Accelerated Stability Assessment Program (ASAP), a QbD case study

Applicazione del QbD nella produzione dei medicinali

Università degli Studi di Milano, 6 Maggio 2016

Approaches for Shelf Life determination

Submissions of new pharmaceutical products (or Line Extensions) must include data showing the stability of both Drug Substance(s) and Drug Product in the commercial primary packaging intended for the market. From a Regulatory perspective, the stability studies must be carried relevant guidelines, namely:

- **ICHQ1A(R2)** ***Stability Testing of New Drug Substances and Products***

in which the Applicant may find: Conditions & Timepoints to apply, Batch Selections, Climatic zones, Evaluation, Specifications, discrimination among storage conditions, specific requirements in case of semipermeable primary packs,etc..

- **ICH Q1E** ***Evaluation for Stability Data***

In which the Applicant my find the procedures & statistical considerations normally accepted by the authorities for extrapolation of Product Shelf Life (related to the indended Storage conditions)

- **Just for Clinical Purposes,** ***MHRA guideline*** *– Points to consider when preparing the IMPD dossier*

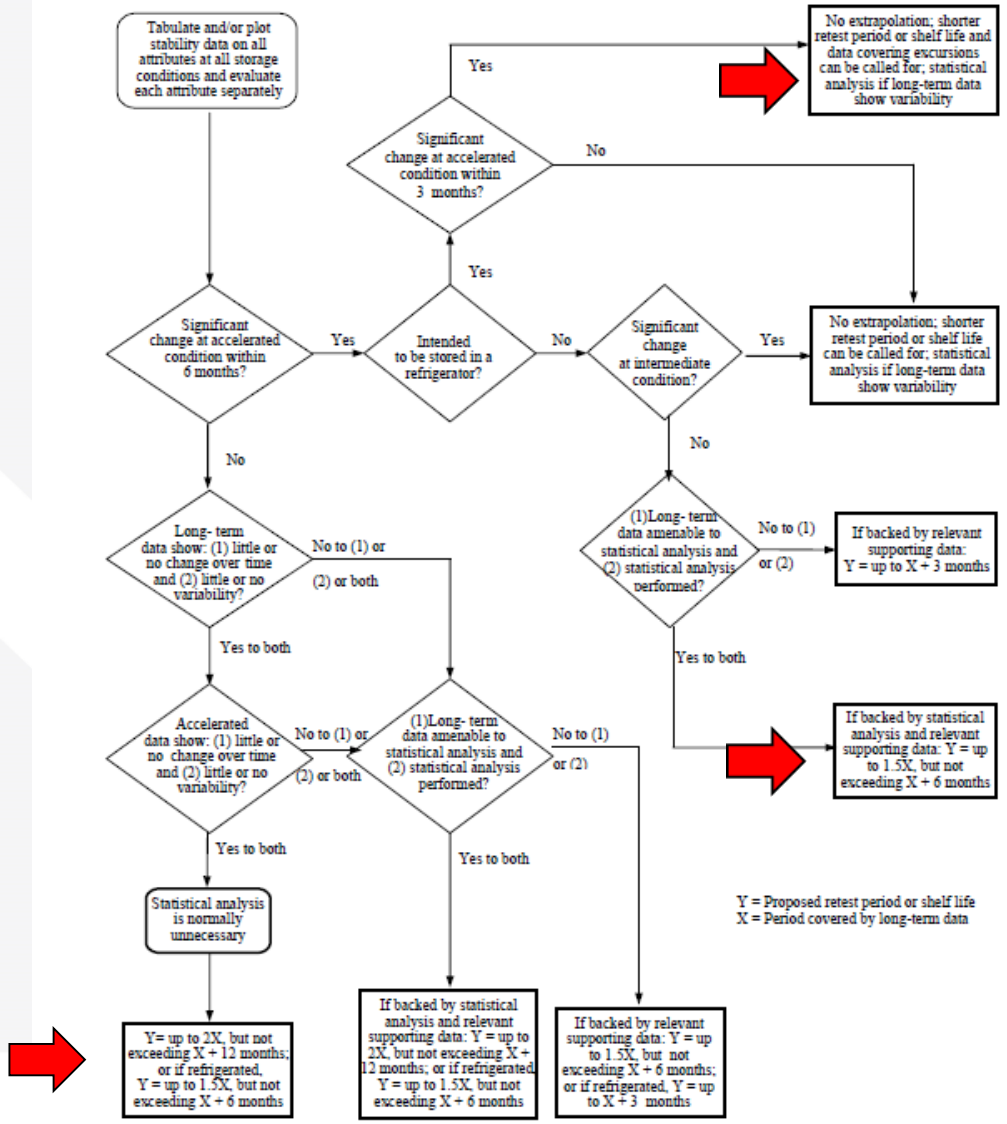
ICH Q1E, Appendix A

Topics:

