A Quality by Design approach for Longitudinal Quality Attributes.

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Abstract

The concept of Quality by Design (QbD) as published in ICH-Q8 is currently one of the most recurrent topics in the pharmaceutical literature. This guideline recommends the use of information and prior knowledge gathered during pharmaceutical development studies to provide a scientific rationale for the manufacturing process of a product and provide guarantee of future quality. This poses several challenges from a statistical standpoint and requires a shift in paradigm from traditional statistical practices. First, to provide "assurance of quality" of future lots implies the need to make predictions regarding quality given past evidence and data. Second, the Quality Attributes described in the Q8 guidelines are not always a set of unique, independent measurements. In many cases, these criteria are complicated longitudinal data with successive acceptance criteria over a defined period of time. A common example is a dissolution profile for a modified or extended release solid dosage form that must fall within acceptance limits at several time points. A Bayesian approach for longitudinal data obtained in various conditions of a Design of Experiment is provided to elegantly address the ICH-Q8 recommendation to provide assurance of quality and derive a scientifically sound Design Space.

Keywords : Quality by Design, Design Space, Bayesian modeling, Dissolution

1 Introduction

The concept of Quality by Design (QbD) is a regular topic in current pharmaceutical literature. It is most often applied to drug discovery, method development and production. However, this concept is not new. Roots go back as far as the 1950s, when Juran [10] and Deming [3] introduced the concept within the tenets of quality management. More recently, Design For Six Sigma was introduced as a complementary method to the improvement methods of Lean Six Sigma, specifically to use for new product or process development. The fundamental idea is that quality of a product begins, and is sustained, through rigorous product design. If each production process is designed to deliver robust quality, most problems related to the manufacturing of the product could be avoided. Business efficiency resulting from these design methods has led to an expansion of the QbD concept in the pharmaceutical industry.

More recently, the Food and Drug Administration (FDA) and the International Conference for Harmonization (ICH) have seen the opportunity to apply QbD to gain knowledge and understanding about the products and processes of the pharmaceutical industry (see the following regulatory document and guidelines: Food and Drugs Administration, 2007, 2011) [20,21] and (ICH Q8, 2009; ICH Q9, 2005; ICH Q10, 2008) [9, 7, 8].

These guidelines rely on the use of information and knowledge gathered during development studies, to provide a scientific rationale for the design of the manufacturing process for a pharmaceutical product (Yu, 2008) [25]. In these guidelines, the Design Space (DS) has been defined as the "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality" for the analytical outputs or processes involved in Pharmaceutical Development. This document is clearly devoted to optimization strategies and robustness studies for various processes having Quality Attributes (QA) assessed by various analytical procedures.

QbD emphasizes the elements of product, process understanding, and process control. It advocates a systematic approach for the development of these elements based on clear and predefined objectives (e.g. the Quality Target Product Profile (QTPP)).

Particularly, the risk that a product or a process will not fulfill the quality requirements must be assessed. Regulatory actions now incorporate this risk-based approach. Hence, pharmaceutical manufacturers must fully comply with these guidelines to be in order to prove their ability to provide high quality medicines. See for instance the recent manual of policies and procedures (MaPP) published by the Food and Drug Administration (2011) [22]. Of course, the interest of the industries is high and goes beyond simply meeting evolving regulatory expectations, as QbD will result in improved quality control (QC). Indeed, as quality is proven during each production step, the final product quality requirements will be more likely met, although final product (release) specifications will still be mandatory. With better understanding and more reliable processes, both variability and rejection rates will be reduced which is a noticeable gain for both the consumers and the producers, in line with risk management expectations (ICH Q9, 2005) [7].

While conceptually meaningful and relevant to ensure future quality of products, the QbD recommendations pose several challenges from a statistical standpoint, and require a shift in paradigm from traditional statistical practices. First, the concept of providing "assurance of quality" for future lots implies the need to make predictions about the future quality given the past evidence and data. This naturally implies the use of Bayesian statistics to properly address this goal. Second, the Q8 guidelines mention Quality Attributes in general terms, as if there were a unique single attribute or a set of independent attributes. In many cases, the Quality Attributes may be more complex, with complicated correlations structures such as longitudinal data that should successively fall within specifications to meet their global quality requirement. A common example is the dissolution profile of a modified or extended release solid dosage form product that must fall within acceptance limits at several time points. Evaluating the predictive probability of success of jointly meeting each set of specifications given the assumed underlying model and high dependencies between measurements is a challenge that may prove cumbersome or even impossible using frequentist statistics. Bayesian approach provides elegant and natural answers.
This work will present a practical solution for the implementation of QbD strategy for repeated measure data with multiple testing time points and conditional retesting of additional units, using dissolution profiles as supporting example. The key statistical challenges to overcome to make QbD a reality for such longitudinal data are critical:

- Multi-factorial Design of Experiments (DoE) for longitudinal responses
- Modeling of longitudinal responses in a multi-factorial design
- Deriving the joint predictive probability of meeting acceptance criteria at each testing time point and at all stages of successive testing
- Finding the Design Space (DS) that ensures the joint probability of success of the multiple tests and retests

It can be postulated that a Bayesian approach is the only option to practically achieve such an objective as required by ICH-Q8. The justification and added value of the use of Bayesian statistics for proper QbD implementation has been discussed extensively by several authors such as Peterson et al. [13-17], Miró-Quesada [12] and Lebrun et al. [11].

