Workshop - Mercoledì 10 giugno

Risk-based thinking come vera intelligenza per il mondo farmaceutico

SIMPOSIO AFI

Moderatori

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Workshop schedule

10:10 – 10:40	La nuova era dell'intelligenza del rischio
10:40 - 11:10	Nuova ICH Q1: product intelligence per un approccio innovativo alla stabilità
11:10 – 11:35	ICH Q3E: approccio risk-based integrato per la valutazione di E&L
11:35 – 12:00	Il dato come bussola: l'analisi statistica a supporto del rischio
12:00 – 12:25	**Dalla teoria alla pratica: dalla gestione dello studio di stabilità all'analisi dei dati**
12:25 – 12:30	Conclusione dei lavori

From theory to practice: from stability study management up to data analysis

Stefano Selva

General Director – Monteresearch S.r.l

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Contents

Introduction to Enhanced Stability Model

Enhanced Stability Models, a new paradigm outlined by ICHQ1A Draft guideline

....from ancestral times till present days....

- CQAs tested on Commercial Batches within commercial packaging (primary) at specifically «prescribed» storage conditions.
- 25°C/60%RH + (30°C/65%RH)+40°C/75%RH are <u>mandatorly</u> required at the time of submission; <u>**a fixed bivariate**</u> coordinate set is the current «non sense» rule.
- Simple (linear) extrapolations allowed OR a «scheme prebased» decision tree to follow.
- Stability is then retested yearly by selecting 1-3 Annual Stability Batches.

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ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF
NEW DRUG SUBSTANCES AND PRODUCTS
Q1A(R2)

Data required at time of submission:

- Data on 3 commercial batches to commercial scale in representative packaging.
  - Substance and product
- 12 months long-term data (for example 30°C/75% RH)
- 6 months accelerated (for example 40°C/75% RH)
- Material must be stable to allow for extrapolation to longer shelf lives.
- Extrapolation usually follows a decision tree, or very simple linear regression.
- No simulations and limited opportunity for kinetic modelling (only as supportive data).

Enhanced Stability Models: ASAP and more..

- 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). Despite univariate, the Arrhenius equation is applicable for lyo products, liquids or solid packaged in impermeable primary packaging (where RH effect is known *a priori* to be negligible..)
- **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 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.)
- ASAP is based on DoE but several «mechanicistic/first principle» based models are available in literature and applied by Pharma Companies.

Models quoted & used by Pharma Companies (examples)

Accelerated Predictive Stability

A term intending to cover all kinetic modelling approaches which use elevated temperature (or other variables) to accelerate substance/product stability related quality decline. Many companies / academics use their own terms to describe subtle differences between approaches. Currently, we are aware of the following approaches which are broadly similar, utilising slightly different equations:

Named Approach	Differences	Reference	Similarities
ASAP: Accelerated Stability Assessment Program	Aims to degrade material to the specification limit and uses the 'time to breach' as the data set for modelling. Typically relies on linear degradation models.	https://freethinktech.com/freethink-publications/	• All utilise modified Arrhenius based equations. • All utilise purposefully degrading the material at higher temperatures (and across other variables, typically %RH), over time. • All rely on analytical methods which are suitably validated to determine the quantitative change in the SICQA (e.g. degradant content). • All use regression (linear or non-linear) to determine parameter values of the modified Arrhenius equations. • All assess the model for goodness of fit and feature some validation methodology. • All approaches typically have a manner of calculating prediction confidence, via confidence intervals or otherwise. • All approaches acknowledge the importance of verifying model performance with long-term stability studies.
AKM: Advanced Kinetic Modelling	Specifically developed with biologics and non-small molecule materials in mind. Utilises multi-step reaction models. Allows for curved degradation profiles.	https://doi.org/10.1038/s41598-023-35870-6 https://doi.org/10.1016/j.ijpharm.2021.121143	
ASM: Accelerated Stability Modelling	Focuses on determining the best model type for each material. Allows for curved degradation profiles. Similar in practice to AKM.	https://www.sciencedirect.com/book/9780128027868/accelerated-predictive-stability	
AF: Acceleration Factor	Applicable to stability dissolution slowdown of solid oral products only.	https://doi.org/10.1016/j.xphs.2018.10.025	
'General' APS models	Individual model types or applications that haven't been popularised under a different term. Many different publications exist offering modelling of other material attributes.	Overarching Book: https://www.sciencedirect.com/book/9780128027868/accelerated-predictive-stability Drug load: https://doi.org/10.1016/j.xphs.2018.12.003 Molecular Mobility: https://doi.org/10.1016/j.ijpharm.2014.11.063 Excipient content: https://doi.org/10.1248/cpb.c20-00443 FDA review: doi: 10.1208/s12249-022-02498-0	

