2nd part:
Friedrich Möll

- Critical steps & what could happen where
- Focus on Preparation & Administration
- Proposal for a Risk Assessment

Critical steps: what can happen where ?

Temperature:

High, Thaw-Freezing

Preparation:

Dilution, Pumping, Shearing, Shaking…..

Administration I:

Primary Packing material, Flushing, Filtration, Freezing…..

Administration II:

Location, Time, Co-medication, Patient….

- Chemical degradation(s)
- Aggregations

- Denaturation
- Adsorption: Association to surfaces as container walls, tubes ± denaturation
- Aggregation: reversible – not reversible
- Precipitation (macroscopic Aggregates) → *Particles* → *Source ?*

- Aggregation
- Interactions

Immunogenicity ?

Critical steps: Temperature control

Check of the receipt

- Check of the temp. device: are limits clear?
- Isolation of the box enough – for how long?
- Extreme climate conditions: summer – winter?

Validation of the fridges, temperature devices & -loggers:

- Validated fridge-room: hottest - coldest point → Documented validation
- Fridges on the ward: responsibility
- Fridges on the ward: min-max temperature dev.

Transportation to the ward:

- Validated transport boxes
- Max time from pharmacy to fridge on the ward

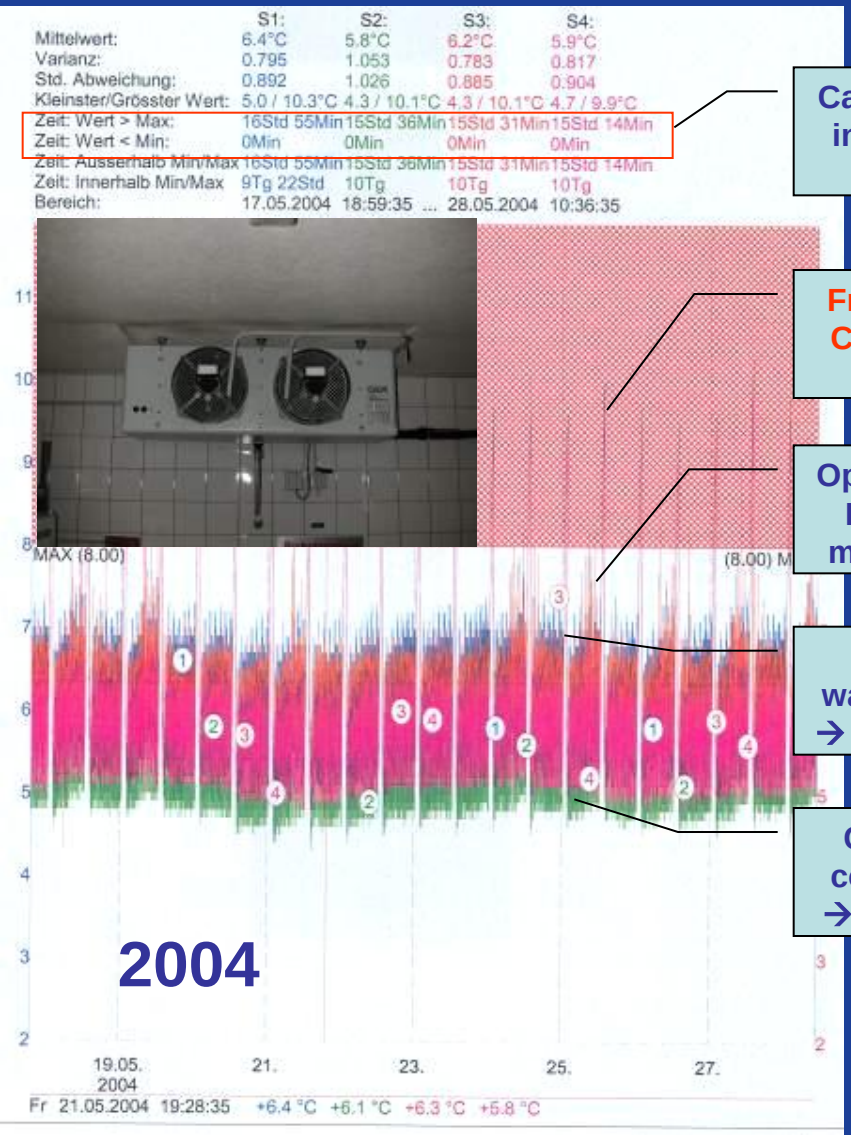
Critical steps: Temperature mapping I

Example:

Validation of a Fridge-Room in a Hospital Pharmacy:

- **WHO Guide to Good Storage Practices for Pharmaceuticals; 4.18:** "Temperature mapping should show uniformity of the temperature across the storage facility."

Critical steps: Temperature mapping II



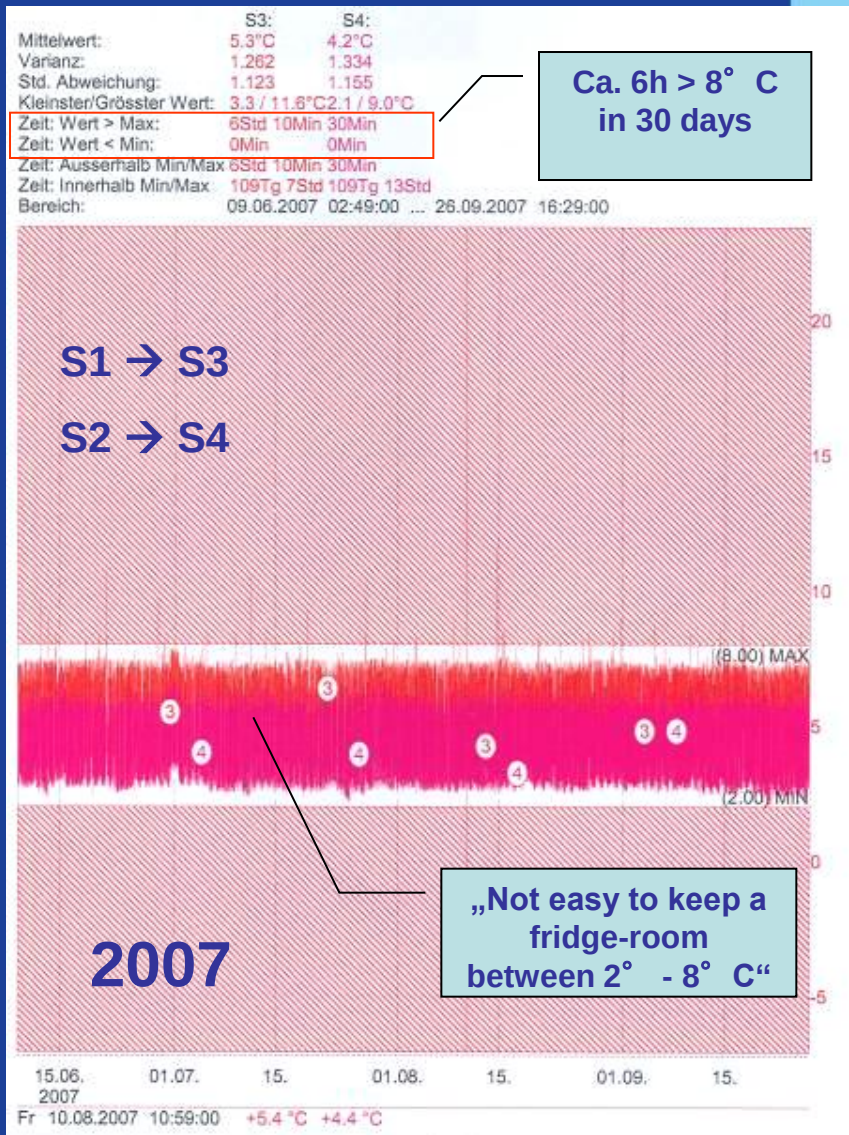
Ca. 16h > 8° C in 15 days → relevant ?