2 An example with Longitudinal Quality Attribute

2.1 The dissolution test.

For various dosage forms of products, in vitro dissolution tests or profiles are required for release. In particular, a dissolution profile rather than a single dissolution result is reported to assess the ability of the dosage form to deliver the active pharmaceutical ingredient (API) during an extended release time claimed. In vitro dissolution data, together with chemistry, manufacturing and control data, are components of new drug applications or release testing. The USP provides information in the way of a general chapter on dissolution, and chapters on disintegration and drug release (USP 32-NF 27 <711>, 2009) [23]. The FDA and ICH also provide guidelines on development and validation of dissolution procedures (ICH-Q2R guideline, 2005; Guidance for Industry 1997, 1997)[6, 18, 19].

The dissolution procedure has several distinct components including: a dissolution medium, an apparatus with vessels, and the assay (Vaghela et al. 2011) [24]. A dissolution test or procedure is as follows: the dosage form, such as a tablet or capsule, is placed into a medium to dissolve. The resulting solution is sampled over time, and assayed (often by HPLC) for concentration of active pharmaceutical ingredient (API). For extended release dosage forms, for example, measurements are usually performed at several time points, e.g. 2, 8 and 14 hours.

The USP <711> dissolution procedure allows for three successive stages of testing, such that if the acceptance criteria are not met at the first stage, additional units may be tested and modified criteria applied at the next stage. According to USP <711>, at least six test units (e.g. tablets) should be tested and in the first stage of testing every individual concentration value should fall within the stated range at each of the time points. In our example, the limits for the concentration of API are successively: within 0%-20% at 2 hours, 40%-70% at 8 hours, and 60%-100% at 14 hours. If any of the six test units fail to meet the criteria at any of the testing time points, then additional units are tested and assessed against criteria based on average and individual results. The details of the three stages are included into Table 1.

These limits are product-dependent and defended by the company during the submission process. Since all individual measurements must fall within the limits, it is critical to be able to predict future individual results, instead of a (conditional) mean as is usually done in a frequentist approach. This is further justification for the choice of a Bayesian approach.

<insert Table 1 here>

Acceptance Table 2

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Table 1: USP <711> three stages acceptance for dissolution testing applied to extended release formulation.

2.2 The design of experiments and the design space.

In this example, two critical factors were identified and chosen, based on a risk assessment using historical process data, to analyze their impact on the dissolution profiles. They are named X1 and X2 for simplicity. A designed experiment was conducted to model the impact of X1 and X2, varying both factors across a range centered on the current nominal target settings. Specifically, eight commercial scale batches of the tablets, covering a range of X1 and X2 were used, creating a designed experiment over the X1 and X2 ranges. N=12 tablets were tested at each dissolution interval for each batch, except at the central condition where 24 tablets were analyzed.

The results of one experiment over the 8 over the experimental space, the acceptance time points, and the individual unit dissolution results at each testing time point are represented in Figure 1 (simulated data). The complete experimental domain can be seen on Figure 2. It was observed that all six results from the first stage of testing fall within the limits at the center of the experimental space (X1=28 and X2=3.9). As conditions move away from the center into the corners of the design, results partially fall outside the acceptance criteria. The central objective in the experiment was to identify the X1 and X2 set of conditions that result in a high probability that the dissolution profile will pass for most future batches, i.e. to estimate a Design Space (DS) for this processing step.

<Figure 1 here>

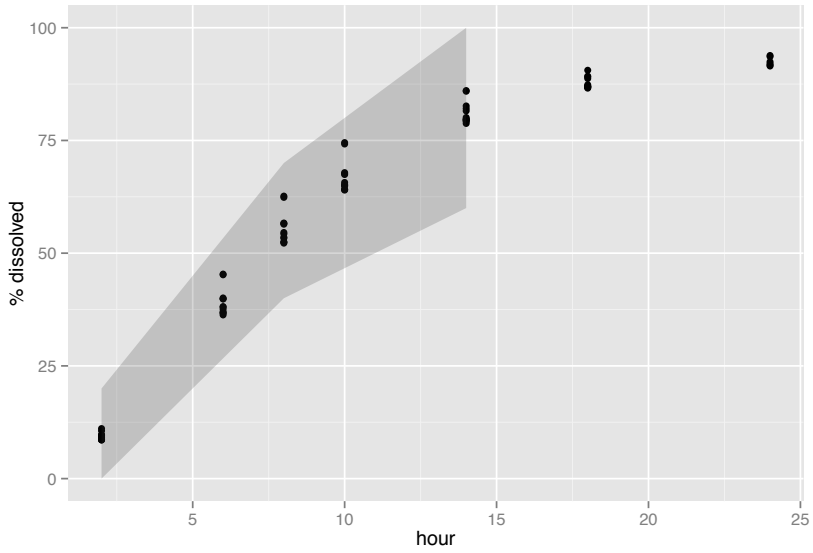

Figure 1: Representation of one of the experiments performed (simulated), the acceptance criteria (grey shaded area) and the individual measurements (dots) obtained.