Moisture Vapour Transmission Rate Modelling (Packaging Simulations)	Applicable to packaging only. Used to model packaging performance for materials at different temperature over time. Used in tandem with any APS approach to provide internal %RH to the model.	See https://www.sciencedirect.com/book/9780128027868/accelerated-predictive-stability

*There may be other approaches in industry / literature which fit into the 'APS' definition which we are not aware of.

Slide taken from: Dr. Luke Scrivens, Principal Scientist, Astra Zeneca; DDF Berlin 2026

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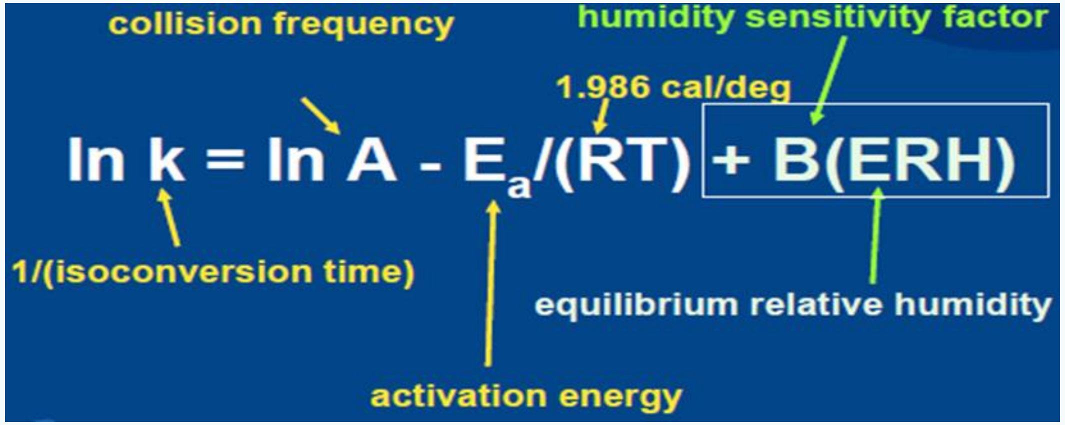
Enhanced Stability Model: ASAP concepts

- 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
- -Ea/R: first factor's coefficient
- ERH: second factor of the model (%Relative Humidity)
- B: second factor's coefficient

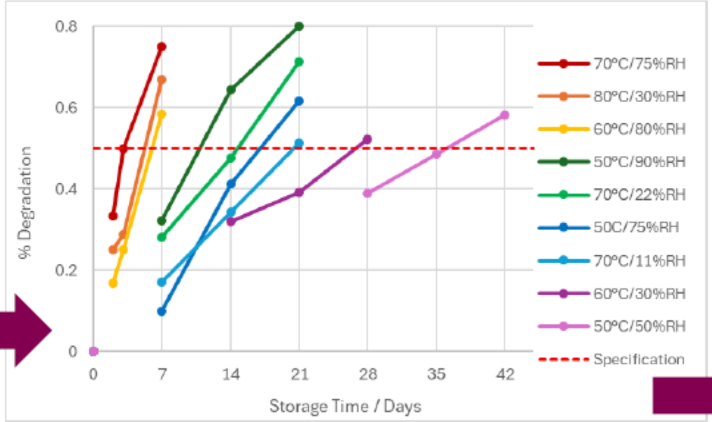


The ASAP is a «time to failure» Model: once built the Design Space (ln K), a **t(iso)** model can be used to determine the extrapolated Shelf Life of the Product.

