Welcome to the STABILIS users for this Twenty-seventh Newsletter!

Test your knowledge on stability

Stabilis® in Chinese!

News from congresses
News from the SNPHPU Congress September 2014
News from the GERPAC Congress October 2014
News from the ADKA Congress May 2014

« Dose-banding : a way to rationalize the production of chemotherapy » : Results of the Stabilis® survey.

New monographs
Metaraminol, Belinostat, Obinutuzumab, Conivaptan, Dalbavancin, Tedizolid

New references from international publications
Cefuroxime, Ertapenem, Doxapram, Analgesics and sedative drugs

New documents on Infostab website

Statistics
Focus on Japan

Answer to the test
Test your knowledge on stability!

You read an article about the stability of an injectable drug in sodium chloride. You read this sentence in the discussion paragraph.

« The coefficients of variation of the analysis during the stability study were between 6 and 8%. The within-day and between-day coefficients of variation and the error of the assay were <15%. These values are classically admitted in pharmacokinetic studies. »

What do you think about this interpretation?

See the answer on the last page.

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News from the SNPHPU Congress

In September, the congress of the French association of University Hospital Pharmacists (SNPHPU) held in Juan Les Pins in the South of France.

228 posters were presented. We have selected 4 posters of stability studies.

**Stability of spironolactone capsules by HPLC with DAD detection**

Jérémy Sorrieul, Thomas Briot, Mérédith Boutet, Christine Truffaut, Virginie Cogulet, Frédéric Lagarce

*University Hospital of Angers, France*

The authors have studied the stability of spironolactone capsules for a clinical trial, by evaluating the visual aspect and the quantification of spironolactone by HPLC with detection at 240 nm. The analytical method was validated according to ICH guidelines.

No visual modifications were observed and the quantification was between -9.9 and +4.9% of the initial quantification. No visual modification was observed. The stability was demonstrated over a period of 6 months.

**Stability of phenylephrine eyedrops for paediatrics**

Claire Dréno, Thomas Gicquel, Marine Thibault, Gilles Dollo

*University Hospital of Rennes, France*

Eye drops of 2% phenylephrine were prepared by using disodium phosphate as excipient and dissolved with normal saline. The pH value was 6.9 and the osmolality 285 mOsmol/kg. The solution was stored at room temperature in amber glass bottles. The concentration of phenylephrine was determined by HPLC-HR-MS. Microbiological stability was also evaluated.

Physical, chemical and microbiological stability were demonstrated over 60 day.
Stability study of caffeine syrup for a clinical trial
Laurent Moret, Clémentine Le Roy, Marie Gasperini, Laetitia Nee, Amélie Marsot, Audrey Boulamery, Stéphane Honore, Bénédicte Deluca
University Hospital La Timone, Marseille, France
A caffeine solution made with 400 mg caffeine and 32 ml Orablend® was prepared. The stability was evaluated by HPLC with UV detection. Variation of the concentration did not exceed 10% and no degradation products were detected. The stability was demonstrated over a period of 60 days.

Stability study of a 25% lidocaine cream
Claire Hamel, Hassane Sadou Yaye, Agnès Bellanger, Patrick Tilleul.
University Hospital Pitié Salpêtrière, Paris, France
A cream containing 25% lidocaine, guar gum and Emulsan® was formulated. Color, odor, and microscopic evaluation were used for the physical stability. pH and HPLC with detection at 210 nm for the chemical stability. The cream was stable at room temperature and at 40°C for 3 months.

News from the GERPAC Congress
The congress of the French association GERPAC took place like every year in Giens, South of France, October 2014. The topic was « Simulation and risks assessment for pharmaceutical preparation at hospital pharmacy ».

Giens is a nice place on the Mediterranean sea!

We have selected oral communications dealing with the stability of drugs.

Batch preparation of a speciality to reconstitute: case of cyclophosphamide
Menard C, Michel G, Sankhare D, Faure P, Levert H, Jourdan N.
University Hospital Saint Louis, Paris, France
The authors have used the extended stability of cyclophosphamide infusions to standardized 3 doses (1000, 1200 and 1400 mg) which are the most commonly prescribed dosages (44% of the prescriptions). The preparation of 3 lots of 40 bags covers nearly 70% of the monthly requirements of these dosages. For a dose between 950 and 1050 mg, the patient will receive 1000 mg, so the maximum deviation between the dose calculated according to the body surface area and the dose administered is 5%.