Freeze-Thaw-Cycles of the Cooler

Opening of the Door in the morning time

Blue (S1): warmest point → most critical

Green (S2): coldest point → less critical



Ca. 6h > 8° C in 30 days

„Not easy to keep a fridge-room between 2° - 8° C“

Critical steps: Cold Chain Supply Chain

Example:

Validation of transport boxes to the ward

For many years……

Walls to thin, cask cover to loose…..

Good fit of the cask cover. Most important: cool down in fridge without cask cover

Critical steps: Preparation

Preparation skills:

- **Where to prepare:**
  - Pharmacy
  - Ward
- **Who prepares - Know How:**
  - Of a hospital pharmacist
  - Of a nurse (with experience)
- **“….aseptic handling or technique”:**
  - Only possible with LF
  - “Normally on the ward”…..
- **Teaching:**
  - By Pharmaceutical Company ?
  - By Hospital Pharmacy ?

LF, lamina flow

Example: Remicade®
(Infliximab)

Clear description of the handling (UK):

- Instant use or delayed use → stability ?
- Preparation: direct the stream of the sterile Water to the glass of the vial…. → shear stress….
- Preparation: Avoid vigorous agitation.. Only gently swirling the solution…… reproducible done ?
- Filter: because of aggregates → really used ?

Question: is this really all done on all wards ?

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Use aseptic technique.

REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE solution required.
2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.
4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). Any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Example: Xolair®

(Omalizumab, E25)

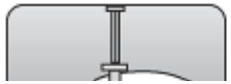
Clear description of the handling (UK):

- Instant use or delayed use → stability ? No preservatives
- Preparation: inject the SWFI directly onto the product
- Preparation: gently sweep the vial for approx. 1 minutes… do not shake…. reproducible done ?

Question: is this really all understood and done on all wards ?

1. Draw 1.4 mL of SWFI, USP, into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.

2. Place the XOLAIR vial upright on a flat surface and, using standard aseptic technique, insert the needle and inject the SWFI, USP, directly onto the product. Remove the syringe and needle from the vial.



Note: Some vials may take longer than 20 minutes to dissolve completely. If this is the case, repeat STEP 4 until there are no visible gel-like particles in the solution. It is acceptable to have small bubbles or foam around the edge of the vial. Do not use if the contents of the vial have not dissolved completely after 40 minutes.

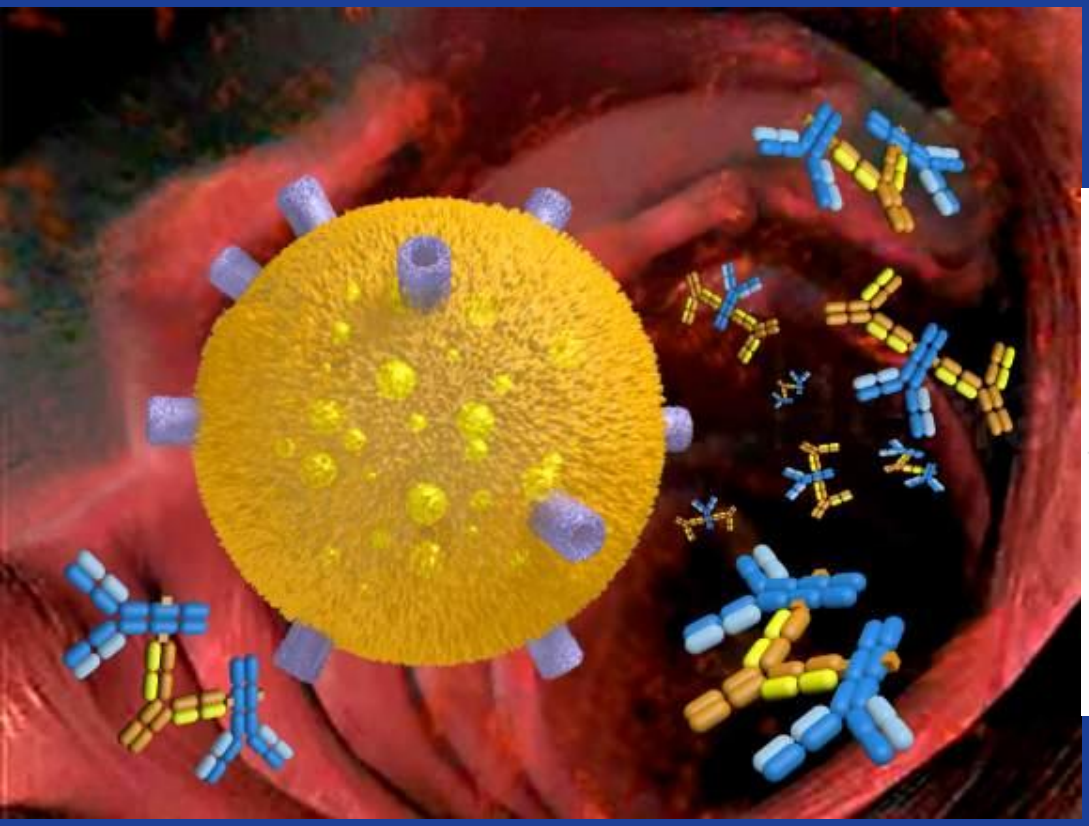
4. After completing STEP 3, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present.

Example: Xolair®

(Omalizumab; E25)

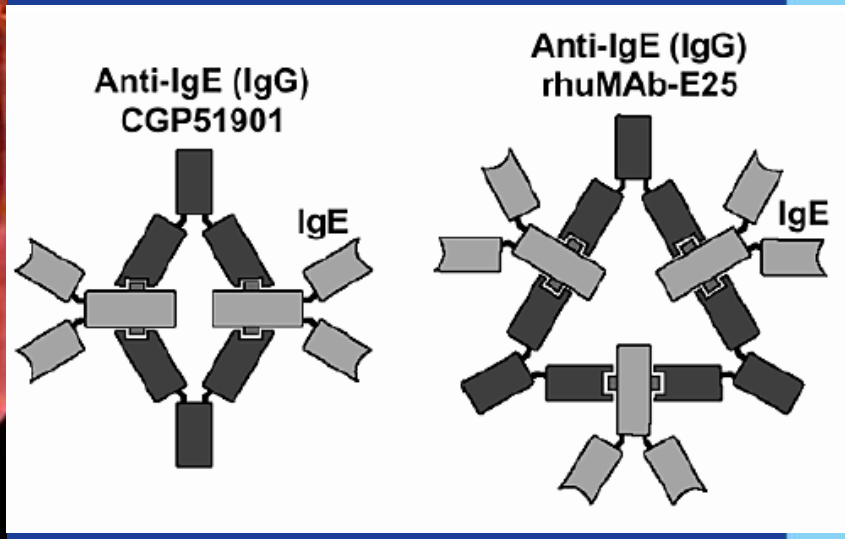
Problem:

- Aim: to obtain a very high concentrated protein solution: 75 – 150mg/ml = 7.5 - 15% !
- → High viscosity → shear stress shaking → Aggregation! → sc application



http://www.novartis.se/news/images/Xolairmodeofaction4.JPG

→ Formation of E25-IgE aggregates:



Chang, T.W. (2000) Nature Biotechnology 18, 157-162

sc, subcutaneous

Example: Xolair®

(Omalizumab; E25)