Enhanced Stability Model: ASAP concepts

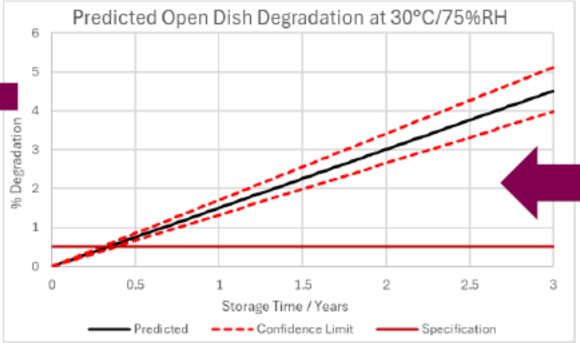
Example Approach - ASAP

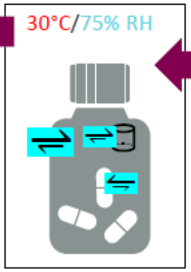
Condition °C/%RH	Storage time / days
80/30	2, 3, 7
70/75	2, 3, 7
70/22	7, 14, 21
70/11	7, 14, 21
60/80	2, 3, 7
60/30	14, 21, 28
50/90	7, 14, 21
50/75	7, 14, 21
50/50	28, 35, 42



Condition °C/%RH	t_{iso}
70/75	3.0
80/30	5.2
60/80	6.0
50/90	10.8
70/22	14.7
50/75	17.0
70/11	20.5
60/30	26.8
50/50	36.0

$$Ln(t_{iso}) = Ln(A) + \frac{E_a}{RT} + B.RH$$

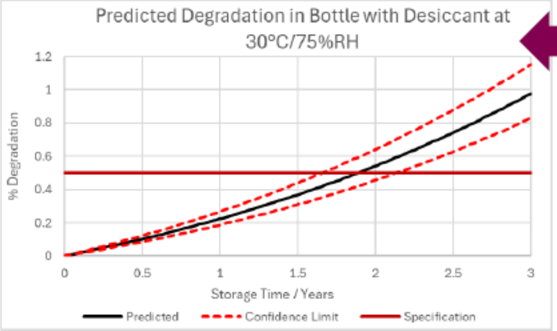




Moisture Isotherms

Packaging permeability

Desiccant mass



Multi-year shelf-life predicted within 42-day study

Slide taken from: Dr. Luke Scrivens, Principal Scientist, Astra Zeneca; DDF Berlin 2026