- Different evaluation (and extensions) for *refrigerated products (2-8˚ C)*
- Both long term (X) and accelerated conditions must be evaluated in terms of variability
- Normally the shelf life extension does not exceed 1.5X or 2X (where X = period covered by long-term data), with a limitation of X+6 or X+12 months.
- **It is applied for MA/Commercial purposes; it represents a limit for IMP shelf life prediction!**

3. APPENDICES

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)



MHRA guideline for IMP

Topics:

- Both long term (real-time) and accelerated conditions must be evaluated in terms of data&trends
- It is more *flexible* in terms of shelf life extension: as stated, it may be up to 4 times the available real-time data to a max of 12 months OR 12 months plus the available real-time data.
- **It is applied ONLY for Clinical Shelf Life determination.**

MHRA
Regulating Medicines and Medical Devices

- specification against which the product is tested
- criteria used to extrapolate data
- analysis of trends
- proposed extension based on available real time data and acceptable accelerated data – this should not exceed four times the available real-time data to a maximum of 12 months or 12 months plus the available real-time data, ie:

Three months real-time data	12 months shelf life
Six months real-time data	18 months shelf life
12 months real-time data	24 months shelf life
24 months real-time data	36 months shelf life

Technical limitation of the former guidelines…

- They are focused on thermal/hygrometrical conditions which normally ‘simulate’ the (extreme) environmental conditions

- Quality of the Drug Product is evaluated for coupled and fixed combination of temperature and moisure (i.e. 40° C/75%RH, 30° C/65%RH or 75%RH, 25° C/60%RH)

- **Thus, these approaches cannot allow to define the interactive effect of T & RH in terms of Drug Product quality**

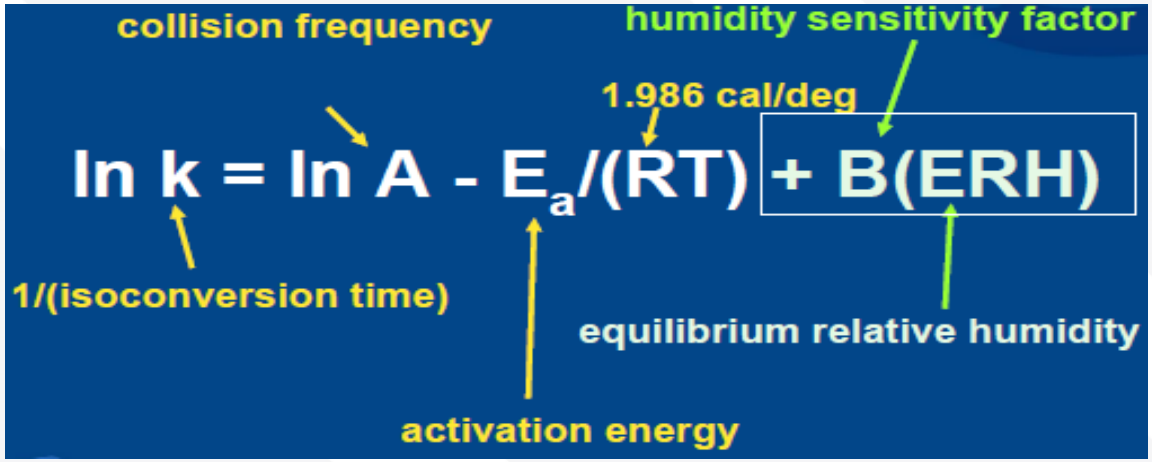
A QbD method: ASAP concepts

- A QbD *Univariate* approach for defining the relationship among Quality Properties & Temperature is the Arrhenius equation, representing the starting point for the further Watermann bivariate model (ASAP). Even if univariate, the Arrhenius equation is applicable for lyo prods, liquids or solid packaged in impermeable primary packaging (where RH effect is known a priori to be neglegible..)