Problem:

- Risk of Anaphylaxis
- sc-Application

Xolair (omalizumab)

Audience: Pulmonary healthcare professionals, asthmatic patients

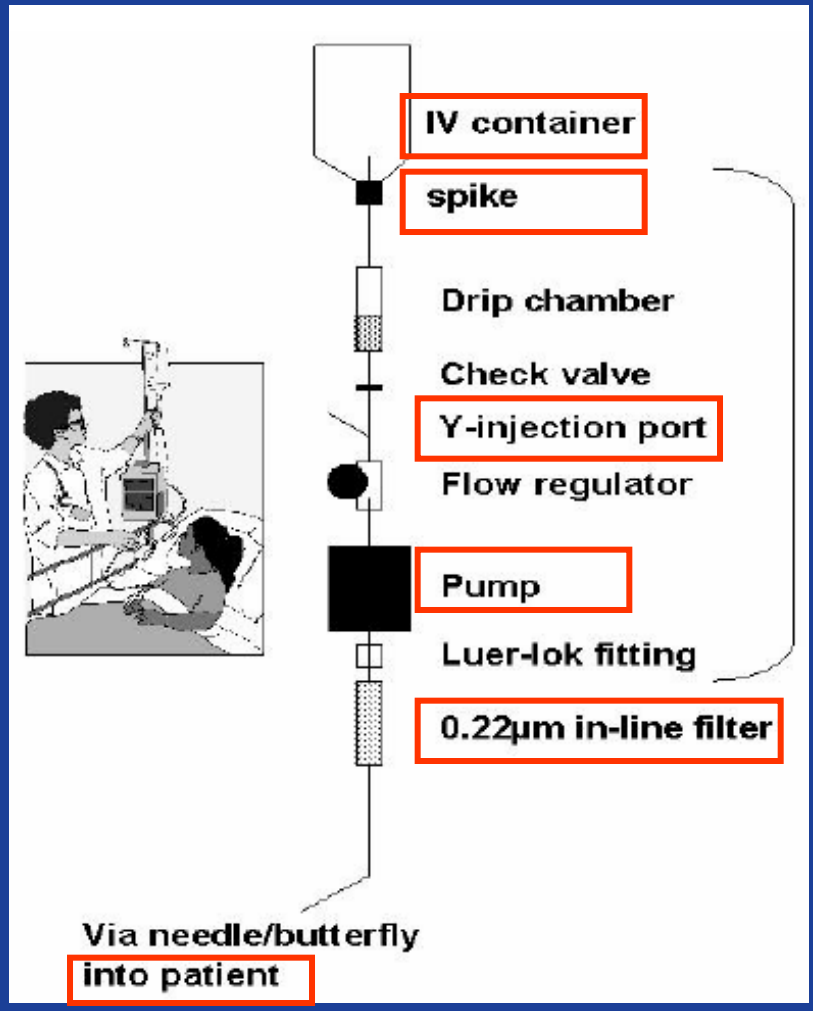
Indications and Usage: for treatment of adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

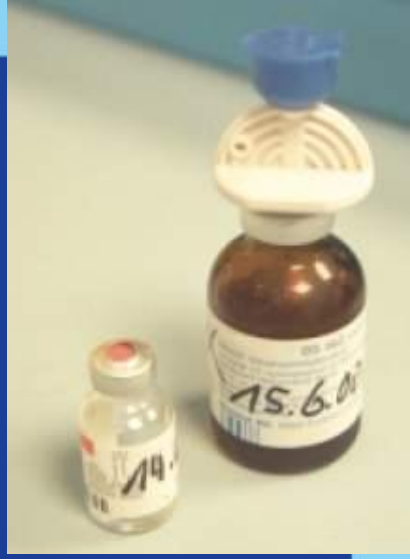
[UPDATE 07/02/2007] Genetech and FDA informed healthcare professionals and asthmatic patients that the prescribing information for Xolair was revised to include a new BOXED WARNING, and updated WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections that address the risk of anaphylaxis (the onset of action can be delayed for 24 hours or more) when taking this medication. In addition, a new MEDICATION GUIDE was developed and will be provided to patients when a prescription for Xolair is filled or refilled at the pharmacy. Due to the risk of anaphylaxis, Xolair should only be administered to patients in a healthcare setting under direct medical supervision. Patients should be observed for an appropriate period of time following each Xolair injection.

[Posted 02/21/2007] FDA notified asthmatic patients and healthcare professionals of new reports of serious and life-threatening allergic reactions (anaphylaxis) in patients after treatment with Xolair (omalizumab). Usually these reactions occur within two hours of receiving a Xolair subcutaneous injection. However, these new reports include patients who had delayed anaphylaxis—with onset two to 24 hours or even longer—after receiving Xolair treatment. Anaphylaxis may occur after any dose of Xolair (including the first dose), even if the patient had no allergic reaction to the first dose. Health care professionals who administer Xolair should be prepared to manage life-threatening anaphylaxis and should observe their Xolair-treated patients for at least two hours after Xolair is given. Patients under treatment with Xolair should be fully informed about the signs and symptoms of anaphylaxis, their chance of developing delayed anaphylaxis following Xolair treatment, and how to treat it when it occurs. FDA has requested Genentech add a boxed warning to the product label and to revise the Xolair label and provide a MEDICATION GUIDE for patients to strengthen the existing warning for anaphylaxis.

Critical steps: Administration

- Stability after opening & reconstitution ?
  - Microbiological stability
  - Physico-chemical-stability (temp., light)
- Particles: sources ?
- Concomitant medication:
  - Mixing with solutions for infusions ?
  - Y-site co-administration ?
- Compatibility / Adsorption to administration material
- Physical instabilities due to mechanical (pump) stress, syringes, Foaming (bubbles)
- In-line “safety-filters” ?





Critical steps:

Microbiological stability after first opening:

- Multiple use: preservation necessary
- Single use: no preservation necessary:
  - *„From a microbiological point of view, unless the method of opening, reconstitution, dilution preludes the risk of microbial contamination,* ***the product should be used immediately****. If not used immediately, in-use storage times and conditions are the* ***responsibility of the user*** *and would normally not longer than* ***24 hours at 2 to 8° C****, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions. (...)"„EMEA NfG (CPMP/QWP/159/96)*
  - ***Under aseptic conditions in a clean room with LF → longer microbial stability is possible → time limiting step will be the chemical stability → cost savings…..***
  - Often to be used within hours at RT or within 24h at 2 – 8° C:
    - Infliximab (Remicade®): 3h at RT
    - Adalimumab (Humira®): - (Pre filled Pen: refrigerated up to the exp date)
    - Etanercept (Enbrel®): - / multi use with benzylalkohol: up to 14d: only US
    - Apatacept (Orencia®): 24h at 2° - 8° C

Critical steps: Off-label Preparations I

Example:

- Tailor made preparation with **Bevacizumab (Avastin ®)** for maculadegeneration
- Reason: costs of a dose Bevacizumab approx. 1/10 of Ranibizumab (Lucentis ®)

SIX-MONTH STABILITY OF BEVACIZUMAB (AVASTIN) BINDING TO VASCULAR ENDOTHELIAL GROWTH FACTOR AFTER WITHDRAWAL INTO A SYRINGE AND REFRIGERATION OR FREEZING

SOPHIE J. BAKRI, MD,* MELISSA R. SNYDER, PHD,†
JOSE S. PULIDO, MD, MS, MPH,* COLIN A. MCCANNEL, MD,*
WILLIAM T. WEISS, RPH,‡ RAVINDER J. SINGH, PHD†

Purpose: To determine the change in anti–vascular endothelial growth factor (VEGF) activity of bevacizumab (Avastin, Genentech, Inc., San Francisco, CA) after refrigeration or freezing.