3 Methodology

3.1 Bayesian regression and prediction

Two main quantities are of great interest in the QbD context. First, the posterior distribution of the model parameters quantifies the effects of the experimental factors on the response(s). Second, the predictive distribution of responses Y, given a prior distribution and observed data is used to compute the DS. The amount of uncertainty in the predictive distribution and the variability in the DS provide information regarding the underlying process and the quality of the statistical model. A non-hierarchical or fixed-effect linear response surface (RS) model in the form of a polynomial with p parameters is usually fitted to the responses. Lebrun et al. [11] proposed an alternative Bayesian multivariate linear model with informative priors by extending the non-informative models proposed by Box and Tiao [1]. When using conjugate prior distributions –informative or not – Lebrun et al. [11] have shown that the (joint) predictive distribution of the responses follows a (multivariate) non-central Student's distribution.

Another important result is that the predictive distributions, using either non-informative or informative priors, are of β-expectation (Guttman, 1970) [4]. This means that the highest probability density (HPD) intervals derived from the predictive distribution are the β-expectation joint tolerance intervals (Hamada et al., 2004) [5].

3.2 Bayesian Hierarchical longitudinal model

For longitudinal Critical Quality Attributes such as dissolution profiles for extended or modified release dosage forms, a hierarchical (or mixed effect) response surface (RS) linear model (Chib and Carlin, 1999) [2] must be envisaged. When hierarchy is envisaged on one or several parameters of a linear model (i.e. in the presence of random effects), there is generally no closed form available for the predictive distribution of the responses, as the one described in Lebrun et al. [11]. Markov-Chain Monte-Carlo methods (MCMC) must therefore be used to sample from the posterior predictive distribution.

For the DoE described above and the dissolution test data shown in Figure 1, the following mixed-effect model was developed and applied:

$$\begin{aligned} logit(\%dissolved) = {} & (b_0 + \beta_0) + b_1 * X1 + b_2 * X2 + b_3 * log(hour) + b_4 * log(hour)^2 + \\ & b_5 * X1 * X2 + b_6 * X1 * log(hour) + (b_7 + \beta_7) * X2 * log(Hours) + \\ & b_8 * X2 * log(hour)^2 + b_9 * X1 * X2 * log(hour) + \varepsilon \,, \end{aligned}$$

where $(\beta_0, \beta_7) \sim \text{MVNormal}(\mathbf{0}, \mathbf{\Sigma}_{\text{vessels[X2]}})$,

$\varepsilon_i \sim \text{Normal}(0, \sigma^2)$, and (Equation 1)

$\mathbf{\Sigma}_{\text{vessels[X2]}}$ is structured to account for the variability of the tablets in the vessels and X2 levels.

Because the percentage of API dissolved is a value bounded between 0 and 1, a logit transformation was applied in order to assume a normal distribution for this response. This has the advantage that the transformed data are well modeled by a simple linear regression with a small quadratic effect on the log(hour) factor. This linearization allows the use of a RS model with the addition of the effects and interactions for X1 and X2. An alternative solution would have been to use a Beta distribution to model the percentage dissolved as a function of time, but the logit transformation was found

simple to use and appropriate in this example. Combined with the use of the natural logarithm of the dissolution test time expressed in hours, it was found that the dissolution profile could adequately be modeled using this linear model. The transformed data with the fitted linear model are represented in Figure 2.

<Figure 2 here>

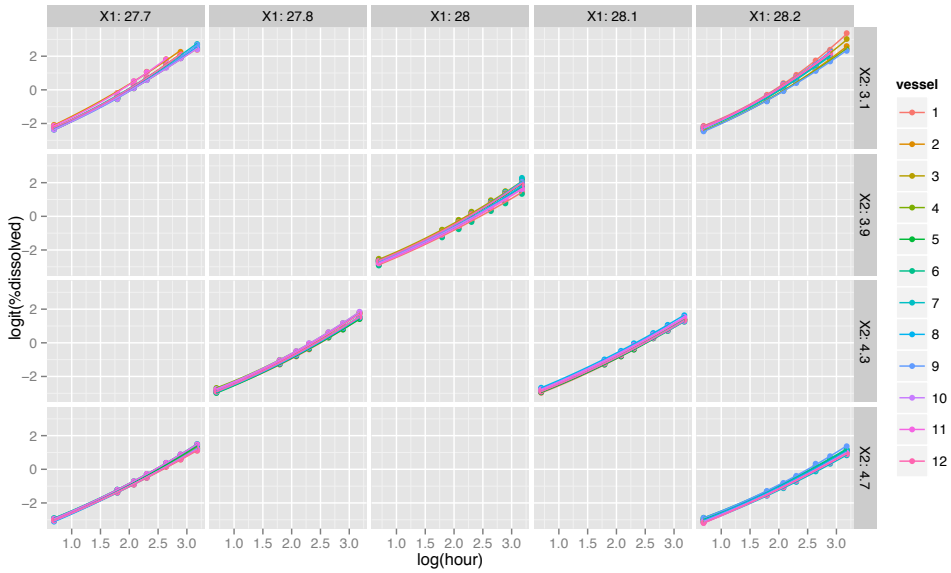

Figure 2: Model and individual data points over the complete experimental domain in the new transformed axes: logit(%dissolved) as a function of the ln(hour).