Stability study of an injectable preparation for neonatology
Tall ML, Diouf E, Hays S, Ducarre B, Lenfant M, Bador M, Koog N, Salmon D, Pirot F, Pivot C.
University Hospital of Lyon, France
The solution consists of 138.8 mmol anhydrous dextrose and 35.1 mM sodium chloride. The solution was stored in glass vials at 22°C ± 3°C. The solution was sterilized by autoclaving. PH, osmolality, particle count, assay of dextrose, assay of sodium, assay of 5hydroxymethylfurfural, sterility test and search of endotoxins were performed to evaluate the stability. The stability was demonstrated over one year.

Repackaging of solid oral dosage forms: interest of the evaluation of tablet physical parameters
Garces M, Gaudas J, Guerrault-Moro MN, Vasquez R, Charneau C, Crauste-Manciet S.
Saint Germain en Laye Hospital, France
The objective of the study was the evaluation of the risk of degradation by exposure to relative humidity on repackaged tablets prepared into dose administration aids ( DAA ). 3 drugs were selected ( Modopar® 125 mg, Depakine® 500 mg and Esidrex® 25 mg ) for their sensitivity to moisture demonstrated by the hygroscopicity assay of the European Pharmacopoeia. Esidrex® tablets show significant variations in weight, hardness and desintegration time when stored in PERO’s packaging. In contrast the chemical stability of hydrochlorothiazide was not affected regardless of the packaging. Physical test must not be neglected when evaluating the stability of oral solid form after repackaging.
News from the ADKA Congress

The congress of the German association of hospital pharmacists (ADKA) took place in Hamburg, Germany, May 2014. Four posters were presented on the topic of stability.

Chemisch-Physikalische stabilität einer konsservierten sotalol hydrochloridlösung 20 mg/ml
Metze C, Fenske D.
From the Hospital of Erfurt
The composition of the preparation was
- Sotalol hydrochloride 2 g
- Potassium sorbate 140 mg
- Citric acid 70 mg
- Purified water >> 100 ml
The authors used HPLC with UV detection. Visual inspection and pH measurement were also performed. The solution in glass vials protected from light was stable for 5 months at room temperature or at 2-8°C.

Stabilität von applikationsfertigen glyceroltrinitrat-Spritzen
Holpner M.
University Hospital of Saale, Germany
The authors have compared the stability in two kind of syringes, 2 parts syringes with only polypropylene and 3 parts syringes. The solution at 0.1 mg/ml in 5% dextrose was stable for 28 days in the two part syringes but the concentration fell under 90% of the initial concentration after 2 days in the 3 parts syringes and to 50% after 28 days.

Dose Banding of chemotherapy agents and its implications for hematology-oncology practice
University Medical center Freiburg
The authors have presented the possibilities to use the Dose Banding concept in hematology-oncology practice. Many molecules are eligible to dose Banding (gemcitabine, vincristine, doxorubicine, rituximab, irinotecan, 5-Fluourouracile bolus, 5-Fluourouracile 48h Baxter-pump, etoposide phosphate, fludarabine, bortezomib).

Stability of ampicillin and sulbactam in Perfusor® syringes
Blassman U, Vetter-Kerkhoff C, Rohr A, Frey O.
Hospital of Heidenheim, Germany
The authors have studied the stability of Ampicilin-Ratiopharm 2g/50ml and Unacid® 3g/50ml. The solution was stable for only 12 hours. After 12 hours, the concentration of both molecules fell under 90% of the initial concentration.

« Dose-banding : a way to rationalize the production of chemotherapy » :
Results of the Stabilis® survey
Throughout the world, the calculation of a chemotherapy dose is based on the body-surface area (BSA), which can be estimated with different formulae. The most common is the formula of Du Bois and Du Bois. Yet, as it’s only based on 9 subjects, its accuracy is questionable. For some other molecules, as targeted therapies, the dose is fixed and not related to the BSA. In 1990, a study showed that using the BSA wasn’t more meaningful than using the weight or the height alone. In 2002, another study showed that this way of calculation reduced inter-patient variability only for 5 drugs among the 33 studied. They suggested another strategy to calculate the administered dose should be considered.
What is dose-banding?
Dose-banding is a British concept, initiated in the late 90s and developed by Pr Graham Sewell. It is defined as « a system whereby, though agreement between prescribers and pharmacists, doses of intravenous cytotoxic drugs, calculated on an individual basis, which are within defined ranges or bands, are approximated to pre-determined standard doses. The maximum variation of the adjustment between the standard dose and the doses constituting each band is 5% or less. A range of pre-filled syringes or infusions, manufactured by pharmacy staff or purchased from commercial sources, can be used to administer the standard dose » 5.