Methods: Samples of bevacizumab were drawn up from new vials into plastic tuberculin syringes and refrigerated at 4°C for 1 week, 3 weeks, 1 month, 3 months, and 6 months. The vials and syringes were stored at 4°C, and the syringes were capped with a needle. One syringe was frozen at −10°C. The bevacizumab concentration was measured, via its binding to VEGF-165.

Results: The percentage of degradation of bevacizumab in the previously pierced vials stored at 4°C compared with that in the unpierced vial was 9.6% at 3 months and 12.7% at 6 months. The bevacizumab drawn into the syringe and stored at 4°C was degraded by 1.6% at 1 week, 0% at 3 weeks, 8.8% at 3 months, and 15.9% at 6 months. The bevacizumab frozen in a syringe at −10°C was degraded by 12.0% at 6 months.

Conclusion: The anti-VEGF activity of bevacizumab may degrade minimally over time, with storage.

RETINA 26:519–522, 2006

Anti-permeability and anti-proliferative effects of standard and frozen bevacizumab on choroidal endothelial cells

Swaantje Peters [1*], Sylvie Julien [1], Peter Heiduschka [1], Salvatore Grisanti [1], Focke Ziemssen [1], Martin Adler [1], Ulrich Schraermeyer [1], Karl U. Bartz-Schmidt [1] and The Tuebingen Bevacizumab Study Group [1]

Br J Ophthalmol. Published Online First: 19 December 2006. doi:10.1136/bjo.2006.109702
Copyright © 2006 by the BMJ Publishing Group Ltd.

Background: Bevacizumab is an anti-angiogenic compound developed to target tumor vessels. Off-label use in ophthalmology requires in vitro testing on ocular cells. Consequently we quantified the anti-permeability and anti-proliferative effect of bevacizumab on cultured choroidal endothelial cells. It was examined whether deep-freezing of bevacizumab attenuates its anti- angiogenic activity.

Methods: Porcine choroidal endothelial cells (CEC) were cultured in permeable insert systems. Permeability of the cell monolayers was quantified in an FITC-dextran assay after treatment with VEGF (20-100 ng/ml) alone and in combination with bevacizumab (0.1 & [minus]1 mg/ml). Proliferation of the CEC was tested using a wound scratch assay. The experiments were repeated with bevacizumab after -20C freezing for 5 days.

Results: Bevacizumab significantly reduced VEGF- induced permeability in a dose dependant manner. A molar ratio of 2.6:1 of bevacizumab to VEGF was required for complete blocking of VEGF-induced rise in permeability. CEC proliferation was significantly blocked by bevacizumab (0.5 mg/ml). Thawed bevacizumab after deep- freezing showed a moderate, but statistically not significant loss in activity.

Conclusion: Bevacizumab significantly reduces VEGF-induced permeability and proliferation of choroidal endothelial cells. Freezing and thawing of bevacizumab will affect its biological activity.

Critical steps: Off-label Preparations III

Example:

- Tailor made preparation with **Botulinus Toxin Type A (Botox®)**
- Reason: aliquots of 10UI for treatment of “cross-eyed” children

Clinical Efficacy of Botulinum Toxin Type A Reconstituted and Refrigerated 1 Week before Its Application in External Canthus Dynamic Lines

Mónica Lizarralde, MD,* Sara Helena Gutiérrez, MD,† and Adriana Venegas, MD†

BACKGROUND Allergan Inc. recommends that its botulinum toxin type A (BTX-A; BOTOX) must be refrigerated and applied within 4 hours after its reconstitution to avoid losing its biologic effectiveness.

OBJECTIVE The objective was to compare clinical efficacy in treating external canthus dynamic lines with reconstituted and refrigerated toxin (BTX-A) 1 week before its application versus fresh toxin (BTX-A).

METHODS This study was a double-blind, randomized, clinical trial. A total of 30 patients aged 30 to 60 years having a minimum of one and maximum of six external canthus dynamic lines were treated in one canthus with 15 U of BTX-A reconstituted and refrigerated at 4°C 1 week before being applied and in the other with 15 U of fresh BTX-A. Patients were followed-up on Day 10 and Weeks 6, 12, and 18; assessment included a neuroconduction study of the facial nerve and the investigators' photographic evaluation of the number of external canthus dynamic lines at maximum smile.

RESULTS Outcome measurement did not show statistically significant differences between both groups.

CONCLUSION BTX-A, reconstituted and refrigerated 1 week before its application, has similar clinical efficacy in treating external canthus dynamic lines as does fresh BTX-A.

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ISSN: 1076-0512 • Dermatol Surg 2007;33:1–6 • DOI: 10.1111/j.1524-4725.2007.33284.x

Multicenter, Double-Blind Study of the Efficacy of Injections With Botulinum Toxin Type A Reconstituted Up to Six Consecutive Weeks Before Application

Doris Maria Hexsel, MD,* Ada Trindade de Almeida, MD,† Marcio Rutowitsch, PhD,* Inês Alencar de Castro, MD,‡ Vera Lúcia Bauer Silveira, MD,* Daniela Orso Gobatto, MD,‡ Mônica Zechmeister, MD,* Rosemari Mazzuco, MD,* and Dêbora Zechmeister, Pharm*

*Private Clinic, ‡Hospital dos Servidores do Estado (HSE-RJ/MS), and †Hospital do Servidor Publico Municipal de São Paulo, Brazil

BACKGROUND. It is recommended that botulinum toxin be used immediately or within 2 weeks after its reconstitution because its efficacy might be compromised by prolonged storage.

OBJECTIVES. To evaluate the efficacy of botulinum toxin type A (BTX-A) reconstituted over 6 consecutive weeks for the treatment of glabellar frown lines.

METHODS. Four vials of BTX-A were reconstituted each of 7 days over a period of 6 weeks, totaling 28 vials, corresponding to seven reconstitution dates. During this period, the BTX-A was stored according to the manufacturer's instructions. On the day after the last reconstitution, all of the reconstituted vials were injected in patients from four dermatologic centers taking part in this study. A total of 88 patients were treated on the same day and were followed every 2 weeks for 4 months. All patients were photographed at all stages. A number of professionals assessed the efficacy of reconstituted BTX-A based on the reduction of the maximum frowning capacity of the treated muscles.

RESULTS. Of the 88 patients who were selected, 3 were excluded. Three forms of evaluation were applied, and no statistically significant differences were found in the results presented.

CONCLUSION. BTX-A may be applied up to 6 weeks after reconstitution without losing its effectiveness. Other factors, which are probably individual, may influence the response to BTX-A injections.