3.3 Design Space Definition

Assume a process with k process parameters (PP)

$$\chi = \{x_1, \dots, x_k\},$$

belonging to an experimental domain χ. A definition of the Design Space has been proposed as (Peterson, 2008)

$$DS = \{x \in \chi \,|P(Y \in \mathrm{A}|x, data) \geq \pi\},$$

where Y is a vector of responses that is likely to fall within an acceptance region (A) with a minimal probability or "quality level" π. Acceptance limits are usually previously defined or imposed by regulations before experiments and data analysis are performed. They reflect the quality to be achieved and maintained. The DS is then the set of combinations of input conditions (here, X1 and X2) where the joint posterior probability that future responses lie within acceptance limits is sufficiently high. The

effects or contributions of the factors (process parameters), i.e. model parameters, remain unknown and their values are estimated with uncertainty. The predictive posterior probability is then computed using the model estimates and incorporating the uncertainty of parameter estimates. This uncertainty is highest in the case of new product or process development or for new process validation when limited full-scale manufacturing data are available.

4 Results

4.1 Bayesian Hierarchical longitudinal model

The model described in Section 3.2 was fit to the experimental data using the *MCMChregress* function of the *MCMCpack* package freely available for R. R 2.14 has been used to compute the predictive probabilities at the specified dissolution test time points (hours) and the factor levels. Figure 3 illustrates the predictions of a mean future individual dissolution profile in the original scale, with the prediction (β-expectation tolerance) intervals shown in red. In this last graph, the grey areas indicate the acceptance criteria. Confronting the model to the data allows confirming that the model fit well the data. The MCMC methods allow direct estimation of the predictive distribution and therefore the 95% joint prediction interval. It can also be seen in Figure 3 that the prediction interval seems to fall within specifications at this factor setting of X1 and X2. From the predictions, the risk for the profile to fall outside specification appears to be more sensitive to changes in X2 (results not presented). The question remains how much change in X1 and X2 would be allowed to ensure with a high probability that all future dissolution tests will meet acceptance criteria.

<Figure 3 here>

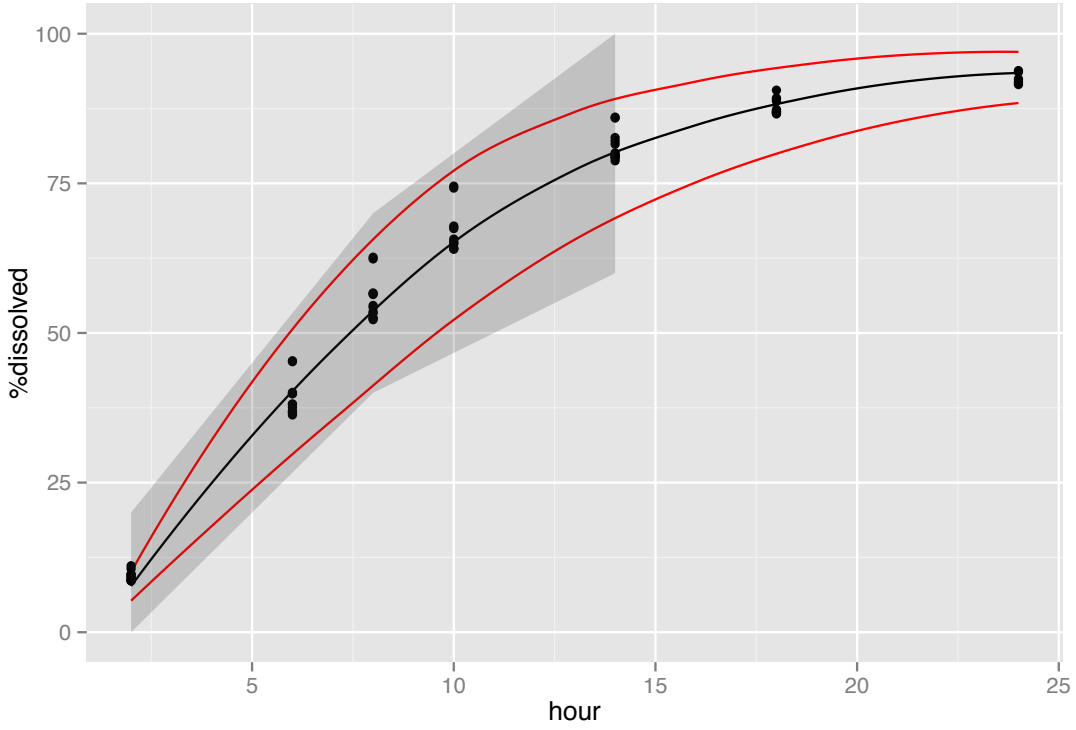

Figure 3: Mean predictions (black) and 95% β-expectation tolerance or prediction intervals (red) and limits or specifications (grey shaded area) for the data depicted in Figure 1 (simulated).