- **A QbD *Bivariate* approach consists in the Ken Watermann's equation, also called ASAP (Accelerated Stability Assessment Program): the second factor RH (B coefficient) is added so to obtain, at least, a 2^2 + 1 (CP) DoE model**

- A QbD *Multivariate (>2 factors)* may be built… but what about the prediction capability? (i.e. strength, composition, particle size of API,etc)

A QbD method: ASAP concepts



Equation's factors & coefficients for DoE:

- Response: ln K equal to ln (slope) of the linear portion of the kinetics (at each condition tested)
- Ln A: model intercept
- 1/T (Kelvin degrees): first factor of the model
- $-E_a/R$: first factor's coefficient
- ERH: second factor of the model (%Relative Humidity)
- B: second factor's coefficient

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A QbD method: ASAP concepts

Ln k is the response for each T/RH coordinate in the DoE. It represents the slope of the *linearized* kinetics followed over the time for each T/RH trials. Following the *Isoconversion rule,* it is possible:

1. For a first-order kinetic, it ‘may’ be possible the linearization thorugh log function

2. **To use only the linear portion of the kinetic** (approach adopted in our case study).

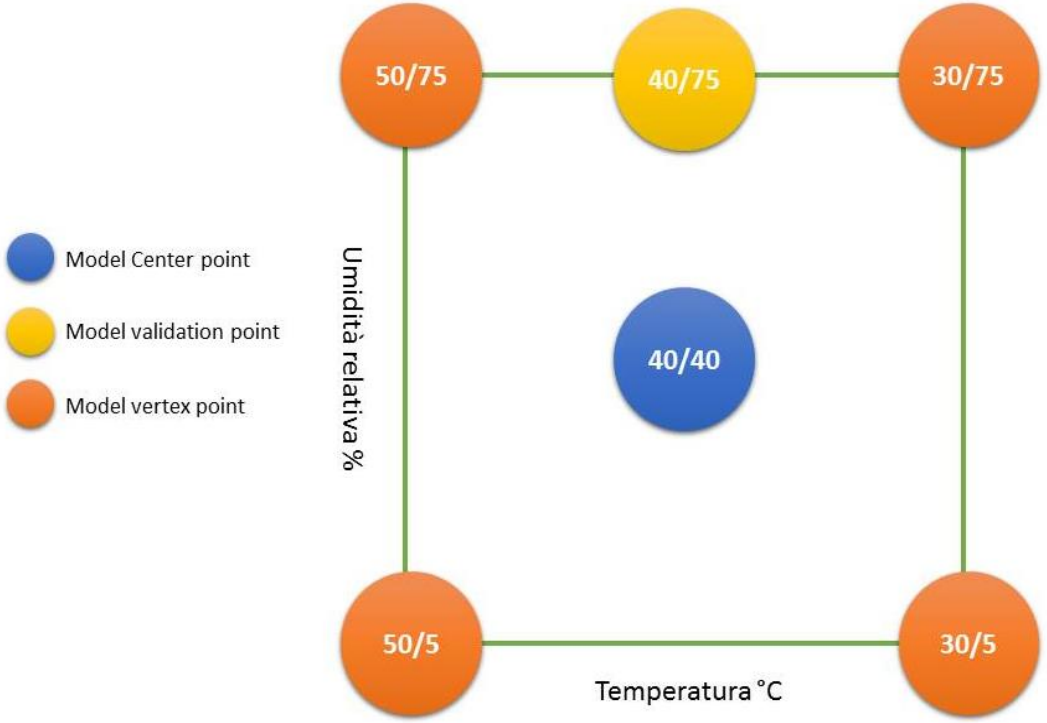
Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg

- Recordati DP already on the market, ICH stability data (also zone IV) as well as stress test stabilities available for comparison

- Most critical Degradation Product: DKP (Dichetopiperazyne)

- Pilot used for demonstrating the ASAP capability to predict shelf lives in a shorter time.

Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg: ASAP (DoE) conditions



- Samples of Tablets from ***3 industrial batches*** were taken
- HPLC methods for Assay&Related Imps validated
- Climatic Conditions 30/75 and 40/75 were tested using ICH climatic chambers
- Other Climatic conditions were prepared via saturated salt solutions.
- **Withdrawal of tablets samples (at each condition) was carried out DAILY for 2 weeks**

Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, saturated salt solutions used

Temperatura (°C)	Soluzione satura di sale	Umidità relativa (%)
30	camera climatica	75 ± 5
30	LiBr	6.16 ± 0.47
50	LiBr	5.53 ± 0.31
50	NaCl	74.43 ± 0.19
40	K_2CO_3	41.17± 1.50

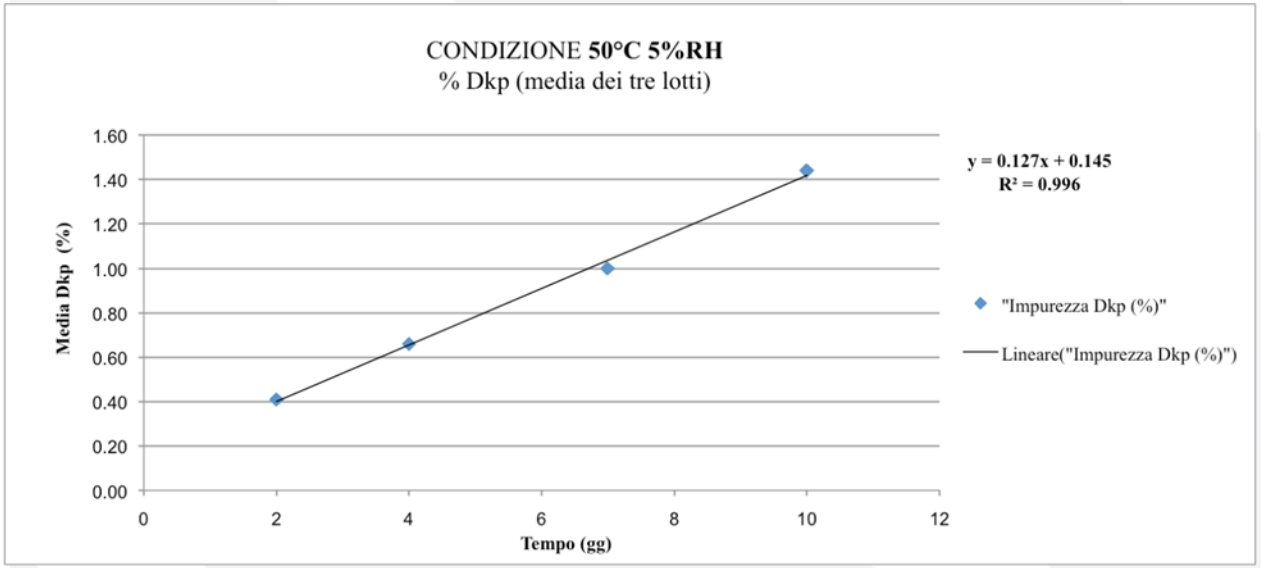
Saturated Salt Solution have been evaluated & validated (Rotronic probes) before starting the experiments.

Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, timepoints for sampling

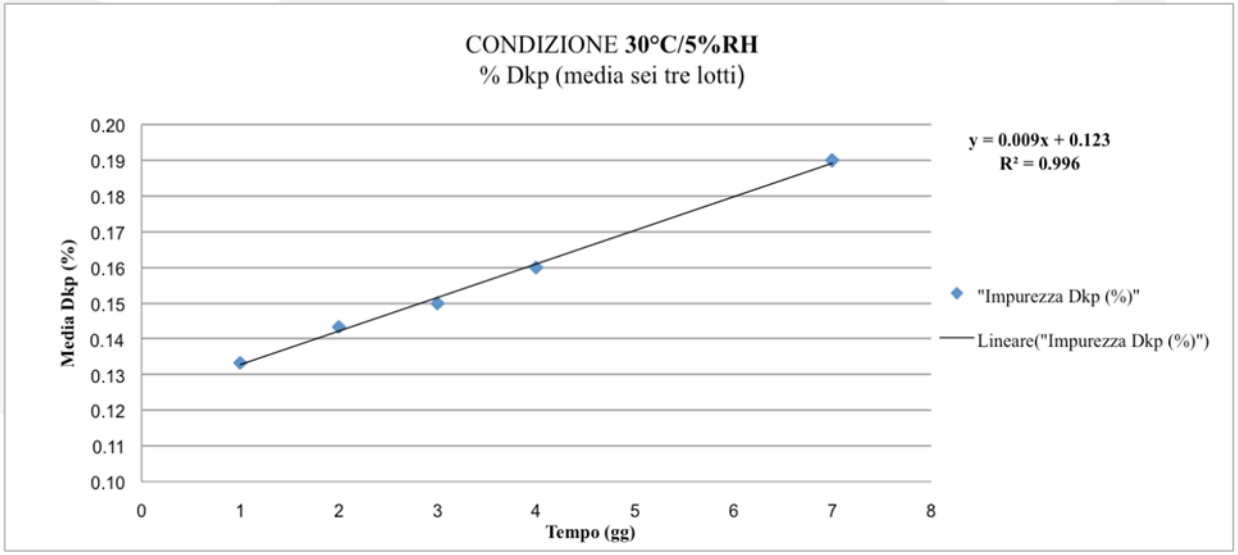
Temperatura (°C)	Umidità relativa (%)	Tempo (giorni/ore)
50	5	2,4,7,10 (gg)
50	75	2,6,8 (h)
30	5	1,2,3,4,7 (gg)
30	75	3,4,5,6,7 (gg)
40	40	1,3,4,5,6 (gg)

