EUROPE DISCOVERY SUMMIT
EXPLORING DATA INSPIRING INNOVATION

Stable or not? Investigating chemical stability of active ingredients in formulations

Marion Janker
Syngenta Crop Protection AG

Scenario

In the development of a formulation, it was found that the formulation had a degradation of active ingredient (AI) of around 5% upon storage for 2 weeks at 54°C.
The question becomes: What's the reality? Can the formulation be stable and classified as such, even by external sources, across the chosen conditions?

Starting Situation

Active ingredient content in a formulation is measured by High Pressure Liquid Chromatography (HPLC). Certain numbers of sample weighings are taken and injected into the column (a typical number like in the example is two weighings and two injections).
These methods allow AI and their by-products / degradation products to be determined.
Degradation is usually determined by comparing a stored sample with a reference sample at a given time point.

FAO Definition

*"After storage at 54 ± 2ºC for 14 days, the formulation must continue to comply with the requirements of appropriate clauses for content of active ingredient, relevant impurities, particulate and dispersion clauses. The **average active ingredient content** should **not decline to less than 95%** of the average content measured prior to the test[…] Alternative conditions are: 4 weeks at 50 ± 2ºC, 6 weeks at 45 ± 2ºC; 8 weeks at 40 ± 2ºC, 12 weeks at 35 ± 2ºC or 18 weeks at 30 ± 2ºC." (1)*

Data generation

During development of a new formulation, the generated data has high degrees of uncertainty. This is due to two factors:

- the analytical method for the determination of the active ingredient needs to be developed (for accuracy and precision)
- the formulation composition is often developing in parallel

In order to improve precision, it was realised that a larger – than – normal dataset would have to be generated.

Data import to JMP

Not as trivial as it sounds when database extraction is difficult! -> Using importing tool for excel & csv files.

Data treatment

The data had to be treated to get from the obtained AI content that is usually reported to the degradation percentage
Two methods for the calculation were used:

1. Within-point analysis

$$100 - \left(\frac{54\,2}{-18\,2} * 100\right)$$

2. Averaging baseline

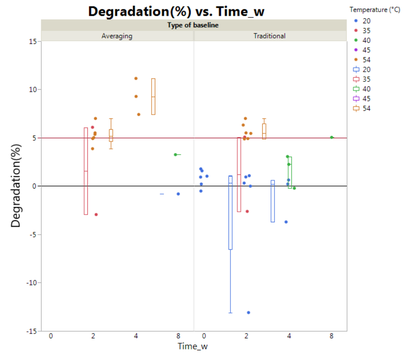
$$100 - \left(\frac{54\,2}{\text{Average reference}} * 100\right)$$

This technique uses the average of all reference samples (stored at -18° C)

18/0 Cols	Degradation 2w/54°C Traditional	Degradation 2w/54°C Averaging
1	5.9623430962	5.9623430962
2	7.4267782427	8.4482758621
3	4.7008547009	4.8025613661
4	•	•
5	3.3261802575	2.6997840173
6	6.3224446786	5.0213675214
7	4.8830111902	3.8725154215
8	9.9492385787	9.9492385787
9	4.9197860963	4.9197860963
10	5.4564533054	5.3571428571
11	5.5093555094	5.5093555094
12	7.0030895984	7.0030895984

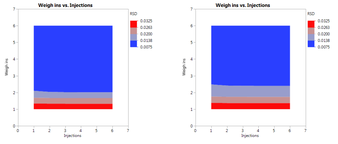
Initial Analysis of Degradation

For the most interesting time point for us, 2w/54° C, two standard deviations stretched between 4 and 7%



Variability of the analytical data

As all data has variability associated with it, it was key to understand what the variability was in this case and if and how it could be improved.



References
(1) FAO/WHO Joint Meeting on Pesticide Specifications (JMPS): Manual on development and use of FAO and WHO specifications for pesticides, second revision of the first edition, Rome 2010, Section 4.6.2

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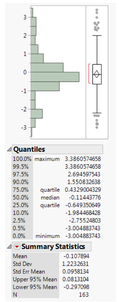
The degradation product

The degradation product can be identified with the same HPLC method. Using molecular weights the following determination about analytical recovery can be made:

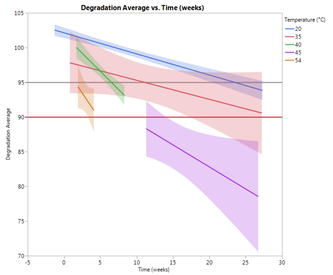
$0 = \text{Mol AI}_{in} - (\text{Mol AI}_{out} + \text{Mol Degradation}_{out})$

This calculation found that whilst the data is centered around zero and appeared to be normally distributed, it was not.