4.2 Design space

For any combination of the X1 and X2 factors, the predictive probability of passing Stage 1, 2 and 3 of the dissolution test procedure has been computed, using the uncertainty of the predictive distribution. For a 3-stage testing of the three time points simultaneously, the following predictive probabilities are computed:

- Probability of passing Stage 1
- Probability of passing Stage 2 conditional on Stage 1 failure
- Probability of passing Stage 3 conditional on Stages 1 and 2 failure.

The predictive probabilities are computed using the joint posterior distribution of the parameters of the model available in the form of chains produced the MCMC method. To identify the DS, a fine grid is created over the two factors X1 and X2. Within each point of the grid, the predictive probabilities indicated above are computed, according to the following sequence:

1) Draw 1000 times 24 profiles from the predictive distribution, including back-transformation to the original scale.

2) For Stage 1, the probability of success was computed as follows:

- Keep only the 6 first profiles out of 24 profiles generated; given in future routine only 6 units will be tested,

- For the 1000 sets of 6 profiles, calculate the proportion of sets where the 6 profiles satisfy the specifications jointly. This proportion is the MCMC estimate of the probability of success at Stage 1.

3) For Stage 2 the probability of success was computed as follows:

- Add the next six profiles from each original set of 24 to obtain 1000 x 12 profiles,

- Compute the average dissolution profile of the 12 profiles for each of the 1000 sets,

- From among the sets not having passed Stage 1, compute the proportion of sets in which the average dissolution profile is within acceptance limits, and at no time point of does any result in any profile exceed the acceptance limit range by more than 10%. This proportion is the MCMC estimate of the probability of success passing Stage 2 conditional on failure in Stage 1.

4) Finally for computing the probability of success of Stage 3:

- Add the next twelve profiles from each original set of 24 to obtain 1000 x 24 profiles,

- Compute the average dissolution profile of the 24 profiles for each of the 1000 sets,

- From among the sets not having passed Stage 1 nor Stage 2, compute the proportion of sets in which the average dissolution profile is within acceptance limits, and at no more than two time points does any result in any profile exceed the acceptance limit range by more than 10%, and at no time point does any result from any profile exceed the stated range by more than 20%. This proportion is the MCMC estimate of the probability of success passing Stage 3 conditional on failure in Stage 1 and Stage 2.

With this approach, the implicit correlation between the Stages is accounted by the fact that the profiles/vessels are performed, as they would be done in laboratory conditions, where the results of Stage 2 are dependent on the results of Stage 1, as 6 units are shared by both analyses. The same applies for Stage 3. However, in real

laboratory practice, the analysis of consecutive testing for Stage 2 and 3 are made in separate runs at different times. If available, data to estimate the variability due to the effect of the runs could be used to improve the simulations.

Figure 4 represents the joint predictive probability to obtain 6 dissolutions profiles within joint specifications at time points of interest at Stage 1.

