

P. Luder, J. Vigneron, I. Gindre, I. May, B. Demoré
Hôpital Brabois Adultes- CHU Nancy - Allée du Morvan 54500 Vandœuvre-lès-Nancy
infostab@stabilis.org

Introduction

No information about the quality of publications on the Stabilis® database

Objective

Create a **quotation system** to provide the **level of evidence** of the stability studies of injectable anticancer drugs



Material & Method

Construction of 2 evaluation systems

For « classical » small molecules

Level of evidence A or A+ if the subvisual examination has been performed
- Separative method and complete analytical validation (linearity, within day and between day reproducibility, stability indicating capability) and low variability (CV<5%)
- Chemical stability defined as the concentration above 95% of the initial concentration and physical examination studied (visual aspect)
Level of evidence B or B+ if the subvisual examination has been performed
- Same criteria as level of evidence A but physical stability not performed
- OR Chemical stability defined as the concentration above 90% of the initial concentration by a validated analytical method and small variability
Level of evidence C or C+ if the subvisual examination has been performed
- Chemical stability defined as the concentration above 95% of the initial concentration but separative method failed because of one or two of the following criteria:
- Stability indicating capability insufficiently studied
- Variability of the results (CV>5%)
- Within day or between day reproducibility not precised or out of the specifications
- Unencrypted results (eg graphic)
- Separation from degradation products and Internal Standard not or badly evaluated
- OR method different from HPLC not justified and chemical stability defined as the concentration above 95% of the initial concentration
Level of evidence D
- Chemical stability defined as the concentration above 90% of the initial concentration but the validation of the separative method with lacking criteria
- OR chemical stability defined as the concentration above 95% of the initial concentration but the validation of the separative method include more than 2 failing criteria
- OR method different from HPLC not justified and chemical stability defined as the concentration above 90% of the initial concentration

For proteins

Level of evidence A or A+ if one of the physical methods is turbidimetry (subvisual)
- Physical examination : at least 2 methods ²
Level of evidence B or B+ if one of the physical method is turbidimetry (subvisual)
- Same criteria as level A but without biological analysis
Level of evidence C
- Only 3 methods including physical, chemical and/or biological methods
Level of evidence D
- Only physical method or less than 3 methods

¹ Physical method which can be used: turbidimetry, Size Exclusion Chromatography, Dynamic Light Scattering, Thermal aggregation curve
² Other methods like UV spectrometry and second derivative, infrared spectrometry and second derivative, mass spectrometry or capillary electrophoresis can be used.

specific "biological" quotation for the stability studies based on biological methods

✓ **Analysis** according with these criteria

✓ **Quotation** : Level of evidence proposed for each stability study (compatibility studies excluded)

✓ **Design of pictograms and screens** for users of the Stabilis® database

✓ **Entering data**

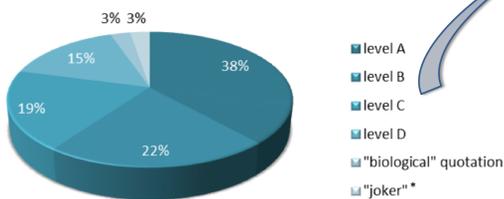
✓ **Updating the website**



Results & Discussion

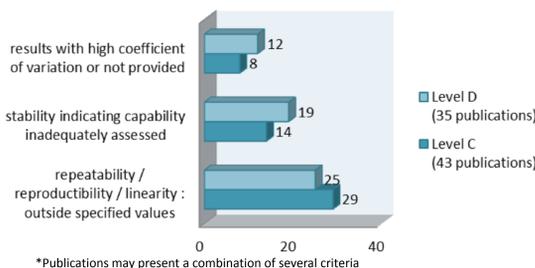
196 publications analyzed

Level of evidence of the stability studies rated



*Joker was attributed when several molecules have different levels of evidence in the same article

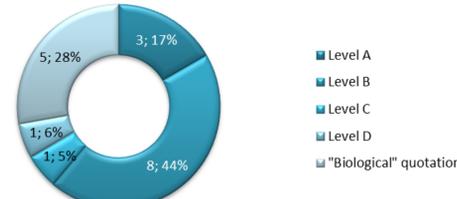
Primary criteria justifying level C or D



*Publications may present a combination of several criteria

What about proteins ?

Level of evidence for stability studies of proteins (18 publications)



✓ Few studies (18 publications)
✓ But good level of evidence

Good level of evidence imputed in most cases

Level of evidence appears for each study

Stability in solutions : Cisplatin					
Container	Concentration	Temperature	Time	Level of Evidence	Count
PVC	0,166 mg/ml	30°C	14	C	147
PVC	0,6 mg/ml	20°C-24°C	9	C	164
PVC	0,1 mg/ml	25°C	28	A+	3183
PVC	0,166 mg/ml	30°C	14	C	147

Click on the level of evidence to see screens !

Level of Evidence : **C**

Physical stability :

Chemical stability : **95%**

Other methods :

Comments : Stability indicating capability inadequately assessed
Repeatability / reproducibility / standard range: results not provided or results outside specified values
No comments for the degradation products

Example of screen for « classical » small molecule (stability study of Methotrexate)

User's guide available online by clicking on the « blue book »

Screen with analytical methods used by the authors available

Some commentaries to precise or justify the level of evidence proposed
25 standardized commentaries, translated into 26 languages

Informations given by 42 new pictograms specially designed to keep the "spirit" of Stabilis®



✓ International recommendations
✓ Training ("Masterclass")

✓ Quotation system on Stabilis®

PROMOTE & IMPROVE stability studies

Conclusion

- Level of evidence = indicator of the quality of publications
- Quotation system will help users of the Stabilis® database and could help to realise more complete stability studies
- Next step = the analysis of the articles of stability studies of injectable antibiotics !