

**ABSTRACT REVIEW**

BAR14-0516

*Extended stability of 2.5 mg/ml-bortezomib solution in syringes and opened vials*

**Co-authors**

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**Background**

Bortezomib is indicated for treatment of multiple myeloma and mantle cell lymphoma for intravenous (i.v.) administration and also for subcutaneous (s.c.) use (which demonstrated a lower incidence of peripheral neuropathy). Intravenous bortezomib is reconstituted with 3.5mL of 0.9% sodium chloride (NS) (1mg/mL) and s.c. bortezomib with 1.4mL of NS (2.5mg/mL). The product information states that in-use stability of the reconstituted solution is 8 hours at 25°C stored in the original vial or a syringe. Several studies demonstrated the stability of bortezomib 1mg/mL in NS for up to 5 days. This allows Hospitals to reduce waste and results in significant cost savings. However, the extended stability for s.c. bortezomib has not been well-supported yet.

**Purpose**

To determine the chemical and physical stability of 2.5mg/mL-bortezomib solution in NS stored in polypropylene syringes and opened vials under refrigerated conditions (5±3°C), and under clinical use conditions (20°-30°C).

**Materials and Methods**

Chemical stability was defined as the retention of ≥ 95% of the initial drug concentration, determined by HPLC. Degradation product levels were also measured. Physical stability was assessed by visual inspection and dynamic light scattering. Physico-chemical stability was defined as solutions with 4.0-7.0 pH values. Statistical analysis were performed (α=0.05).

**Results**

More than 95% of the initial concentration of bortezomib remained in the original vials and polypropylene syringes for 7 days at 5±3°C and for 24 h at 25°-30°C (protected from light). All samples met the acceptance criteria for appearance, physical attributes and pH. At no time, the level of degradation products was greater than the ICH reporting threshold.

**Conclusions**

Bortezomib 2.5 mg/mL, in NS is stable for 7 days at 5±3°C and for 24 hours at 20-30°C, when stored in both polypropylene syringes and vials and protected from light.

Conflict of interest:
Enter Yes or No: No

**Keywords**

bortezomib; stability; subcutaneous;

**Authors letter**

Bortezomib 2.5 mg/mL stability has been investigated by a multidisciplinary team of pharmacist from Hospitals and University. Relevance of the study-Bortezomib is indicated for treatment of multiple myeloma and mantle cell lymphoma. It was initially-approved for intravenous administration (i.v.) and recently for subcutaneous (s.c.) route for multiple myeloma, which has demonstrated a lower incidence of peripheral neuropathy. Bortezomib is supplied in a glass vial containing 3.5 mg of the drug. It must be reconstituted with 3.5 mL of 0.9% sodium chloride (NS) (1 mg/mL) for intravenous administration and with 1.4 mL of NS (2.5 mg/mL) for subcutaneous administration. The product information states that in-use stability of the reconstituted solution is only 8 hours at 25°C stored in the original vial or a syringe. This poses significant problems because only a fraction of the vial is required per dose, resulting in a drug waste. Several studies demonstrated the stability of bortezomib 1 mg/mL, in NS for up to 5 days. Extending the beyond-use time allows to use the full content of the vial, reducing waste and resulting in significant cost savings to health care system. Unfortunately, the extended stability for s.c. bortezomib (subcutaneous administration) has not been well-supported yet. Innovation Our study demonstrates extended stability of bortezomib 2.5 mg/mL for up to 7 days in glass containers and polypropylene syringes under refrigerated conditions, and for up 24 h at 25-30°C (protected from light). Implication for future hospital pharmacy practice Extended stability for s.c. bortezomib (2.5 mg/mL) for up to 7 days in glass containers and polypropylene syringes under refrigerated conditions, and for up 24 h at 25-30°C, will allow to reduce waste, resulting in significant cost savings to the health care system. Also, it will assist the pharmacy workflow, as some of the solutions of subcutaneous bortezomib could be prepared in advance.
BAR14-0526  
Validation of new production facilities – what are the challenges?  

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Background  
Sykehusapotekene HF (SAHF) is a hospital pharmacy enterprise and has the responsibility for 16 hospital pharmacies in the South East region of Norway. During the past three years the hospital SAHF has built or upgraded 6 production facilities.  

Purpose  
To describe the process of validation and suggest improvements to save completion time.  

Materials and Methods  
A user requirement specification (URS) and description of the validation process is included in the tender documents. The units built have varied in size from 20 m² to 60 m² consisting of production and changing rooms. A V model validation process is used. All the protocols are written before validation begins. The validation is done in-house with help of the contractors and check lists verified by the pharmacy. All microbiological tests taken 'at rest' are carried out in house for equipment and rooms. Process qualification (PQ) including particle and microbiological tests are performed in house within 8 weeks of production start.  