<Figure 4 here>

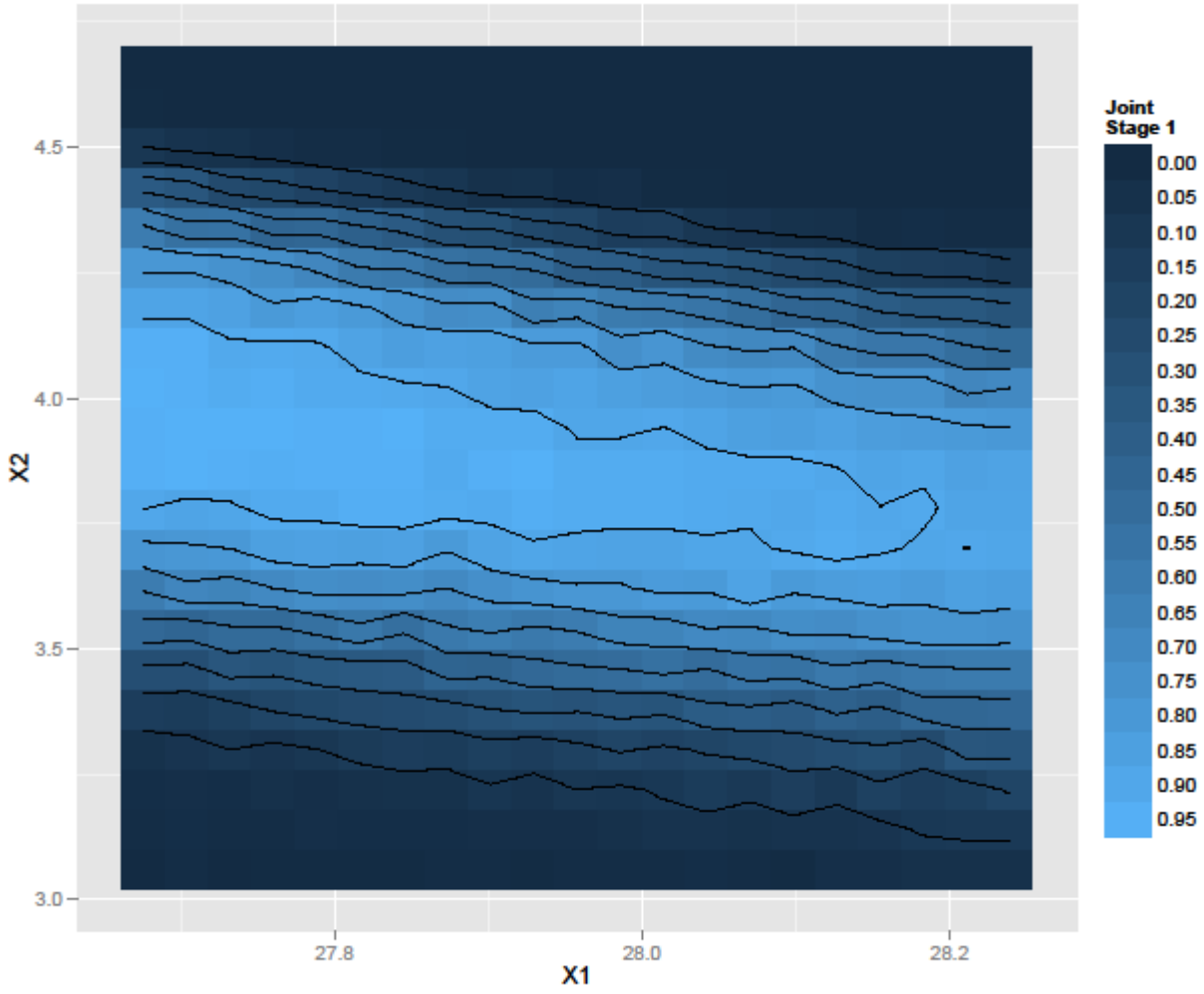

Figure 4 – Stage 1: joint probability of success of passing all specifications at the three time points.

As it can be seen in Figure 4, in the center of the domain of the second factor (X2), it is possible to obtain the six Stage 1 profiles within specifications with a high level of confidence, across the full range of X1. The lighter blue area corresponds to a

confidence level of about 0.95. The X2 is very critical: at low and high levels of X2, the probability quickly drops to near 0% chance of success at any X1 level. A small interaction between X2 and X1 is also identified graphically since the light blue area is not horizontal. Strict control of X2 is key to obtain tablets with good dissolution properties. For Stage 1, it is recommended to maintain X2 within 3.8 and 3.9 while X1 can vary within the whole domain explored, i.e. from 27.7 to 28.2.

When considering each time point separately, then the marginal predictive probabilities of success over the X1 and X2 experimental domain are show in Figure 5.

