Paris, 2018-10-03

https://www.ncs-conference.org/

Quantitative quality assessment during the pharmaceutical process design stage taking into account prior expert knowledge

Abstract:

Anja Bertsche[1], Gerhard Nehmiz[2], Michael Brendel[1]
[1] *Boehringer Ingelheim Pharma GmbH&Co. KG, Biberach, Germany*
[2] *Consultant, Biberach, Germany*

The development of a commercial manufacturing process can be divided into three stages: process design, process qualification and continued process verification. A quantitative rating of the process is already desired at the design stage in order to ensure a successful process development and qualification. As only few data are available, expert knowledge is an essential factor. Bayesian methods offer the possibility for a probabilistic assessment that combines the expert knowledge and experiences from past projects with the data obtained from the current development batches.

We evaluated the sequential application of Bayesian methods[1] during late stage process development for a film coated tablet. We set up models for different attributes/parameters together with the experts; in particular, a hierarchical model with the level batch for content uniformity is presented. This comprises the definition of the data basis, the frequency of the statistical analysis, the elicitation of the prior distributions and the definition of acceptance criteria. We use 2-component mixture priors with a non-informative component for robustness. The informative component consists of an analytic probability distribution based solely on expert knowledge[2] and/or a kernel density estimate to take up the information (posterior density) from the previous analysis. The impact of various prior distributions/beliefs is investigated as sensitivity analyses. These support the discussion about the reliability of the current process assessment and reveal any further development needs.

[1] Gsponer T, Gerber F, Bornkamp B et al.: A practical guide to Bayesian group sequential designs. Pharmaceutical Statistics 2014; 13: 71-80.
[2] Dallow N, Best N, Montague TH: Better decision making in drug development through adoption of formal prior elicitation. Pharmaceutical Statistics 2018 (in press) [17: 301-316].

Paris, 2018-10-03

https://www.ncs-conference.org/

Slides:

Pharmaceutical process development: 3 stages

Stage I
Process Design

Bayesian statistics
Descriptive statistics

Stage II
Process Qualification

Confirmatory frequentist statistics

Stage III
Continued Process Verification

Descriptive statistics
Confirmatory frequentist statistics

A-priori information + information collected from experiments (possibly adapted)

The deliverable is the assurance that qualification will succeed

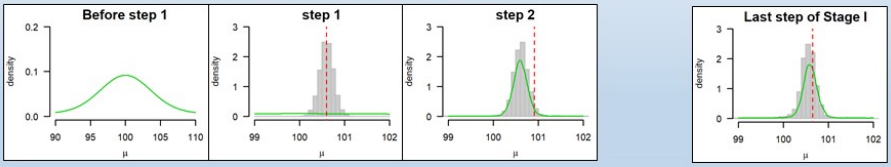
1

For each parameter (e.g. content uniformity): hierarchical linear model

$Y_{kj} = \mu + b_k + \varepsilon_{kj}$ with b_k = random batch effects N(0, τ), K $\geq$ 2
ε_{kj} = error terms N(0, σ)
with usual independence assumptions

Prior distribution:
- 2-component mixture (peaked + flat) for robustness
- Elicited or kernel estimator

Data and prior/posterior distributions, e.g. for common mean μ:

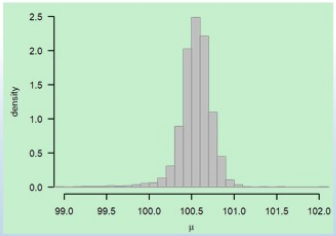


2

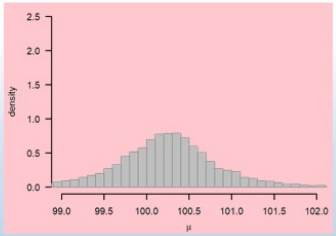
How to support the decision to go to Stage II (confirmatory qualification)

Posterior distributions

Include information on μ from all previous steps



Include information on μ from data of last step only



Thank you!

A. Bertsche M. Brendel G. Nehmiz

3

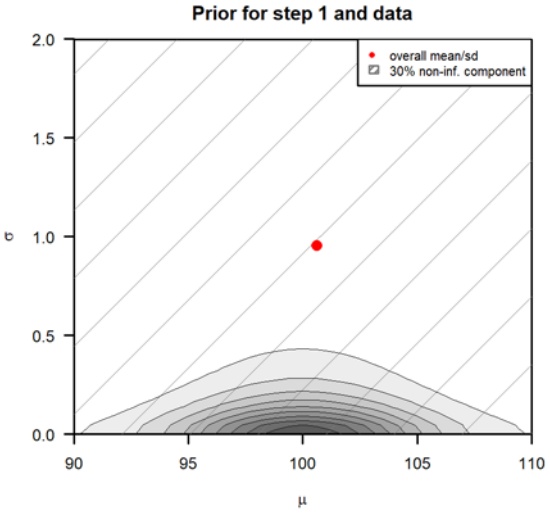
Further remarks to prior distributions, MCMC sampling, information propagation, decision criteria:

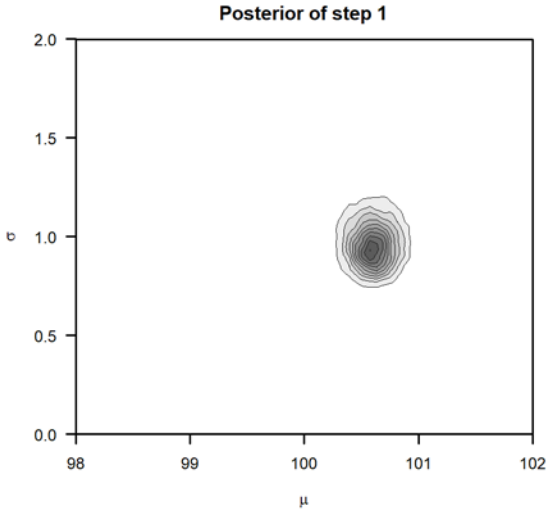
While the examples of Dallow et al. (2018, p. 9-13) relate exclusively to effect sizes, we are here also concerned with estimation of variability (σ and τ). Before Step 1, elicitation of an inverse-Gamma distribution for σ^2 (from an upper and a lower bound, interpreted as 97.5% and 2.5% quantiles, respectively) was not successful; elicitation of a half-Cauchy (HC) distribution for σ (from an upper bound interpreted as 97.5% quantile) was OK. Together, the elicited prior distribution was N(100, 3.5) for μ and HC(0.14) for σ, with no correlation between them. The non-informative components before Step 1 were N(100, 10) for μ and HC(10) for σ. The between-batch variability τ was not modelled in the first step as only one batch was produced. Before Step 2, the kernel density estimates of μ and σ from Step 1 were used as informative component. For the between-batch variability τ, the 97.5% quantile was estimated as 1 and, therefore, the elicited informative prior distribution was HC(0.04), and a HC(10) distribution was the non-informative component (Lambert et al. 2005, Gelman 2006).

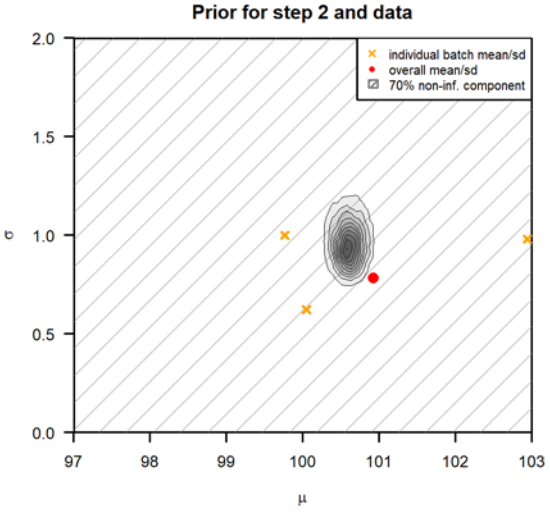
In the robust mixture prior for each step, the elicited and the unspecifically non-informative components were weighted in the ratio 70 : 30 as the feeling towards the elicited ranges was a bit unsecure (compared with 90 : 10 in clinical trials, Schmidli et al. 2014). The further conclusions were however not affected by this ratio.

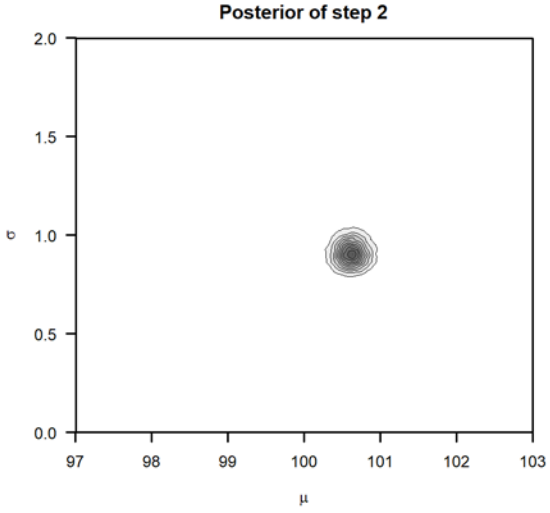
At each step, the joint posterior distribution of μ, σ and of τ (from step 2 on) was determined by MCMC simulation. After a burn-in of 3 000 iterations, 20 000 iterations were performed for 3 chains and a thinning factor of 5 was applied. Convergence was assessed visually from trace plots and autocorrelation plots and no problems occurred throughout. Results were robust w.r.t. widely dispersed starting points. The sampled points from the 3 converged chains were then pooled.