Results  
We recommend performing PQ after normal production has started so the employees have learnt and feel comfortable with the routines. In the future, we will carry out IQ build and IQ/OQ air at the same time and not separately because the contractors have not been able execute the tests on time and cannot produce the ‘as built’ drawings fast enough. The biggest challenge has been performing the PQ on three working days within 6 working weeks (plus 2 weeks for incubation period). This involves taking particle and microbiological measurements ‘in operation’ for rooms and isolators. Daily tasks have to be performed at the same time as testing is done which make a very stress full situation in the production room.  

Conclusions  
Performing the validation process in house ensures that the pharmacy employees gain knowledge of the process giving the pharmacy staff a feeling of achievement and ownership of the new production facilities!  

No conflict of interest  

Keywords  
Validation;Production facilities;Validation challenges;
Validation of new facilities is detailed and time consuming. Experience with in house validation reduces the cost and gives the pharmacy staff a feeling of achievement and ownership of their new production facilities.

Score: 140

Remarks all reviewers:
Bonnabry, Pascal: Conclusion NOT warranted
Conflict of interest clear
Rejected

Rieutord, André: Conclusion warranted
Conflict of interest clear
Accepted
Nominee: No

BAR14-0543
Advanced preparation of chemotherapy - consequences

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Background
Delivering chemotherapy efficiently and economically to the right patient at the right time is becoming more difficult. This is a challenge for both the hospital ward and pharmacy. They must find a way to increase capacity using the same facilities and the same number of personnel.

Traditionally chemotherapy doses are prepared after the patient’s blood tests have been confirmed by the doctor. The orders come in at a rush causing an enormous work load for the pharmacy resulting in long delays for the wards and for the treatment of the patient.

Purpose
Determine the consequences of advanced production.

Materials and Methods
The Hospital pharmacy Lillehammer (since May 2011) has made up all the doses with the ingredients costing less than NOK 1000 (125 euro) before the blood test results are confirmed. This advanced production of cheap drugs provides an efficient work flow in the hospital pharmacy resulting in less waiting time for hospital departments.

Results
Practice shows that advanced production provides the ward with ‘zero’ waiting time for the cheap drugs, and approx. 15 minute wait for expensive drugs.

The average production time for reconstitution per dose is 5-10 mins.

Total production time has been reduced from 11 mins. to 6 mins.

Unfortunately advanced production produces some drug waste. The cost of drug waste has been measured to less than 1% of total drug cost.

Conclusions
An effective work flow in the pharmacy can help to increase the production capacity while increasing throughput of patients on the ward. The hospital pharmacy has a continuous, less stressful and less error prone production instead of working in bursts when lots of chemotherapy is confirmed at the same time.

The cost of waste (both labour and drug costs) were minimal compared to the advantages for both the pharmacy and wards.

No conflict of interest

Keywords
Advanced production; zero waiting time; increased efficiency;

Authors letter
Advanced preparation of cytotoxic doses increases pharmacy efficiency and results in zero waiting time for the wards. The costs of waste are minimal compared with the advantages for both pharmacy and wards.

Score: 220

Remarks all reviewers:
Bonnabry, Pascal: Conclusion warranted
Conflict of interest clear
BARI4-0572

The automated compounding of paclitaxel albumin as a sustainable alternative to the traditional compounding

Co-authors

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Background
Paclitaxel albumin is indicated for the treatment of metastatic carcinoma of breast after failure of anthracycline therapy. It is notoriously a delicate drug to handle because it is a suspension with high tendency to foam. According to the information sheet, the drug reconstitution requires particularly attention during solvent injection. Furthermore, the vial needs to stand for 5 and 15 minutes, respectively before and after shaking, to reduce the foam. As a consequence, the therapy compounding appears laborious and demanding for technicians.

Purpose
To automate the compounding of Abraxane with APOTECAchemo and analyze the related performances.

Materials and Methods
The manual procedure was deeply analyzed to evaluate the feasibility to robotize the compounding of Abraxane. 10 preparations were compounded manually, according to the data sheet. Afterwards, 10 preparations of Abraxane were carried out with APOTECAchemo, following the standard procedure of the system. However, the vials were left to rest for 10 minutes after reconstitution, before going on with the compounding.

The preparations are analyzed in terms of dosage accuracy and compounding time.