<Figure 5 here>

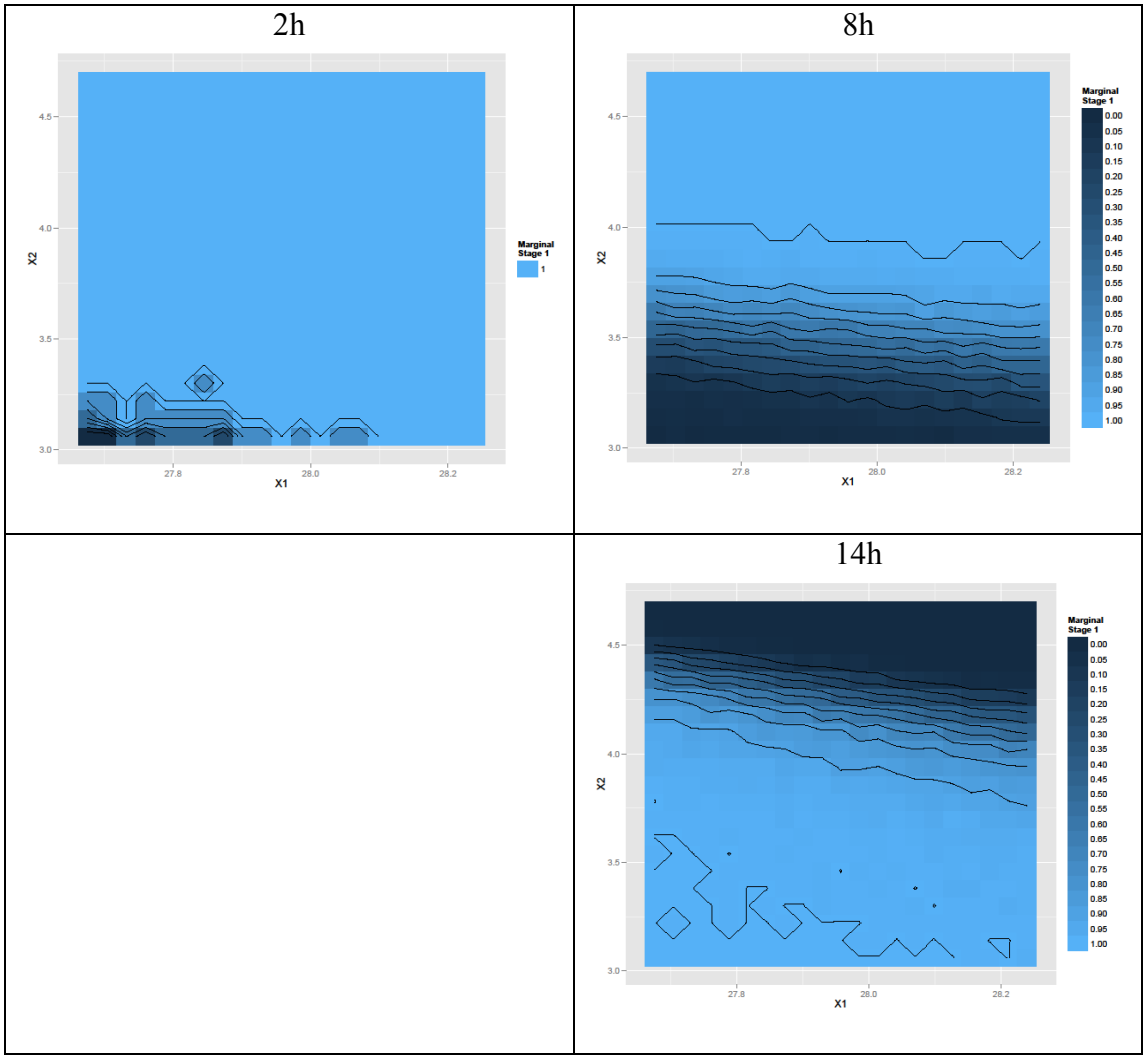

Figure 5 – Stage 1: conditional probabilities of success by time point defining the Design Space

As it can be seen in Figure 5, there is high likelihood to pass specifications at 2 hours, whatever the X1 and X2 levels. However the risk of failure at 8 hours and 14 hours depends heavily on the level of X2, The requirement to control X2 within 3.8 and 3.9 is essential due to these two time points in the form of a compromise.

The predictive probabilities of passing Stage 2 or Stage 3, conditional on failure in Stage 1 or in Stage 1 and Stage 2, respectively, are represented in Figure 6 A and Figure 6 B, respectively.

<Figure 6 here>

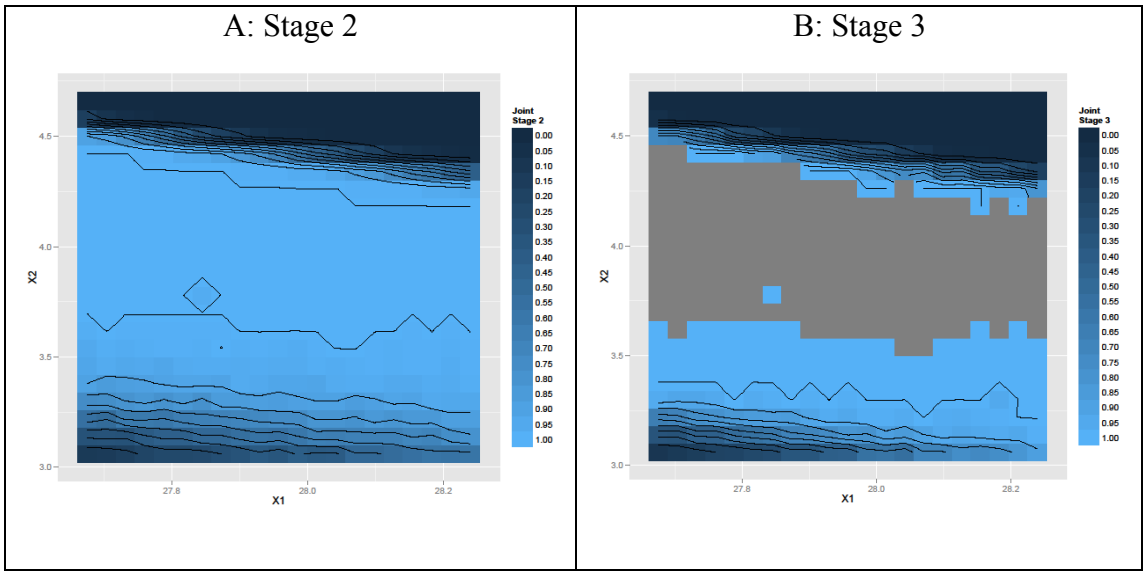

Figure 6 – Joint probabilities of passing at Stage 2 (A) and Stage 3 (B) for all time points conditionally to a failure of Stage 1 or Stage 1 and 2, respectively. The grey area on the right figure reflects almost no chance that Stage 3 testing is required.

As it can be seen in Figures 6A and 6B, the DSs for Stage 2 and Stage 3 are larger than the one for Stage 1 (Figure 4). The fact that the DS didn't shrink for Stage 2 and 3 as compared to Stage 1 suggests that, as long as the factors are within the DS, the main reason for Stage 1 failure is the variability of the individual dissolution results around the mean (i.e. variability in the test procedure). Also the prediction indicates that as long as tablets are produced in the X1 and X2 combinations indicated by the bright blue area (Figure 6, B) dissolution testing beyond Stage 2 will never be required.