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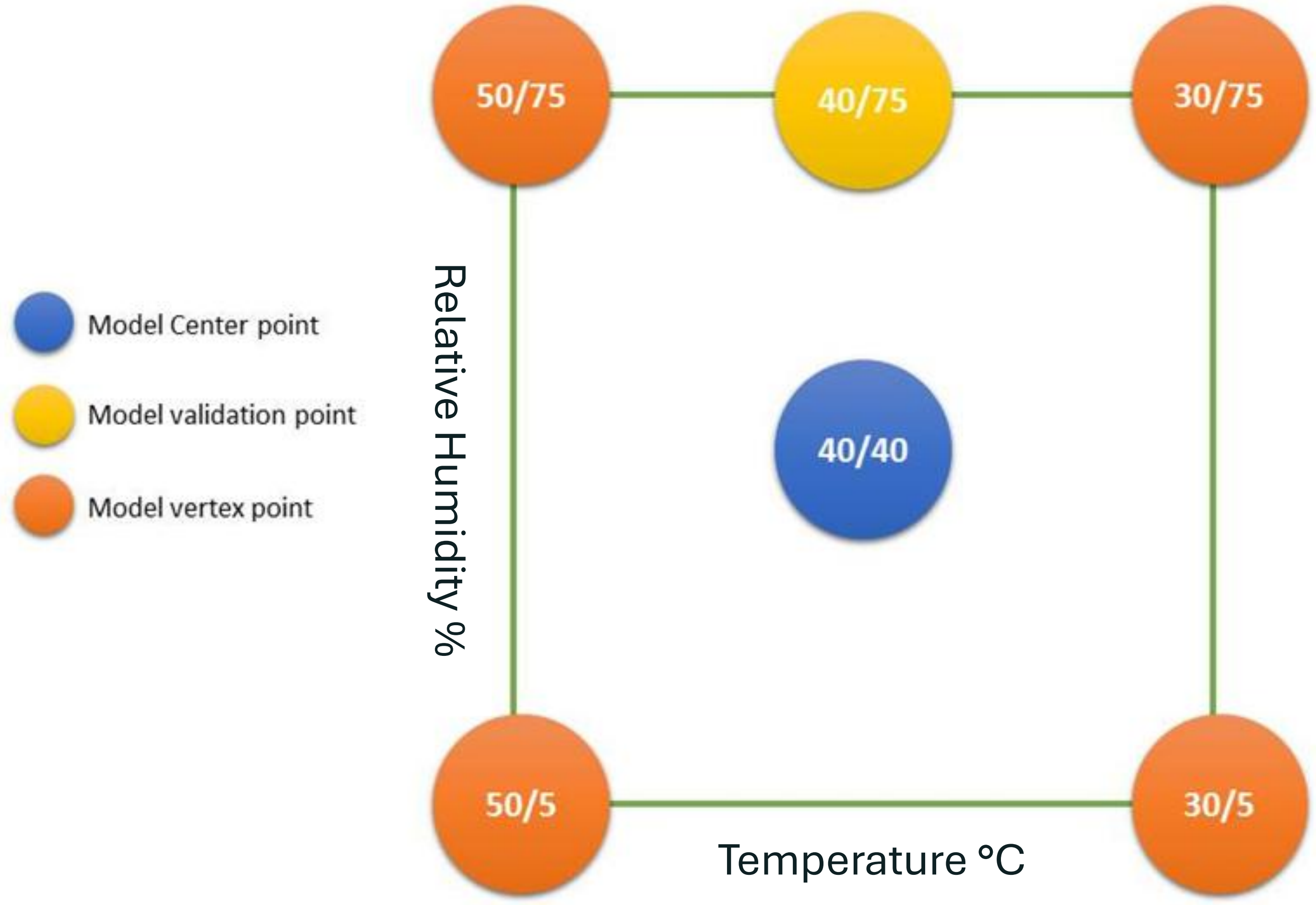
Case study deployment

“Stressed” Design Space Plan of ASAP (an example)

- Samples of Tablets from ***3 industrial batches*** were taken.
- HPLC methods for Assay & Related Impurities 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.**



How to set experimentally the ASAP “stressed” conditions?

Temperature (°C)	Salt saturated solution	Relative Humidity (%)
30	Climatic chamber	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

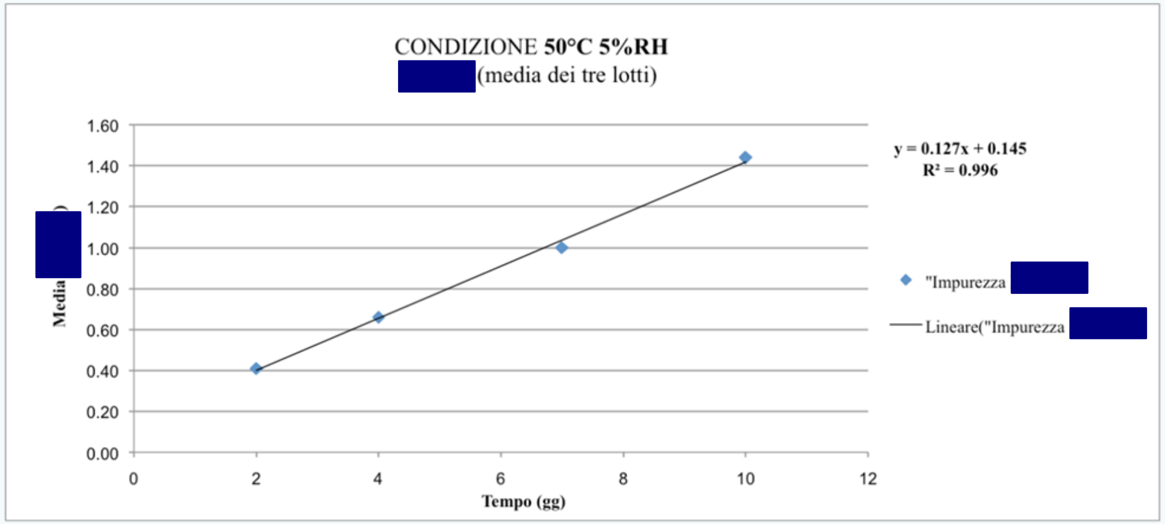
Study (minimal, suggested) timepoints

Temperature (°C)	Relative Humidity (%)	Time (days/hours)
50	5	2, 4, 7, 10 days
50	75	2, 6, 8 hours
30	5	1, 2, 3, 4, 7 days
30	75	3, 4, 5, 6, 7 days
40	40	1, 3, 4, 5, 6 days