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ISSN: 1076-0512/03/$15.00/0 • Dermatol Surg 2003;29:523–529

Recommend shrinking the graphs and moving the callout box down

Critical steps: altered Preparations I

Example:

Working steps: Freeze-Thaw cycles

Pikal-Cleland K.A. et al.;

J Pharm Sci 91, 9 (2002) 1969 - 1979

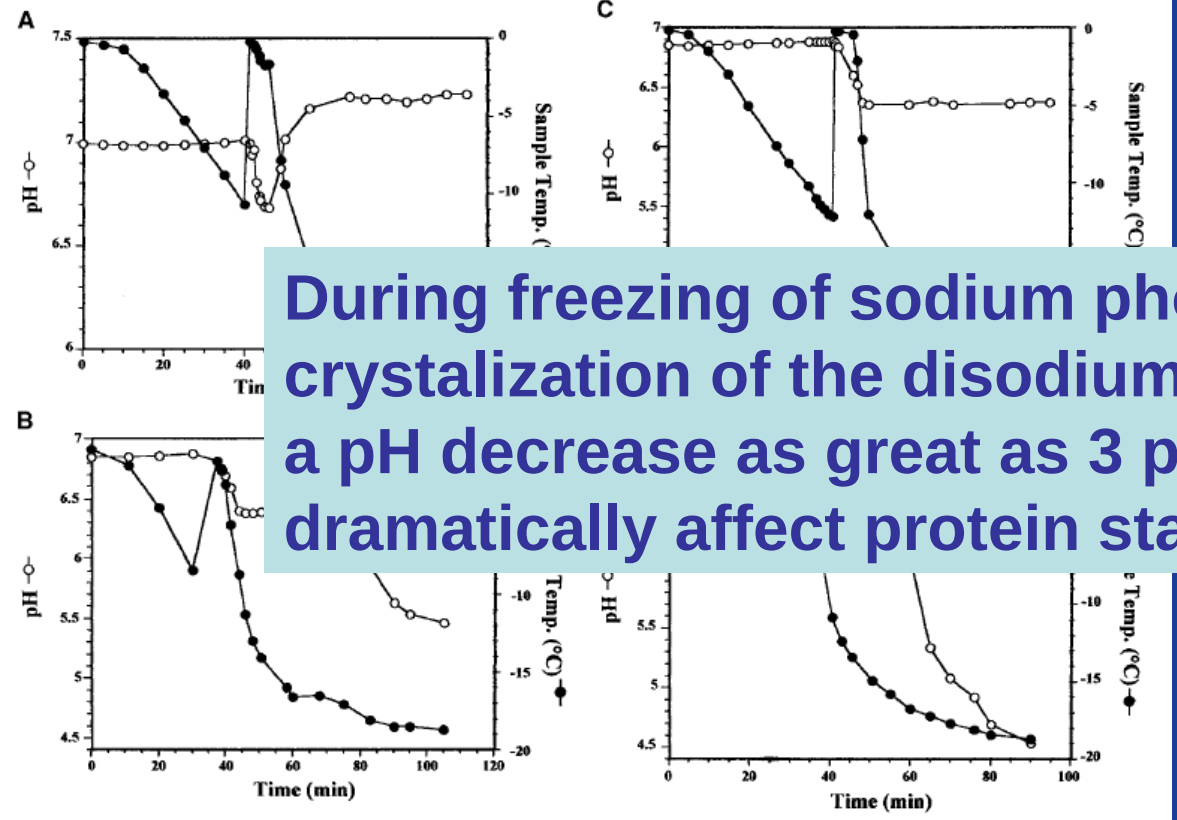


Figure 1. pH (○) and temperature (●) changes during freezing in different phosphate buffers with and without glycine. (A) 10 mM KP, (B) 10 0mM NaP, (C) 10 mM NaP and 50 mM glycine, and (D) 10 mM NaP and 100 mM glycine.

During freezing of sodium phosphate solutions, crystalization of the disodium salt can produce a pH decrease as great as 3 pH units which can dramatically affect protein stability.

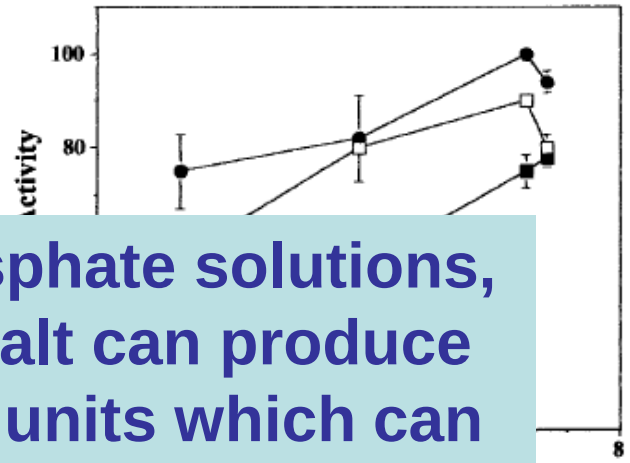


Figure 4. Effect of pH changes during freezing on protein stability. Data for monomeric β-gal (□) and tetrameric β-gal (■) are from Pikal-Cleland et al.[1] Another tetrameric protein, LDH (●), was also assessed for recovery of activity after freeze–thawing. Freeze–thawing was performed in phosphate buffers with an initial pH of 7.0. The pH of each frozen solution was measured: 10 mM sodium phosphate (NaP) frozen pH 5.5, 100 mM NaP frozen pH 3.8, 10 mM potassium phosphate (KP) frozen pH 7.1, and 100 mM KP frozen pH 7.3.

Critical steps: altered Preparations II

Example:

Working steps:
Freeze & Thaw cycles

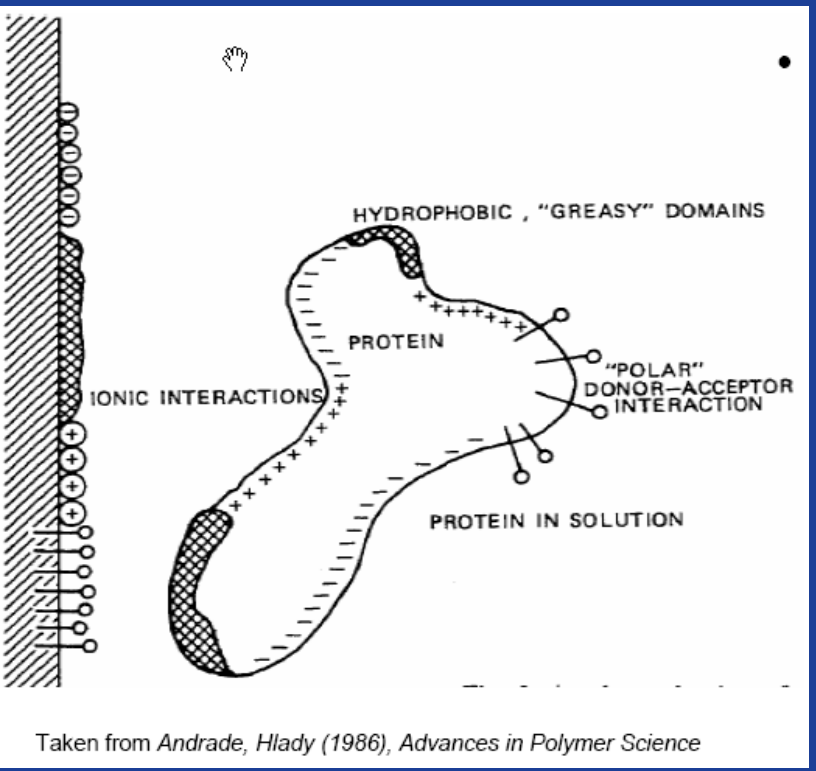
Figure 2: Fluorescence photographs of aggregates of a therapeutic protein stained with Nile red. In Formulation 1 (above; T=0, 1 freeze-thawing, 5 freeze-thawing) the protein aggregated strongly after freeze-thawing cycles. In Formulation 2 (below; T=0, 1 freeze-thawing, 5 freeze-thawing) the protein was stable regarding aggregation after 5 freeze-thawing cycles. The bar in a) represents 300 µm; all figures are at the same magnification. The Nile red fluorescence staining of aggregates and microscopy procedures were similar to those published in Ref. [8].