Results
The preparations compounded manually showed an average dosage error of 1.5% and a compounding time of 30 minutes. The dosage accuracy of preparations done automatically was -0.5%. The total compounding time resulted in 22 minutes for preparation, 7 minutes for reconstitution of 2 vials, 10 minutes for vial standing and 5 minutes for compounding. The 10-minute rest time resulted enough to significantly reduce the foam.

Dosage accuracy of the automatic procedure resulted similar or better than the manual compounding. In contrast, the use of APOTECAchemo implied a notable reduction of compounding time of 26%.

Conclusions
The automation of Abraxane preparation resulted feasible and sustainable. Because the dosage accuracy of APOTECAchemo is comparable with manual activity and compounding time is even shorter, the automatic compounding represents an easy and convenient alternative to the traditional practice.

Conflict of interest:
Enter Yes or No: No

Keywords
Pharmacy automation; Abraxane; Cytotoxic compounding;

Authors letter
Automation represents the future of the oncology pharmacy practice, assuring the quality in all the critical phases of the therapies compounding and minimizing also the risk of human exposure to toxic agents. Here we demonstrated that automation is also a very powerful tool to support operators with the most laborious and tricky preparations.

Score: 240

Remarks all reviewers:
Bonnabry, Pascal: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
5.
Modifications needed:
Specify the dosage method used
Rieutord, André: Conclusion warranted
Conflict of interest clear
Accepted
STABILITY TEST ON DRUGS USED IN PREMEDICATION THERAPY

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Background
The creation of drugs admixture unit at the National Cancer Institute of Milan, has engaged the Pharmacy on several fronts. The analysis of the harmonization of therapeutic regimens used is one of the steps; therefore dilution and mixing instructions of some necessary and essential drugs used in premedication, such as proton pump inhibitors (pantoprazole), dexamethasone and ondansetron have been revised.

Purpose
The study objective has been to evaluate the physical stability of four different types of infusion solutions made ??by mixing pantoprazole, ondansetron and dexamethasone in sodium chloride 0,9% solution, assuming microbiological stability, having used aseptic preparation process controlled.

Materials and Methods
The stability tests have been conducted using 20 Sodium Chloride 0,9% 100 mL glass bottles Baxter ® (the glass is reactive and transparent material), 20 infusion bags 50 mL of physiological saline Baxter ®(these bags are used within hospital), 30 dexamethasone 8 mg vials Hospira®, 30 pantoprazole 40 mg vials Sun®, 30 vials 8 mg ondansetron Kabi ®.

The glass bottles and bags have been filled using 10 mL syringes Omnifix®.
Excel database has been used to catalog the collected data.
5 bottles containing a pantoprazole, dexamethasone and ondansetron solution have been positioned at room temperature (25 ° C) and five others in the refrigerator between 2 - 8 ° C for 5 days; 5 bottles containing dexamethasone and pantoprazole, have been preserved under the same conditions.
The same was repeated replacing glass bottles with Baxter ® polyolefins bags.

Results
The test has showed identical behavior of the solutions stored at two different temperature ranges.
While white color suspension has been detected, 15 minutes from the beginning of the test, in the bottles and in the bags with pantoprazole, dexamethasone and ondansetron. The pantoprazole and dexamethasone solution within bags and bottles remains transparent for 23 hours and then turns into a pale yellow, without precipitate.
The bottles and bags containing the dexamethasone and ondansetron solution didn’t show obvious physical changes throughout the observation’s period (5 days).

Conclusions
Our tests have shown that pantoprazole in solution with dexamethasone has a physical stability of 23 hours, unlike what is indicated in some published work (Compatibilitè du pantoprazole injectable lors d’administration en Y. Péret H. et al Pharmactuel Vol.37 No 4).

Conflict of interest:
Enter Yes or No: No

Keywords

Authors letter
To set up a drugs admixture unit has been necessary to check the stability and compatibility of the used drugs. The medicines used in the premedication treatment, such as proton pump inhibitors, often formed a precipitate, according to the scientific literature data; The test stability showed that the mixing of dexamethasone and pantoprazole have a solution stability of 23 hours, allowing previous preparation of the admixture.

Score: 120

Remarks all reviewers: Bonnabry, Pascal: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
5.
Modifications needed: ;
Background
Levosimendan (Simdax®) is a calcium sensitizer which is effective in the treatment of heart failure. The available vials contain an adult dose but levosimendan is also used as off label therapy in children.