How to calculate standard doses.
There are several types of dose-banding schemes 6, 7:
- BSA based Banding : the patient’s BSA is rounded up or down to one decimal place and the dose is calculated according to the regimen.
- Drug based Banding : the dose is calculated and then, rounded up or down to the nearest band.
- Logarithmic dose-banding : the previous schemes imply that the variance between the rounded dose and the calculated dose is higher at the bottom of the scale than at the top. With this scheme, the use of a logarithmic scale enables the constant variance between rounded and calculated doses.

Benefits and limits
This concept is well-known in Great Britain where more than 80% of oncologists are aware of dose-banding 8, and the benefits for the patient, the pharmacy and the nursing staff are undeniable. The concept is starting its development through Europe. Concerning the standardized molecules, many cytotoxic drugs can be subjected to Dose-Banding, from expensive molecules like rituximab to cheaper ones like fluorouracil. The choice depends on the extended stability and the production volume.

The main benefit is the reduction in waiting times for patients thanks to a quicker dispensing. It can also reduce drug wastage by re-use of cancelled doses. Moreover, it provides a safer production by reducing the risk of preparation and administration errors, making possible automation in the preparation process and allowing a prospective quality control. It increases pharmacy capacity for chemotherapy and then, with a sufficient nursing time, it can increase capacity to treat more patients daily.

Yet, this concept can’t be used in pediatric oncology, because of the weight inequality between the children. It shouldn’t be applied to obese or cachectic patients, for who a calculation method based on the BSA would more appropriate. Concerning clinical trials, dose-banding can be used only with the sponsor’s agreement 6.

BSA versus dose-banding
The main reason against dose-banding is that « the dose variance introduced by dose-banding, when combined with the estimation of BSA may result in an unacceptable total variance from the intended dose » 5. Even if many prescribers agree with the fact that 5 to 10% is an acceptable variance, yet, they are concerned about under-dosing 8. Nevertheless, a few papers show there is no difference in terms of pharmacokinetic and toxicity between calculated doses and standard doses 9, 10. Moreover, rounding chemotherapy doses is commonly used by oncologists when prescribing and pharmacists when manufacturing the infusions. The calculation of chemotherapy doses should take into account the genetic polymorphism which impact pharmacokinetic parameters. The prescription of individual doses depending on BSA is delusional, so the fear of under-dosing with dose-banding shouldn’t be a reason to be opposed to the concept.

The use of Dose-Banding in hospitals: The Stabilis® survey
During November 2013, we sent by using the mailing list of the Stabilis® Newsletter, a questionnaire about the use of the Dose Banding Concept. 1850 questionnaires have been sent and 50 answers were received from different countries, summed up in Chart 1.
90% of the answers were from European countries but we got some surveys returned from American countries (Canada, Brazil, USA) and Asian countries (Singapore). Considering the fact that 1850 surveys have been sent, the response rate is quite low (2%). It can be explained by the fact that Stabilis® is not a database dedicated to cytotoxics. Therefore, there is a proportion of the newsletter’s subscribers which is not concerned by the survey.

Many pharmacies (61%) prepare chemotherapy infusions in advance, but only 12% use the Dose-Banding concept. Several reasons can explain this observation: ignorance of the concept, wrong idea that Dose-Banding cannot be applied in small pharmacies, reluctance from nursing staff to use several syringes instead of one syringe or infusion bag... This last reason can explain that adapted Dose-Banding seems to be more easily applied than classic Dose-Banding. Adapted Dose-Banding is derived from the original concept. The difference is that the dose is prepared in advance in only one container for one patient. The dose is standardized; this way, the preparation can be reallocated if it is not administered.

References


New monographs

Metaraminol

Metaraminol (also known as metaramine) is a potent sympathomimetic amine used in the prevention and treatment of hypotension, particularly as a complication of anesthesia. It is an 1-adrenergic receptor agonist with some B effect. Metaraminol 3 mg/6ml pre-filled syringes are stable for up to 378 days when stored at room temperature or refrigerated.

Belinostat

Belinostat (Beleo-daq®) is a histone deacetylase inhibitor, indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Solutions of 50 mg/mL of Belinostat in glass vial are stable during 12 hours when stored at 15-25°C. After transfer into an infusion bag containing 250 ml of 0.9% sodium chloride injection, the solution may be stored at ambient room temperature for up to 36 hours.