Arvinte T.;
Formulation for Protein Drugs – Important Points to Consider
Bio World Europe 01 – 2007, 6 - 9

Critical steps: Preparation

Example:

- Physical instability problems of proteins in general: adsorption & aggregation



Taken from *Andrade, Hlady (1986), Advances in Polymer Science*

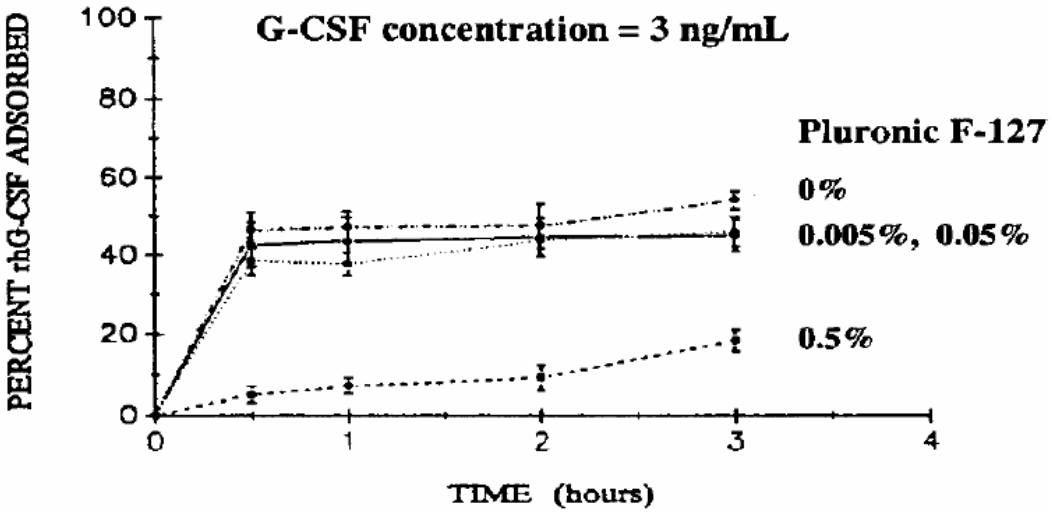


Figure 6—Effect of Pluronic F-127 on the adsorption of rhG-CSF to polyvinyl chloride. — Dextrose 5% in water (D5W); –·–·– 0.005% w/w; ---- 0.05% w/w; ···· 0.5% w/w. Each symbol represents the mean value ± standard deviation for three infusion bags.

From Johnston, T.P. (1996) PDA J. Pharm. Sci, 50, 238

Mahler H.C. et al.; Biopharmazeutika; Krankenhauspharmazie 26 (2005) 303 - 311

Critical steps: Stability data

Tab. 3. Hinweise zur Anwendung sowie publizierte Daten zur physikalisch-chemischen Stabilität ausgewählter Biopharmazeutika

Fertigarzneimittel		Stammlösung				Applikationsfertige Lösung			Bemerkungen zum Fertigarzneimittel
INN (Handelsname)	Gehalt [mg]	Rekonstituens	Menge [ml]	Konz. [mg/ml]	Physikalisch-chemische Stabilität	Trägerlösung	Physikalisch-chemische Stabilität	Hinweise zur Applikation	
Agalsidase alfa (Replagal)	1 3,5	– –	(1) (3,5)	1	Keine Angabe [13][1]	NaCl 0,9 % Nach der Verdünnung Lösung vorsichtig mischen, nicht schütteln [13].	24 h bei RT [13]	Applikation über Infusionssystem mit integriertem Filter[2] [13]	–
Alteplase (Actilyse®)	10 20 50	Aqua ad inject.	5–10 10–20 25–50	1–2	8 h bei 2–8 °C 8 h bei RT [6] 48 h bei 2–8 °C 6 m bei –20 °C [3]	NaCl 0,9 % Minimalkonzentration 0,2 mg/ml, ansonsten Gefahr der Präzipitation (zu starke Verdünnung des Lösungsvermittlers Arginin). Nicht schütteln [6].	Keine Angabe [6] 1 Jahr bei –70 °C [18]	Mit einer Kanüle mit großem Durchmesser (z. B. 18G) das Lösungsmittel direkt auf das Lyophilisat spritzen. Zum Lösen schwenken, nicht schütteln. Lösung anschließend zum Entschäumen ein paar Minuten stehen lassen [20].	Zum Schutz vor Licht in der Originalpackung aufbewahren [6].
Basiliximab (Simulect®)	10 20	Aqua ad inject. Zum Auflösen leicht schütteln [14].	2,5 5	4	24 h bei 2–8 °C 4 h bei RT [14]	NaCl 0,9 % o. Glucose 5 % –	Keine Angabe [14]	–	–
Bevacizumab (Avastin®)	100 400	–	(4) (16)	25	Keine Angabe [7][1]	NaCl 0,9 % –	48 h bei 2–8 °C 48 h bei RT [7]	–	Zum Schutz vor Licht in der Originalpackung aufbewahren. Nicht einfrieren. Nicht schütteln. Inkompatibel mit Glucose 5 % [7]
Cetuximab (Erbitux®)	100	–	(50)	2	24 h bei 2–8 °C 20 h bei RT [10][1]	– Unverdünnte Applikation via 0,2 µm In-line-Filter [10]	–	–	Nicht einfrieren [10].
Daclizumab (Zenapax®)	25	–	(5)	5	Keine Angabe [17][1]	NaCl 0,9 % Zum Mischen Beutel vorsichtig mehrere Male drehen, nicht schütteln [1].	24 h bei 2–8 °C 4 h bei RT [17]	–	Zum Schutz vor Licht in der Originalpackung aufbewahren. Nicht einfrieren. Nicht schütteln [17].

[1] Mikrobiologische Standzeit in der Verantwortung des Anwenders.
[2] Ohne Angabe der Porengröße [13], in klinischer Prüfung war Einsatz von 0,2-µm-Filtern vorgeschrieben

Tab. 3. Fortsetzung

Fertigarzneimittel		Stammlösung				Applikationsfertige Lösung			Bemerkungen zum Fertigarzneimittel
INN (Handelsname)	Gehalt [mg]	Rekonstituens	Menge [ml]	Konz. [mg/ml]	Physikalisch-chemische Stabilität	Trägerlösung	Physikalisch-chemische Stabilität	Hinweise zur Applikation	
Drotrecogin alfa (Xigris)	5 20	Aqua ad inject. Aqua langsam in das Glas geben, vorsichtig schwenken, nicht schütteln! Konzentrat langsam entnehmen [16].	2,5 10	2	3 h bei RT [16]	Ausschließlich NaCl 0,9 % Beim Zuspritzen Flüssigkeitsstrom an die Beutelwand richten, um Durchwirbeln der Lösung zu minimieren. Zum Transport keine automatischen Auslieferesysteme verwenden [16].	14 h bei RT [16] 12 h bei 2–8 °C + 12 h RT [20]	–	Zum Schutz vor Licht in der Originalpackung aufbewahren [16]. Nicht einfrieren [20].
Epoetin alfa (Eprex®)	1 000 I. E.	–	(0,5)	2 000 I. E./ml	Keine Angabe [9][1] 14 d bei 2–8 °C 14 d bei RT [20]	NaCl 0,9 % Konz. 1 000 I. E./ml [20]	Keine Angabe [9]	Keine Angabe	Zum Schutz vor Licht in Originalpackung aufbewahren. Nicht einfrieren. Nicht schütteln. Max 60 min. bei RT aufbewahren [9].
Etanercept (Enbrel®)	25	Aqua ad inject. Nicht verwenden, wenn sich das Pulver nicht innerhalb von 10 min. gelöst hat [8]. Aqua sehr vorsichtig zum Lyophilisat geben, vorsichtig schwenken, nicht schütteln. Nicht filtern [20].	1	25	6 h kühl [8] 21 d bei 2–8 °C 24 h bei RT [20]	–	–	–	Nicht einfrieren [8]. Kann bis zu 24 h bei RT gelagert werden [20].
Infliximab (Remicade)	100	Aqua ad inject. Aqua mit Kanüle (max. 21 G) entlang der inneren Wand der Durchstechflasche zuspritzen. Zum Lösen vorsichtig schwenken, nicht schütteln. Nach dem Lösen 5 min. stehen lassen [12].	10	10	Keine Angabe [12]	NaCl 0,9 % Konzentration 0,4–4,0 mg/ml einhalten [20].	24 h bei 2–8 °C [12]	Applikation über ≤ 1,2 µm Filter mit geringer Proteinbindungskapazität [12]	Nicht einfrieren [12].
Palivizumab (Synagis™)	50 100	Aqua ad inject. Aqua LANGSAM entlang der inneren Wand der Durchstechflasche zuspritzen, 30 sek. leicht schwenken, nicht schütteln. 20 min. stehen lassen [15]	0,6! 1	100	3 h ohne Temperaturangabe [15] 2 Jahre bei 2–8 °C [20]	Entfällt	Entfällt	–	Nicht einfrieren [15]. Kurzzeitiges Einfrieren hat nur geringe Auswirkung auf Stabilität. Bei RT max. 3 Tage stabil [20].
Reteplase (Rapilysin® 10 U)	10 U	Aqua ad inject. Nach der Rekonstitution Sichtkontrolle, nicht klare oder nicht farblose Lösungen verwerfen. Nicht schütteln.	10	1 E/ml	Sofort verwenden [11]. 4 h bei 2–8 °C 4 h bei RT [25]	Entfällt	Entfällt	–	Zum Schutz vor Licht in der Originalpackung aufbewahren [11].