Purpose
Aseptic preparation of low doses of levosimendan safe costs. We have already demonstrated the chemical stability of levosimendan. Because preparations in syringes, specially of more volatile and lipophilic solutions are problematic, we focused in our new study the leachables out of polypropylene syringes. A syringe is not a totally closed system for volatile solvents and the risk of leachables is higher with lipophilic solvents.

Materials and Methods
The stability of 1ml levosimendan syringes stored at 8°C was tested over 2 months with focus on leachables and loss of solvent. The HPLC-method for levosimendan was validated by stress tests and separates three main degradation products under alkaline conditions. Another HPLC method was validated to detect leachables. To the present study also a new source of Simdax® was tested.

Results
We could confirm our former results about the chemical stability with the new batch of Simdax®. After 2 months a significant amount of leachables could be detected in the samples prepared in 1ml syringes. The relevance of these leachables need further investigation.

Conclusions
If a microbiological validation of the aseptic preparations is done, an in-advance-preparation of levosimendan child-doses in the pharmacy is possible. The preparations are stable for 2 months if they are stored at 8°C. This leads to a relevant economizing of child therapy with levosimendan. Because of detectable leachables in syringes, special care needs to be taken in the choice of the containers.

Conflict of interest: Enter Yes or No: No

Keywords
Levosimendan; Leachables; Stability;

Authors letter
Aseptic preparation of low dose levosimendan aliquots safe costs. Even there are good data of the chemical stability of levosimendan, the preparation in syringes has to be controlled carefully. Our new study shows a significant increase of leachables during the storage of levosimendan solutions in polypropylene syringes.

Score: 240

Remarks all reviewers:
Bonnbaby, Pascal: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
Nominee: No

Add information on the leachables: which ones were identified? Risk of toxicity? Edit the title by including the question of the leachables
Rieutord, André: Conclusion warranted
Conflict of interest clear
Accepted
Nominee: No
Results of treatment of corneal epithelial defects by plasma rich in growth factors eye drops application

Co-authors

Background
Plasma Rich in Growth Factors (PRFC) preparations are being increasingly used as a source of growth factors in bone reconstruction, implant consolidation in dentistry and more recently in eye diseases.

Purpose
Retrospective study of the use of eye drops preparation of plasma rich in growth factors in corneal eye diseases

Materials and Methods
The study period was 1 year (from March 2012 to February 2013). It was performed in an Ophthalmology Hospital. Medical histories of patients that have being treated with PRFC eye drops were reviewed. The following items were collected: demographic data, indication, dosage, treatment duration, adverse reactions and clinical response that was measured as improvement in symptoms and decrease of corneal lesion size. PRFC eye drops were prepared under sterile conditions at a concentration of 50% according to the literature. Data were analyzed by SPSS v19. Statistics values were expressed as median, minimum and maximum data.

Results
11 patients were treated (27% male), the median age was 52 years (range 36 to 77 years). 6 Patients suffered from dry eye with keratitis and corneal ulcer, 3 patients suffered from Sjogren’s Syndrome and 2 patients suffered from keratitis due to previous corneal transplant. In the group of patients with dry eye the median age was 51 years (range 36 to 77 years), the mean treatment duration was 3 months and all the patients showed improvement and healing of the corneal ulcer. In the group with Sjogren’s Syndrome the median age was 60 years (range 60 to 74 years), one patient did not tolerated the eye drops and no improvement was observed after 1 month of treatment, in the rest of patients the mean treatment duration was 6 months, they showed improvement in symptoms and disappearance of keratitis. In the group of patients with previous corneal transplant the median age was 37.5 years (range 36 to 39 years), the mean of treatment duration was 3.5 months, all the patients showed improvement and disappearance of keratitis. The dose was one drop/6h and only in one patient with dry eye the dose was 1 drop/4h.

Conclusions
PRFC eye drops are 100% autologous platelet product. The preparation is easy and it has an optimal concentration of growth factors which makes it highly effective in eye diseases with persistent epithelial defects requiring rapid corneal repair. Only one patient did not tolerate the preparation and showed any improvement. The other patients showed an evident improvement of the signs and symptoms. Therapy duration was long (for 3 to 6 months). Future studies will help to discern whether chronic eye diseases related with dry eye non-responders to conventional treatment require continuous or discontinuous treatment with topical PRFC eye drops.

No conflict of interest

Keywords
plasma growth factors; eye drops; corneal epithelial defects;

Authors letter
The use of PRFC eye drops can bring patients benefit in eye pathologies.

Score: 260

Remarks all reviewers:
Bonnabry, Pascal: Conclusion warranted
Conflict of interest clear
Rejected

Rieutord, André: Conclusion warranted
Conflict of interest clear
Accepted
Nominee: No