipment.

HTA indicator on the inner side of the cytokine box lid:



Indicator not activated
Temperature of +50°C was not exceeded ✓
Product safe for use ✓

Indicator activated
✘ Temperature of +50°C was exceeded
✘ Product might be compromised, contact CellGenix or local representative

Shipment Stability Studies

We performed stability studies at elevated temperatures to ensure that the product quality of our cytokines is not compromised by shipment at ambient temperatures. Exemplary test results are shown in figures 1 and 2 for the validation of our GMP grade SCF.

Test Conditions

Temperature conditions and associated exposure times during shipment were determined using temperature monitoring devices placed in our standard CellGenix packaging. These were shipped to several destinations in the USA, Asia and Europe. Temperatures never exceeded +50°C. To determine the effects beyond the worst case scenarios we included stability studies at +60°C for 16 hours and at +30°C for up to 6 weeks.

The following temperature conditions were included in the shipment stability studies:

Exposition time	Temperature
16 h	+60°C
16 h	+50°C

Exposition Time	Temperature
16 h	+40°C
24 h	+30°C

Exposition Time	Temperature
Untreated (t=0)	-
0-6 weeks	+30°C

[1] Temperatures above 50°C (122°F), which is the specified validated threshold up to which the cytokines temporarily can be exposed without being damaged

After incubation of the freeze-dried cytokines at elevated temperatures the activity and protein integrity were determined. Cytokine activity was determined by performing a proliferation assay of the respective cytokine. Protein integrity was determined by using SDS-PAGE (Coomassie stain).

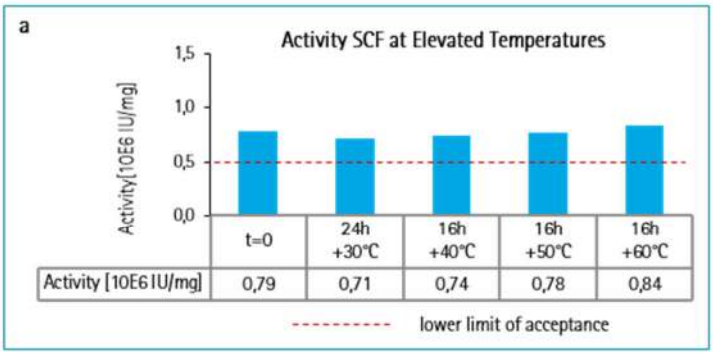


Fig 1: Stability study performed for CellGenix® GMP rh SCF (#1418LG23) to demonstrate that shipment at ambient temperatures does not compromise the product quality.
a) Activity was determined using SCF dependent TF-1 cells. b) Formation of oligomers was determined by SDS-PAGE.

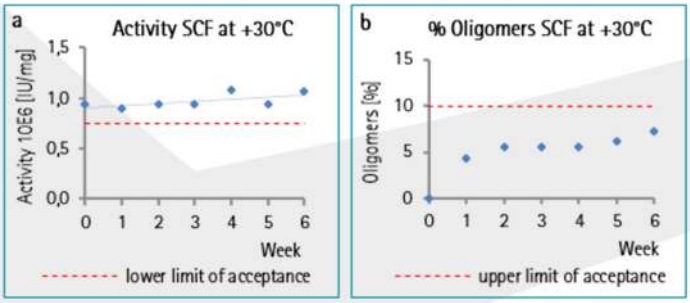


Fig 2: Stability study performed for CellGenix® GMP rh SCF (#1418JJ11) at +30°C to demonstrate that shipment at ambient temperatures does not compromise the product quality.
a) Activity was determined using SCF dependent TF-1 cells.
b) Formation of oligomers was determined by SDS-PAGE.

Conclusion

The product quality of our CellGenix® preclinical and GMP cytokines is not compromised by shipment in our standard packaging at ambient temperatures. The results of the associated stability studies confirm that all freeze-dried CellGenix® cytokines are stable at +50°C for at least 12 hours and at +30°C for at least 4 weeks.

Regulatory Excellence

CellGenix GMP products are based on three major quality standards:

- **Safety** - Safe and qualified raw materials in compliance with our animal-derived component-free and serum-free policy.
- **GMP Compliance** - Manufacturing and quality control following all applicable GMP guidelines to provide documented evidence of purity, potency, consistency and stability.
- **Regulatory Compliance & Support** – GMP products are manufactured, tested, released and distributed under an ISO 9001:2008 certified Quality Management System and allow for the safe use in accordance with USP Chapter <1043> and Ph. Eur. General Chapter 5.2.12. GMP cytokines are tested and released according to USP Chapter <92> as applicable.

We offer expert regulatory and technical support as well as FDA Drug Master Files for most of our products. Customized solutions can be provided to meet special compliance needs.

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