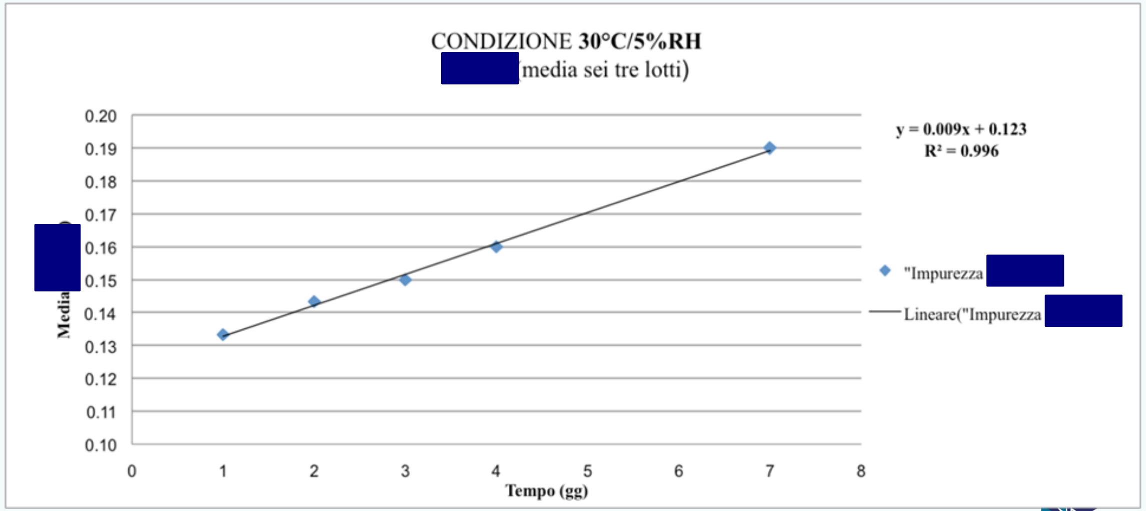
Timepoints sampled at different conditions

Objective: gather data on the linear portion of the kinetics

ASAP basic Concept: to model the “linear” part (of a first order kinetic) for each T/RH



- IMP% vs sampled time points: each measure is the mean of 3 different representative batches.



How to “feed” the DoE (ASAP) Model....

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

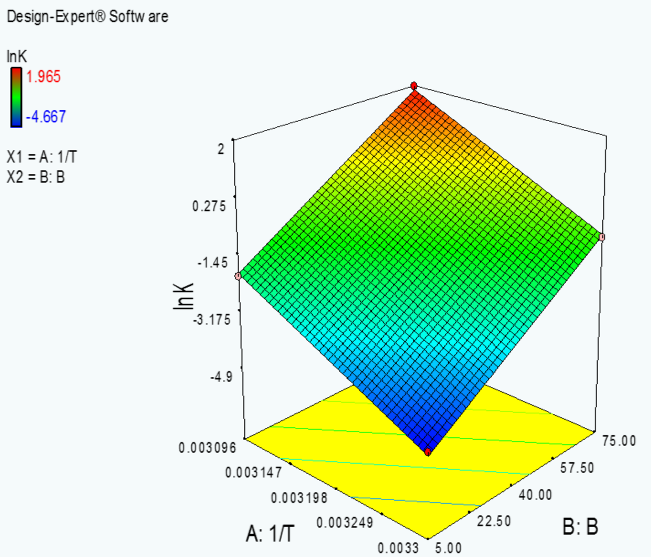
Slopes values (m) and related R2 at each T/RH condition