Timepoints sampled at different conditions (obj: gather data on the linear portion of the kinetics)

Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, linear regression at each T/RH condition



DKP% vs sampled timepoints: each measure is the mean of 3 different industrial batches.



Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, model values

Condizione	Coefficiente angolare (m)	Coefficiente di regressione (R^2)
50°C/5%RH	0.1273	0.997
50°C/75%RH	7.1343	0,982
30°C/5%RH	0.0094	0.997
30°C/75%RH	0.3540	0.999
40°C/40%RH (lotto 1)	0.1707	0.995
40°C/40%RH (lotto 2)	0.1472	0.993
40°C/40%RH (lotto 3)	0.1219	0.989

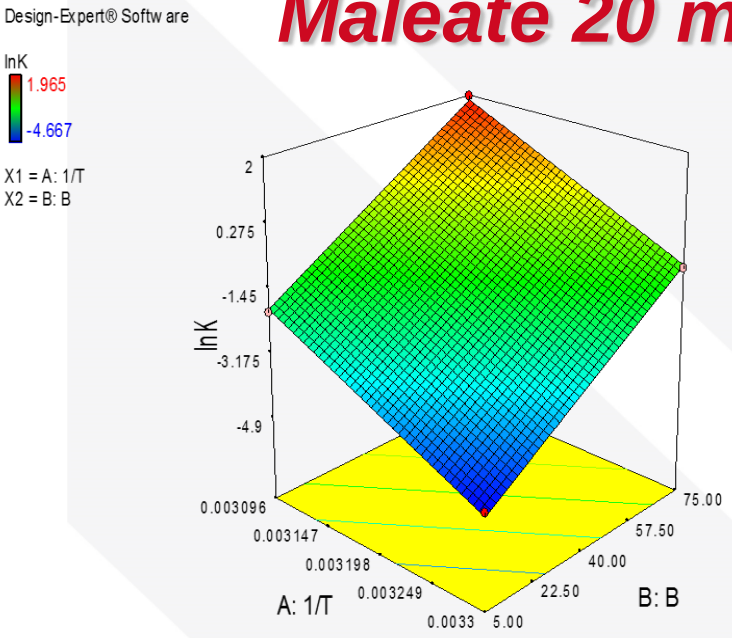
Slopes values (m) and related R^2 at each T/RH condition