*Summary of Product Characteristics, Spectrum Pharmaceuticals*

Obinutuzumab

Obinutuzumab is a humanized monoclonal antibody which targets CD20 and kills B cells. Obinutuzumab was approved under the tradename Gazyva® by the US FDA in 2013, for the treatment of chronic lymphocytic leukemia in combination with chemotherapy in treatment-naive patients.

Obinutuzumab solutions diluted in 0.9% sodium chloride infusion at the final concentration of 0.4 mg/ml to 4 mg/ml are stable for up to 24 hours when stored at 2-8°C in PVC or polyolefin infusion bags.

*Summary of Product Characteristics, Genentech*

Conivaptan

Conivaptan (Vaprisol®) is a non-peptide inhibitor of antidiuretic hormone (vasopressin receptor antagonist). It was indicated to raise serum sodium in hospitalized patients with euvoletic and hypervolemic hyponatremia.

Conivaptan is incompatible with Lactated Ringer’s Injection and furosemide injection.

*Summary of Product Characteristics, Astellas Pharma*

Conivaptan is incompatible when diluted in 5% dextrose injection with dopamine.

*Am J Health-Syst Pharm 2014; 71:1534-1535*

Dalbavancin

Dalbavancin (Dalvance®) is a novel second-generation lipoglycopeptide antibiotic. It belongs to the same class as vancomycin, the most widely used and one of the few treatments available to patients infected with methicillin-resistant Staphylococcus aureus (MRSA).

The Food and Drug Administration approved dalbavancin in May 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by designated susceptible strains of Gram-positive microorganisms.

Diluted with 5% dextrose infusion to a final concentration of 1 mg/ml to 5 mg/ml in intravenous bag or bottle, Dalbavancin may be stored either refrigerated at 2 to 8°C or at a controlled room temperature of 20 to 25°C during 48 hours. Saline-based infusion may cause precipitation.

*Summary of Product Characteristics, Durata Therapeutics*

Tedizolid

Tedizolid (Sivextro®) is an oxazolidinone drug for complicated skin and skin-structure infections (cSSSI), including those caused by methicillin-resistant Staphylococcus aureus (MRSA).

As an oxazolidinone, it has activity against several other gram-positive pathogens including methicillin-susceptible Staphylococcus aureus (MSSA), Streptococcus pyogenes, Streptococcus agalactiae, enterococci, coagulase-negative Staphylococci and linezolid-resistant staphylococci.

Solutions of Tedizolid 50 mg/ml reconstituted in glass vial are stable during 24 hours when stored at room temperature or under refrigeration at 2 to 8°C.

After transfer in an infusion bag containing 250 ml of sodium chloride injection, the solution may be stored at ambient room temperature or under refrigeration during 24 hours.

*Summary of Product Characteristics, Cubist Pharmaceuticals*
New references from international publications

Stability and compatibility of injectable drugs

Cefuroxime
Ready to use syringes of cefuroxime 10 mg/ml in 0.9% sodium chloride injection were stable at -18°C for up to 120 days.

Eur J Hosp Pharm 2014 ;21:34-38

Ertapenem
Ertapenem 100 mg/ml prepared in 20 ml polypropylene syringes was stable at room temperature for approximately 30 minutes. Room temperature stability was extended to 4 hours after 24 hours of refrigeration. After being frozen for 14 or 28 days, ertapenem was stable for 3-5 hours after removal from the freezer.

Am J Health-Syst Pharm 2014 ; 71:1480-1484

Doxapram
Doxapram diluted at 2.5 mg/ml and 8 mg/ml in 5% dextrose injection is chemically stable for respectively 36 and 24 hours after storage at room temperature with exposure to light.

Archives de Pédiatrie 1998 ; 5, 10: 1170-1171

Analgesics and sedative drugs
A study of Knudsen and coll established the physicochemical compatibility for several clinically relevant combinations of commonly used analgesics and sedatives (clonidine, sufentanil, midazolam, lormetazepam, ketamine, piritramide, sodium oxybate).

Eur J Hosp Pharm 2014 ;21:161-166

New reference of incompatibility

- Incompatibility of aminophylline 25 mg/ml with dopamine 3 mg/ml
(Yakugaku Zasshi 2014 ; 134, 2: 293-298).