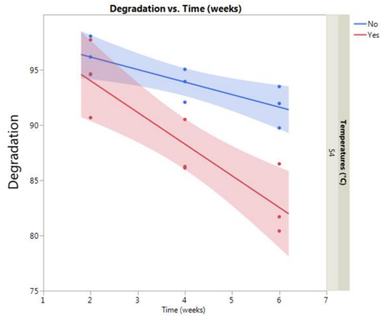
Alternative storage conditions

Higher temperature accelerated storage helps us understand the activation energy of a system, but does not necessarily correlate with how the AI responds at lower temperature, longer time.
Formal longer time, lower temperature storage data provides an alternative in long term stability studies required for registration.
In this case, no such avenue was open as degradation was observed at all possible regulatory alternatives. This means that an alternative stability study regime would not lead to a registerable product.



Alternative formulation options

In order to further the development of a formulation fit for market, an analytical study was undertaken to find out if there was a link between the decomposition and the raw material(s). This took 12 weeks and involved around 250 samples (500 weighings, 1000 injections). This identified a specific combination of the raw materials that triggered the degradation.
This learning influenced the product development decisions.



Conclusion

Having a formulation experiencing chemical degradation is challenging, especially when the method and formulation are being developed simultaneously.
A key element was making sure that the analytical method was fit for use by understanding the precision and accuracy associated with it.
This problem area brought different technical groups together and through statistical analysis and a collaborative approach it enabled the progress.
The data generated through the time and the level of confidence in it was key for the success for development and project success. A commercially viable option is progressing through our development pipeline.

Acknowledgements:
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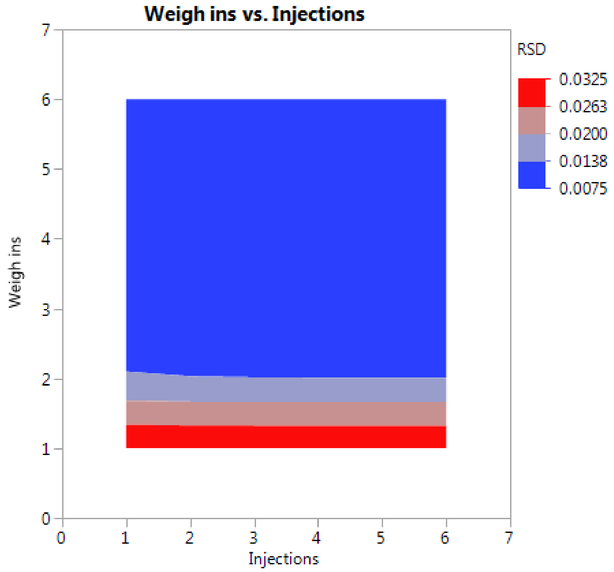
The variability of the analytical data

This required looking into each single data point, instead of using the average of two weighings and two injections that is usually reported back.

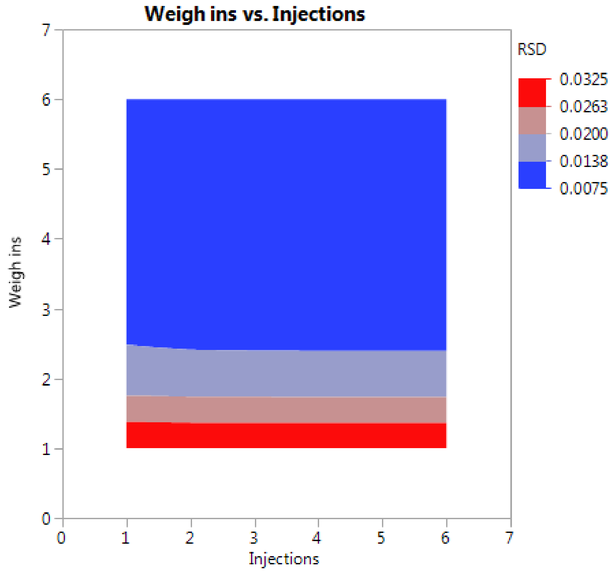
Though this, it was possible to assess the RSD between analytical sampling, instrument, method, day – to – day and one operator.

In order to improve the RSD, more samples would be required to be analyzed –> There is a trade-off between different analysis samples and accuracy.

Data confirmed method was fit for use.



One Day



Three Days