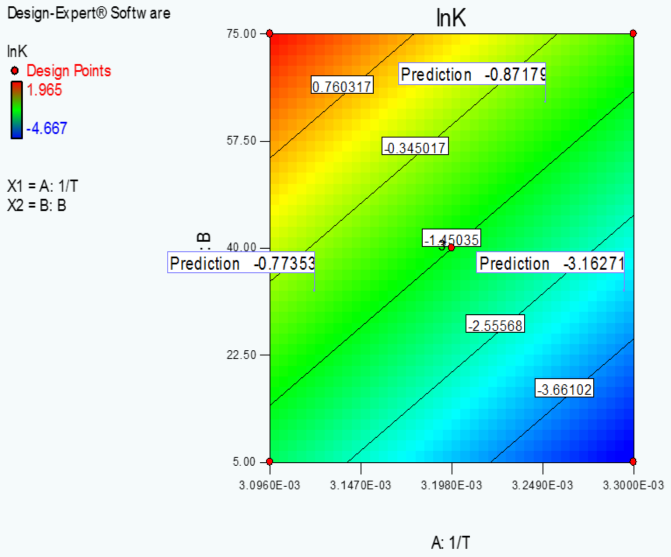
Transformed values for DoE modeling

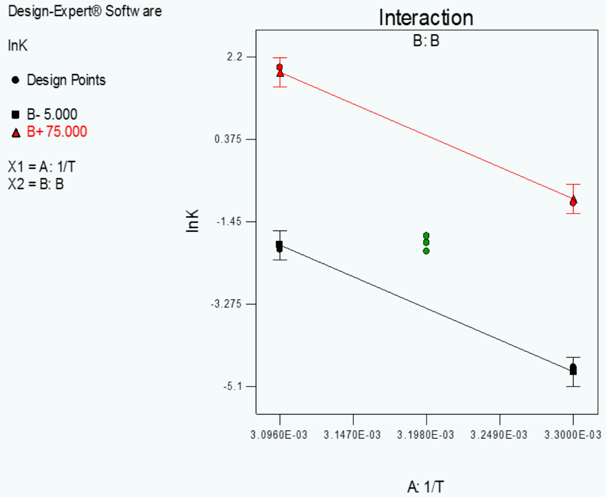
Tabella 10.4: Valori utilizzati per il *Design Space* ASAP.

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

“Stress” Design Space, including model fitting with CP







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				

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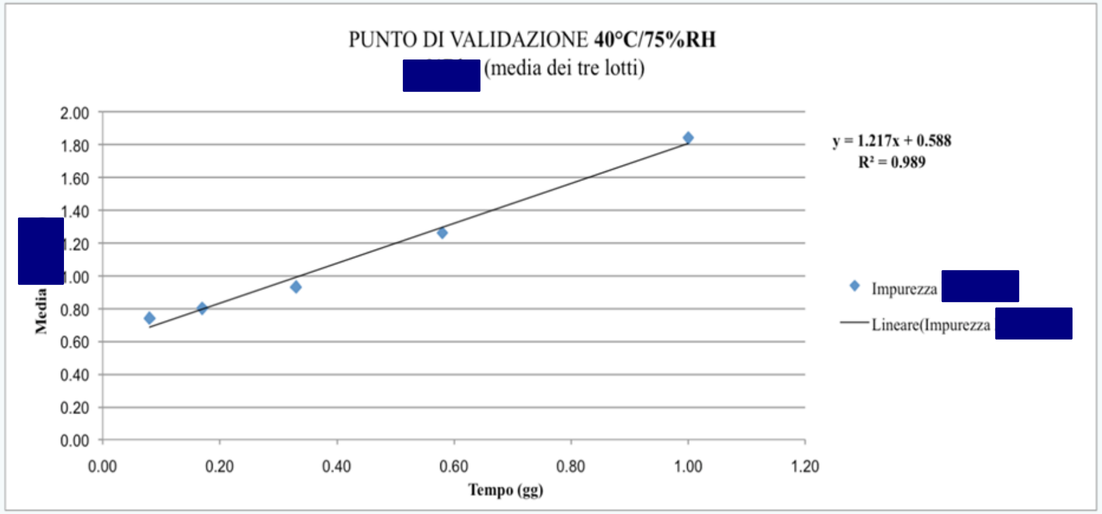
External Validation