Recommend keeping the slide but deleting the stabil – liste (mention this in the notes)

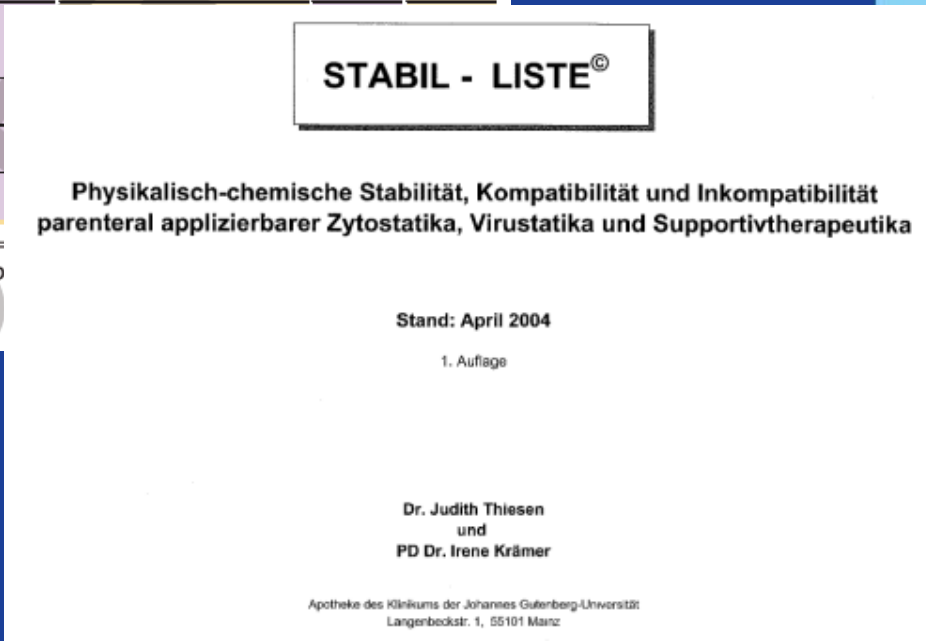
Critical steps: Stability data

Generic name	Brand name	Storage temperature	Stability RT	Stability Refs.	Reconstitution solution	Stability after reconstitution RT	Stability after reconstitution Refs.
Adalimumab	Humira®	2–8°C	NA	ex da	RTU	NA	NA
Darbepoetin Alfa	Aransep®	2–8°C	NA	ex da	RTU	NA	NA
Epoetin alfa	Epogen®, Procrit®	2–8°C	14 d	21 d aie, mdv	RTU	NA	NA
Etanercept	Enbrel®	2–8°C	NA	ex da	dil (SBWFI)	NA	14 d
Glatiramer acetate	Copaxone®	2–8°C	7 d	ex da	RTU	NA	NA
Interferon-β1a prefilled syringe	Avonex®, Rebif®	2–8°C	12 h	ex da	RTU	NA	NA
Interferon-β1a Reconstitutable vial	Avonex®, Rebif®	2–8°C	30 d	ex da			
Interferon-β1b	Betaseron®	25°C	ex da	NA			
Pegfilgrastim	Neulasta®	2–8°C	48 h	ex da			
Trastuzumab	Herceptin®	2–8°C	NA	ex da			

Abbreviations: aie=after initial entry into vial; d= days; dil sol=once in diluted solution; dil= ex da= h= not applicable/not available; Refs.= room temperature; RT= RTU=Ready to use; SBWFI= see exp injection; sterile water for injection; supplied diluent; SWFI= under refrigeration.

Table 3 ■ Storage, Stability, and Reconstitution of Selected Biotechnology Products

Biopharmaceutical Biotechnology; Edited by Daan JA Crommelin and Robert D Sindelar; 3nd Edition – in press



STABIL - LISTE©

Physikalisch-chemische Stabilität, Kompatibilität und Inkompatibilität parenteral applizierbarer Zytostatika, Virustatika und Supportivtherapeutika

Stand: April 2004

1. Auflage

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Example: Sources of particles ?

- From the Formulation (protein, excipients) or stoppers ?
- Monograph “Parenteral Preparations” (PhEur 2.9.19): ……..clear and practically free from (visible) particles:
  - **SVP (≤ 100ml): max. 6000 ≥ 10 µm / max. 600 ≥ 25 µm per container**
  - **LVP (> 100ml): max. 25 ≥ 10 µm / max 3 ≥ 25 µm per ml**

PS: visible aggregates (from about 50µm) = precipitate

SVP, small volume parentals; LVP, large volume parentals

pergierens ist die Aggregatbildung von Partikeln zu vermeiden.

Allgemeine Vorsichtsmaßnahmen

Die Prüfung wird unter Bedingungen, vorzugsweise in einer Laminarflow-Einheit, durchgeführt, die eine zusätzliche Kontamination mit Partikeln begrenzen.

Die verwendeten Glas- und Filtrationsgeräte, mit Ausnahme der Membranfilter, werden mit warmer Detergens-Lösung gewaschen und mit reichlich Wasser gespült, um alle Detergens-Rückstände zu entfernen.

Unmittelbar vor der Verwendung wird die Glasapparatur außen und anschließend innen, von oben nach unten, mit partikelfreiem Wasser *R* gespült.

Das Einbringen von Luftbläschen in die Prüfzubereitung ist zu vermeiden, besonders während ein Teil der Zubereitung in das Gefäß, in dem die Bestimmung durchgeführt werden soll, überführt wird.

Um zu überprüfen, ob die Umgebung für die Prüfung geeignet ist, die Glasapparaturen ordnungsgemäß gesäubert wurden und das verwendete Wasser partikelfrei ist, wird die folgende Prüfung durchgeführt:

Die Partikelkontamination von 5 Proben zu je 5 ml partikelfreiem Wasser *R* wird nach der im Folgenden beschriebenen Methode ermittelt. Wenn die Anzahl der Partikel, die 10 µm groß oder größer sind, für die gesamten 25 ml mehr als 25 beträgt, sind die für die Prüfung der Probe getroffenen Vorsichtsmaßnahmen unzureichend. Die Vorbereitungen müssen so lange wiederholt werden, bis Umgebung, Glasapparaturen und Wasser sich für die Prüfung als geeignet erweisen.