- Incompatibility of Acetylcysteine
(Pharmactuel 2014 ; 47, 3 : 161-165),
- Incompatibility of Thiopental
(Pharmactuel 2014 ; 47, 3 : 167-172)

Stability of oral solutions

1 - Bourget P., Amin A., Pieyre M., Dosso eo ;, Beauvais R., Loeuillet R.
Physicochemical and microbiological stabilities of hydrocortisone in Inorpha® Suspending agent studied under various conditions

The authors demonstrated that hydrocortisone is stable in InOrpha® suspending agent for 28 consecutive days upon daily bottle opening and for a maximum of 42 consecutive days with the first opening from the 28th day of the compounding time, when stored either at room temperature or under refrigerated conditions. The microbiological quality of the mixture was never altered by repeated opening of bottle.

2 - Beata J; Stanisz, Sylwia K; Paszun, Anna Zalewska.
Stability of cilazapril in pediatric oral suspensions prepared from commercially available tablet dosage forms.

The presented study provides evidence of 28 days stability of cilazapril in Orablend® suspending agent at the concentration of 1 mg/mL. Stable, that means that throughout 28 days storage in capped bottles of amber material glass or plastic retains within specified limits the same properties as at the time of its manufacture.

3 - Ensom M.H.H, Décarie D.

The authors evaluated the stability of 1 mg/mL dexamethasone suspensions in Oral Mix® and Oral Mix SF® stored in amber glass or plastic bottles or plastic syringes at 250°C or in amber glass or plastic bottles at 4-8°C. All suspensions maintained at least 96% of the initial concentration of for up to 91 days. No notable changes in color, taste, odor or pH were observed during the test period. No precipitate was observed.
New documents on Infostab website
(www.infostab.com)
See in «Publications» and «Stability and compatibilities»

1 - Moret I., Le roy C., Gasperini M., Nee L., Marsot A., Boulamery A., Honore S., Deluca B.
Etude de stabilité de préparations de sirops de cafécine réalisées dans le cadre d'un protocole d'essai Clinique

Pharmacie AP-HM, Unité de réanimation de chirurgie cardio-que et Laboratoire de pharmacologie médicale et clinique, Timone University Hospital, Marseille, France
Poster presented at the SNPHPU Congress, Juan Les Pins, France, September 2014

2 - Hamel C., Sadou Yaye H., Bellanger A., Tilleul P.
Etude de stabilité d'une crème à la lidocaine
Pitié Saîpêtrière University Hospital, Paris
Poster presented at the SNPHPU Congress, Juan Les Pins, France, September 2014

Statistics

Visits have stabilized around 20,000 per month for the end of the year. In the next newsletter we'll present you the evolution from 2008...

Language | Percentage
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French | 47.5 %
English | 14.0 %
Spanish | 6.9 %
German | 6.6 %
Dutch | 4.2 %
Italian | 3.8 %
Portuguese | 2.5 %
Turkish | 2.1 %
Russian | 1.2 %
Polish | 1.0 %
Croatian | 0.8 %
Hungarian | 0.8 %
Finnish | 0.8 %
Danish | 0.7 %
Swedish | 0.7 %
Czech | 0.7 %
Greek | 0.7 %
Latvian | 0.7 %
Rumanian | 0.7 %
Norwegian | 0.7 %
Slovak | 0.6 %
Slovenian | 0.6 %
Estonian | 0.6 %
Lithuanian | 0.5 %
Arabic | 0.3 %
Bulgarian | 0.2 %
Japanese | 0.1 %
Chinese | 0.0 %

Languages

Chinese language has already entered the statistics as the 28th. Let's suppose it'll be climb the ladder soon! Other languages have maintained their rank, with a regular increase in English speaking users.
The variations observed in pharmacokinetic studies are very different from those observed in stability studies of pharmaceuticals. In the pharmacokinetic field, the composition of the samples is very complex and the samples must suffer extraction, filtration etc. This complexity allows high variations in the results with a 15% variability classically admitted.

In the field of stability studies of injectable drugs, the solution contains usually one drug diluted in sodium chloride or dextrose. This media is not complex and should usually suffer a simple dilution before analysis.

Under these conditions, the variability is very low and is often under 2%. Sometimes, for more complex media (mixture of 2 or 3 drugs, or more complex solvent like mixture for oral administration), the coefficient of variation can be higher sometimes 4 or 5%. Higher variations are not acceptable for stability studies. The argument of a variability inferior to 15% is not acceptable for our topic.