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

ASAP Model Prediction of “m” vs real slope

- Predicted shelf life is approximately -30% of the Actual one, for harsh conditions (open dishes, 40/75).
- **In just 2 weeks, it would have been possible to assign 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…

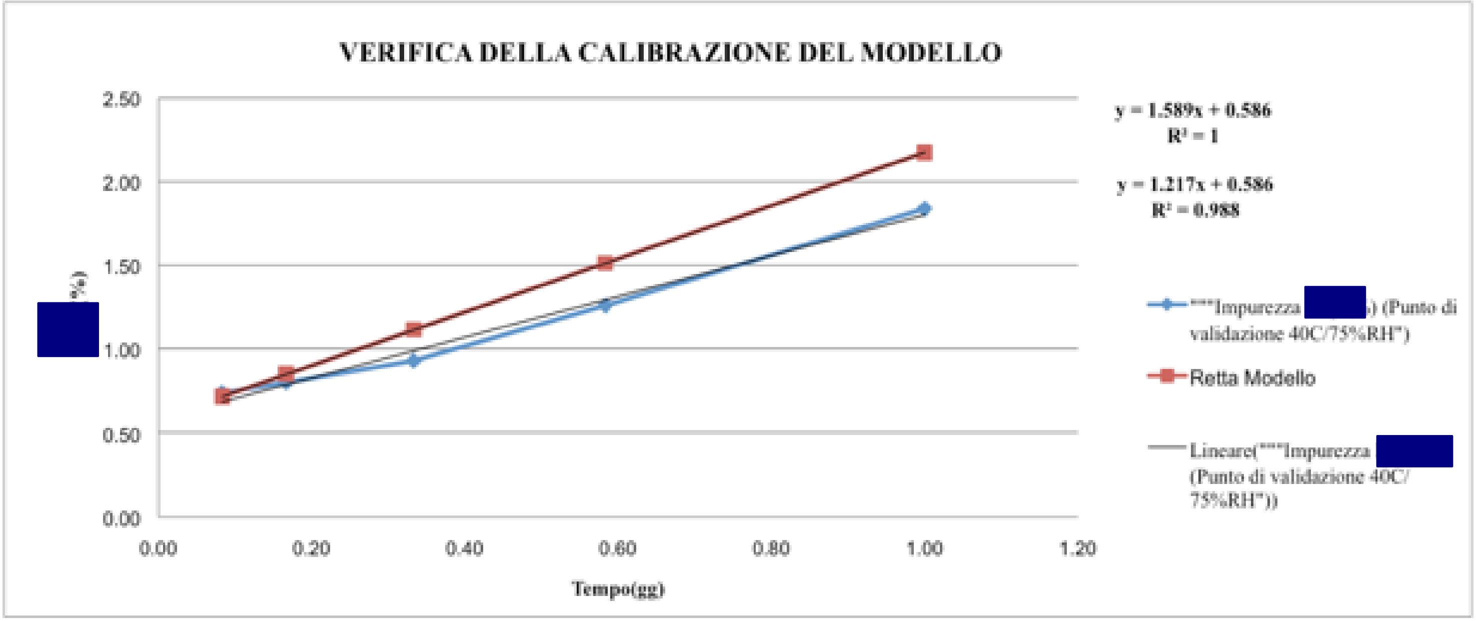


Figura 16.4: Retta del punto di validazione (blu) e retta del modello sperimentale (rossa)

Conclusions and take-home messages

Take-home Facts

Along with others, ASAP is a «DoE-based» Stability Ehnanced Model which may «supersede» the current stability approach. As per any kind of math model used, ASAP needs a validation step before using it for prediction scopes. Be careful that....

.... Despite it is very useful at all R&D levels, should it be adopted for a regulatory scope a skilled «CMC Regulatory» expert is needed to «convert» these concepts with clear wording and summaries.

To note:

Agencies' assessors need to be trained on ASAP and/or analogue prediction models in order to be ready to analyse, challenge MAHs, partecipate to Scientific Advices and eventually approve Enhanced Models submitted in CTDs.

Thanks for listening

Dalla teoria alla pratica: dalla gestione dello studio di stabilità all'analisi dei dati

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Any questions?

Do you need any information?

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