Methode

Der Inhalt der Probe wird durch langsames, aufeinander folgendes 20-maliges Umkehren des Behältnisses gemischt. Falls erforderlich wird der versiegelte Verschluss vorsichtig entfernt. Die äußere Oberfläche der Behältnisöffnung wird mit einem Strahl von partikelfreiem Wasser *R* gesäubert und der Verschluss entfernt, wobei jegliche Kontamination des Inhalts zu vermeiden ist. Gasbläschen werden durch geeignete Maßnahmen wie 2 min langes Stehenlassen oder Einwirken von Ultraschall entfernt.

Bei Parenteralia mit großem Volumen werden einzelne Einheiten geprüft. Bei Parenteralia mit kleinem Volumen von weniger als 25 ml wird der Inhalt von mindestens 10 Einheiten in einem gereinigten Gefäß vereinigt, um ein Volumen von mindestens 25 ml zu erhalten. In begründeten und zugelassenen Fällen kann die Untersuchungslösung hergestellt werden, indem der Inhalt einer geeigneten Anzahl Durchstechflaschen gemischt und mit partikelfreiem Wasser *R* oder, wenn dieses nicht geeignet ist, mit einem geeigneten partikelfreien Lösungsmittel zu 25 ml verdünnt wird. Parenteralia mit kleinem Volumen von 25 ml und mehr können einzeln geprüft werden.

Pulver zur Herstellung von Parenteralia werden mit partikelfreiem Wasser *R* oder, falls dieses nicht geeignet ist, mit einem geeigneten partikelfreien Lösungsmittel rekonstituiert.

Die Anzahl der Proben muss ausreichend sein, um eine statistisch gültige Auswertung zu ermöglichen. Im Falle von Parenteralia mit großem Volumen oder von Parenteralia mit kleinem Volumen von 25 ml und mehr können weniger als 10 Einheiten geprüft werden, wenn ein geeigneter Stichprobenplan zu Grunde gelegt wird.

4 Anteile von je mindestens 5 ml der Probe werden geprüft. Die Anzahl der Partikel, die 10 µm groß oder größer sind, und die Anzahl der Partikel, die 25 µm groß oder größer sind, werden bestimmt. Das mit dem ersten Anteil der Probe erzielte Ergebnis wird nicht berücksichtigt und die mittlere Anzahl der Partikel der zu prüfenden Zubereitung berechnet.

Auswertung

Bei Zubereitungen in Behältnissen mit einem Nennvolumen von mehr als 100 ml werden die Kriterien der Prüfung 1.A angewendet.

Bei Zubereitungen in Behältnissen mit einem Nennvolumen von weniger als 100 ml werden die Kriterien der Prüfung 1.B angewendet.

Bei Zubereitungen in Behältnissen mit einem Nennvolumen von 100 ml werden die Kriterien der Prüfung 1.B angewendet.

Liegt die mittlere Anzahl der Partikel über den Grenzwerten, wird die Zählung der Partikel unter dem Mikroskop durchgeführt.

Prüfung 1.A: Infusions- und Injektionszubereitungen in Behältnissen mit einem Nennvolumen von mehr als 100 ml

Die Zubereitung entspricht der Prüfung, wenn in den geprüften Einheiten die mittlere Anzahl der Partikel, die 10 µm groß oder größer sind, höchstens 25 je Milliliter und die mittlere Anzahl der Partikel, die 25 µm groß oder größer sind, höchstens 3 je Milliliter betragen.

Prüfung 1.B: Infusions- und Injektionszubereitungen in Behältnissen mit einem Nennvolumen von weniger als 100 ml

Die Zubereitung entspricht der Prüfung, wenn in den geprüften Einheiten die mittlere Anzahl der Partikel, die 10 µm groß oder größer sind, höchstens 6000 je Behältnis und die mittlere Anzahl der Partikel, die 25 µm groß oder größer sind, höchstens 600 je Behältnis betragen.

Methode 2: Partikelzählung unter dem Mikroskop

Ein geeignetes Binokularmikroskop und ein Filtrationsgerät mit Membranfilter, um die kontaminierenden Partikel zurückzuhalten, werden verwendet.

Das Mikroskop ist ausgestattet mit einem Okularmikrometer, das mit Hilfe eines Objektmikrometers kalibriert wird, und einem mechanischen Objekttisch als Auflage für das Membranfilter, um dessen Oberfläche nach zurückgehaltenen Partikeln abzusuchen. Das Mikroskop ist ferner mit 2 geeigneten Lampen versehen, wovon die eine für die Beleuchtung von oben, die andere für die Beleuchtung von schräg seitwärts sorgt. Eine 100 ± 10fache Vergrößerung wird eingestellt.

Im Okularmikrometer (siehe Abb. 2.9.19-1) ist ein großer Kreis sichtbar, der durch ein Fadenkreuz in Vier-

Critical Steps: “Equal handling” ?

Education

Education

Education

Risk of false handling

Critical Steps: “Aseptic technique” ?

Examples from Links of „Home Infusion Therapies….“ (US)

„Aseptic manufacturing in a clean room……..“

http://www.columbinehealth.com/poudreinfusion/Mvc-017f.jpg

„Aseptic manufacturing under really „clean control“……..“

http://www.blountmemorial.org/images/pharmweb6.jpg

Critical Steps: Risk Classification I

Proposal:

Risk Factor	„Weighting“	Risk Level
Cold Chain (Temperature)	„normal cold chain“: ≥ 24h at RT	I
	„strong cold chain“: < 24h at RT	II
	„very strong cold chain“: < 2h at RT	III
Handling	„simple handling“: no special requirements	I
	„special handling“: stability lim. after reconst.	II
	„handling only in pharmacy“: special req.	III
Patient education	„simple education“: explanation, training	I
	„application only by educated nurses“	II
	„application only under medical supervision“	III

Critical Steps: Risk Classification II

Prosposal: visualised risk matrix with risk levels:

		Combined risk levels for preparation & administration (P & A)		
	Risk Level	**I**	**II**	**III**
Temperature	I			
Handling	I	T & P	T & HS	P & HS
Patient education	I			
Temperature	II			
Handling	II	T & HS	P & HS	P & HS
Patient education	II			
Temperature	III			
Handling	III	P & HS	P & HS	P & HS & Obs
Patient education	III			

T = Training; P = Patient; HS = Healthcare Setting (eg ward); P = Pharmacy; Obs = Observation

Critical Steps: Summary

Be aware of many issues and follow the chain from the beginning to the end:

- **Delivery and storage: GDP**
  - Responsibility of the distributor vs pharmacy (pharmacist)
  - Validation (incl. documentation) of the whole supply chain
  - Storage during delivery, during holidays (traveling), in the car, at patient….
- **Preparation: WHERE**
  - How is responsible or the right person for the preparation?
  - Where is the right place for these preparations: ward or pharmacy?
  - Tailor made or according to the manufacturer's information: limitations
  - Aware of freezing, thawing, pumping, syringes (needles), filtration
  - Microbial - and physico-chemical stability: handling of these data
- **Administration: BY WHOM AND WHERE**
  - Education necessary ? Education by whom?
  - Home infusion therapy: really safe?
  - Stability after reconstitution and over infusion time: light & temperature

Pharm. Risk Classification