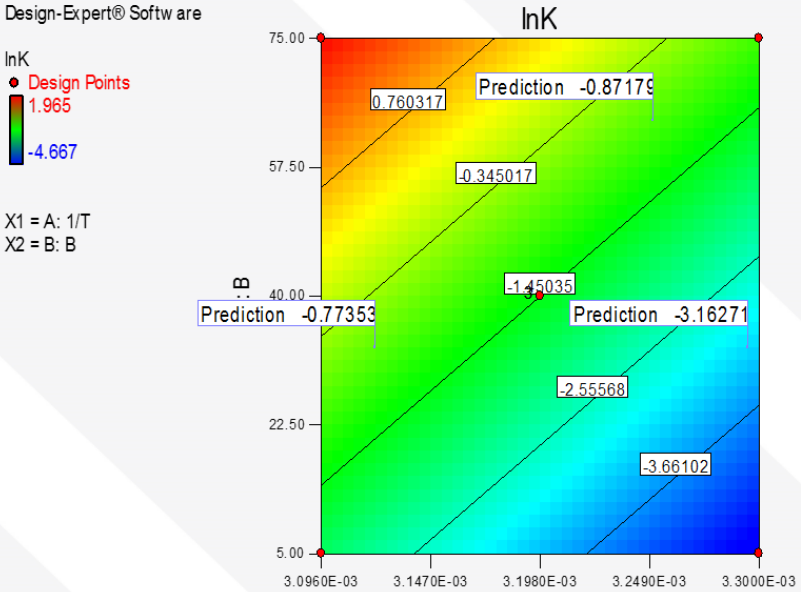
Transformed values for DoE modeling

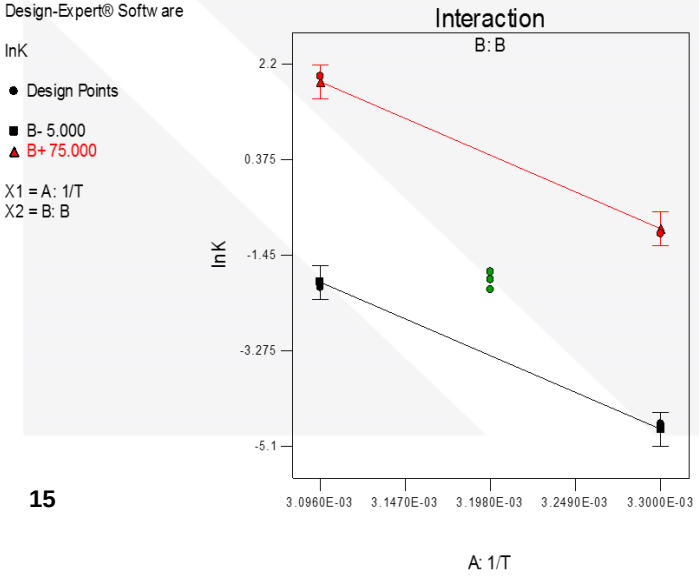
Tabella 10.4: Valori utilizzati per il *Design Space* ASAP.

Condizioni	1/T	ln (k)
50°C 75%RH	0.00309	1.965
50°C 5%RH	0.00309	-2.061
30°C 75%RH	0.00329	-1.038
30°C 5%RH	0.00329	-4.667
40°C 40%RH	0.00319	-1.920

Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, Graphs & Stat validation







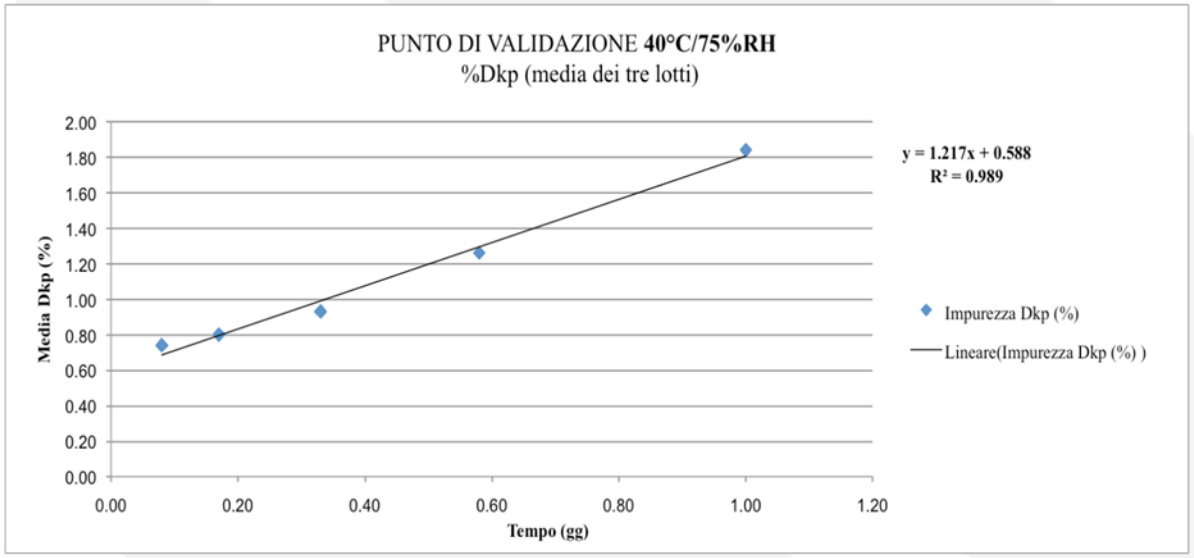
Response 1 lnK

ANOVA for selected factorial model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	22.51	2	11.26	351.07	0.0003	significant
A-1/T	*7.87*	*1*	*7.87*	*245.32*	*0.0006*	
B-B	*14.65*	*1*	*14.65*	*456.82*	*0.0002*	
Curvature	0.39	1	0.39	12.27	0.0394	significant
Residual	0.096	3	0.032			
Lack of Fit	*0.039*	*1*	*0.039*	*1.39*	*0.3594*	*not significant*
Pure Error	*0.057*	*2*	*0.028*			
Cor Total	23.00	6				

Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, External Validation



Empirical data at 40/75 open dish

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	1/T	3.198E-003	3.096E-003	3.300E-003	0.000	Actual
B	B	75.00	5.00	75.00	0.000	Actual

Response	Prediction	SE Mean	95% CI low	95% CI high	SE Pred	95% PI low	95% PI high
lnK	0.4633	0.11	0.11	0.82	0.21	-0.21	1.14

lnK prediction at 40/75 carried out through ASAP

Case Study: Lercanidipine HCl 20 mg + Enalapril Maleate 20 mg, External Validation

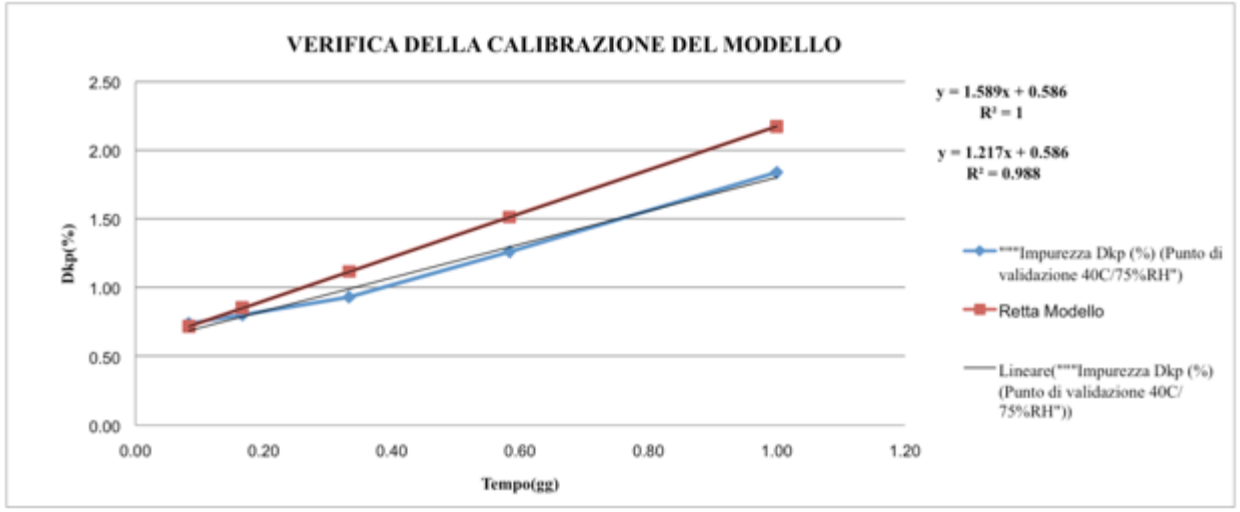


Figura 16.4: Retta del punto di validazione (blu) e retta del modello sperimentale (rossa)

- Predicted shelf life **is approx -30%** of the Actual one, for harsh conditions (open dishes, 40/75).
- **In just 2 weeks, it would have been possible to assign a 8.5 months shelf life (instead of 12 months) at 25°**
- Normally, the ASAP model is a Worst Case if compared to actual shelf life data: this leads to assign *cautelative* shelf lives to IMP…

Conclusion

- ASAP is the only QbD method for the prediction of product (or API) shelf life, it is based on a bivariate model (T/RH)
- Even if ASAP is not currently accepted for MA submission, it was accepted in some Phase I IMPD submission
- AAPS & FDA had recently organised a 2-day congress in US focused on ‘new’ method for assessing DP Stability. ASAP was often quoted in the congress..
- R&D/Development phases: ASAP is a QbD tool useful to screen: 1) excipients effect in prototypes 2) primary packaging for clinical/commercial purposes, 3) lead candidates (among prototypes) to be moved forward for clinical purposes, etc..

Thanks for your attention!