5 Conclusions

A mixed effects model has been used to describe the longitudinal dissolution profiles of extended release tablets as a function of two critical process parameters with a response surface type of model.

A Bayesian approach, namely a hierarchical model with non-informative priors, allowed direct computation of the joint predictive probability that all the individual values of the six dissolution profiles will be fully within the set of three acceptance criteria over time. Even when only considering Stage 1, computing such a probability, given the correlation structure and the random effects would had been cumbersome or impossible to obtain using frequentist statistics. Using MCMC methods and Bayesian models make such a computation straightforward and consistent with the intent of the QbD recommendation.

Moreover, the Bayesian modeling and the availability of the predictive distribution made feasible the conditional computation of passing Stage 2 or Stage 3 given a failure of previous stages.

In the case presented, a non-informative prior was used, so that the mean of the posteriors was nearly equal to the maximum likelihood estimates of the parameters. The main difference was the fact that the joint distribution of the parameters was available to derive numerically the predictive distribution of future responses, whatever the transformations (and the back-transformations) performed.

Such computation can easily be implemented using common statistical languages such as R or SAS, and with MCMC sampler such as MCMChregress, Winbugs or STAN.

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References

[1] Box, G. E. P., Tiao, G. C. (1973). Bayesian Inference in Statistical Analysis. New York, NY: Wiley Classic Library.

[2] Chib, S. and Carlin, B.P. (1999) On MCMC Sampling in Hierarchical Longitudinal Models. Statistics and Computing. 9: 17-26.

[3] Deming, W.E. Out of the Crisis. Cambridge, MA: Massachusetts Institute of Technology Center for Advanced Engineering Study, 1986.

[4] Guttman, I. (1970). Statistical Tolerance Regions: Classical and Bayesian. Griffin's statistical monographs and courses. London: Griffin.

[5] Hamada, M., Johnson, V., Moore, L. M. (2004). Bayesian prediction intervals and their relationship to tolerance intervals. Technometrics 46(4):452–459.

[6] International Conference on Harmonization (ICH) of Technical Requirements for registration of Pharmaceuticals for Human Use, Topic Q2 (R1): Validation of Analytical Procedures: Text and Methodology, Geneva, 2005.

[7] International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, Topic Q9: Quality Risk Management, Geneva, 2005.

[8] International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, Topic Q10: Pharmaceutical Quality System, Geneva, 2008.

[9] International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, Topic Q8 (R2): Pharmaceutical Development, Geneva, 2009.

[10] Juran, J.M. Directions for ASQC. Industrial Quality Control, 1951.

[11] Lebrun, P., Boulanger, B.,Debrus, B., Lambert, P. and Hubert, P. (2013) A Bayesian Design Space for Analytical Methods Based on Multivariate Models and Predictions. Journal of Biopharmaceutical Statistics. Vol. 23, 6, 186-198

[12] Miró-Quesada, G., del Castillo, E., Peterson, J. J. (2004). A Bayesian approach for multiple response surface optimization in the presence of noise variable. Journal of Applied Statistics 13(3):251–270.

[13] Peterson, J. J. (2004). A posterior predictive approach to multiple response surface optimization. Journal Quality Technology 36:139–153.

[14] Peterson, J. J. (2008). A Bayesian approach to the ICH Q8 definition of Design Space. Journal Biopharmaceutical Statistics 18:959–975.

[15] Peterson, J. J., Yahyah, M. (2009). A Bayesian design space approach to robustness and system suitability for pharmaceutical assays and other processes. Statistics in Biopharmaceutical Research 1(4):441–449.

[16] Peterson, J. J., Miró-Quesada, G., del Castillo, E. (2009). A Bayesian reliability approach to multiple response optimization with seemingly unrelated regression models. Journal of Quality Technology Quantitative Management 6:353–369.

[17] Peterson, J. J., Lief, K. (2010). The ICH Q8 definition of design space: A comparison of the overlapping means and the Bayesian predictive approaches. Statistics in Biopharmaceutical Research 2:249–259.

[18] U.S. Food and Drug Administration. Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms. FDA. August 1997.

[19] U.S. Food and Drug Administration. Guidance for Industry: SUPAC-MR. Modified Release Solid Oral Dosage Forms FDA. September 1997.

[20] U.S. Food and Drug Administration (FDA), Department of Health and Human Services, Pharmaceutical Quality for the 21st Century A Risk-Based Approach Progress Report, May 2007.

[21] U.S. Food and Drug Administration (FDA), Department of Health and Human Services, Guidance for industry; Process validation: General Principles and Practices, January 2011.

[22] U.S. Food and Drug Administration. Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review. Chapter 5000 - Pharmaceutical Sciences, MAPP 5016.1, February 2011.

[23] USP 32-NF 27. Chapter 711. August 2009.

[24] Vaghela, B., Kayastha, R. , Bhatt, N. , Pathak, N. and Rathod, D. (2011) Development and validation of dissolution procedures Journal of Applied Pharmaceutical Science 01 (03); 50-56.

[25] Yu, L. (2008) Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control. Pharmaceutical Research, 25:781–791.