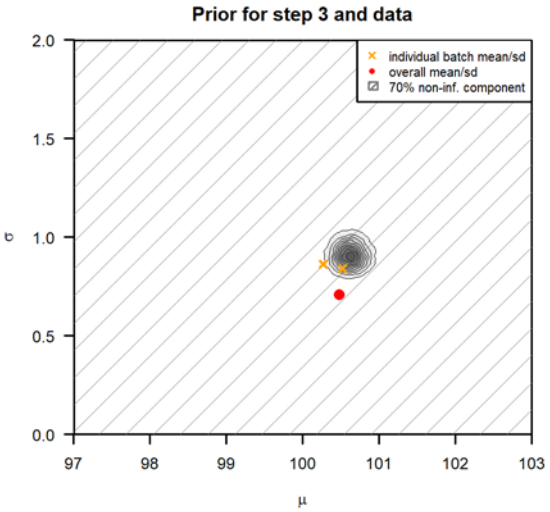
In general, experimental conditions were adapted between each 2 steps. The posterior information of each step was re-interpreted as prior information for the next step and a non-informative component with weight 30 % was added. No formal discounting was performed (as in e.g. Gsponer et al. 2014, p. 74) as the similarities between the steps were much stronger. (For a general discussion, see Weber et al. 2018.) The resulting marginal distributions for μ and σ together are as follows:

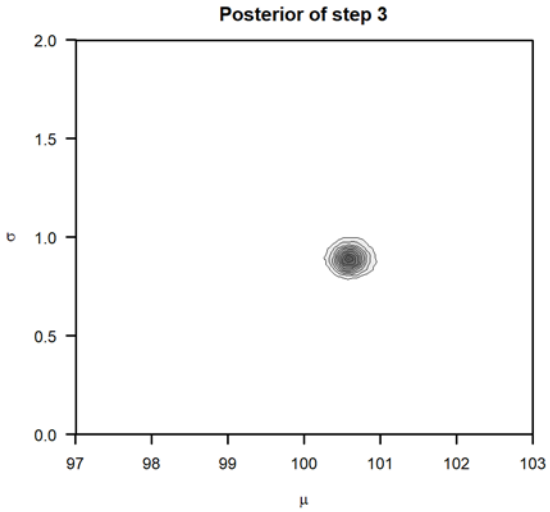

Prior for step 1 and data
overall mean/sd
30% non-inf. component
σ
μ

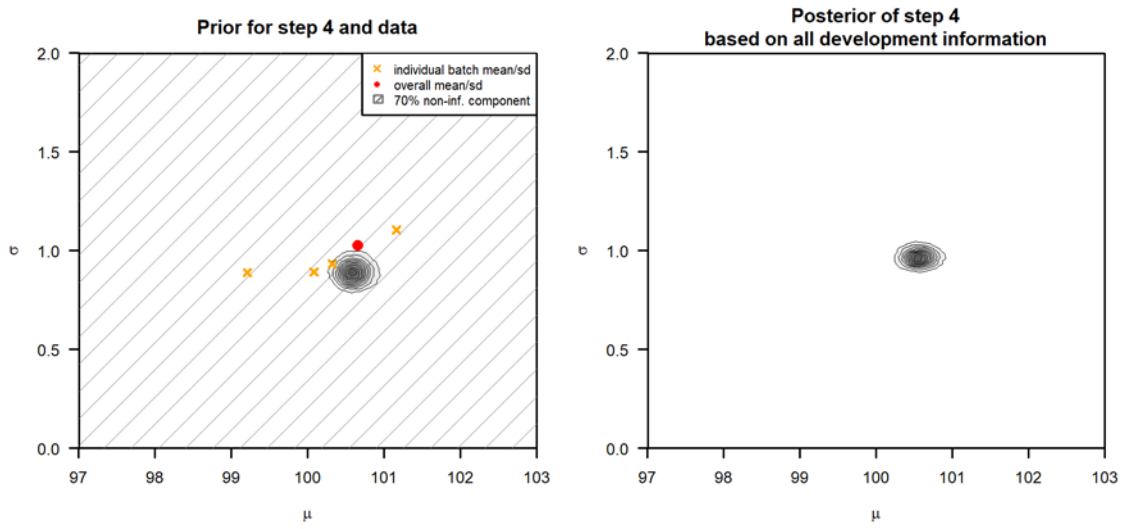

Posterior of step 1
σ
μ


Prior for step 2 and data
individual batch mean/sd
overall mean/sd
70% non-inf. component
σ
μ

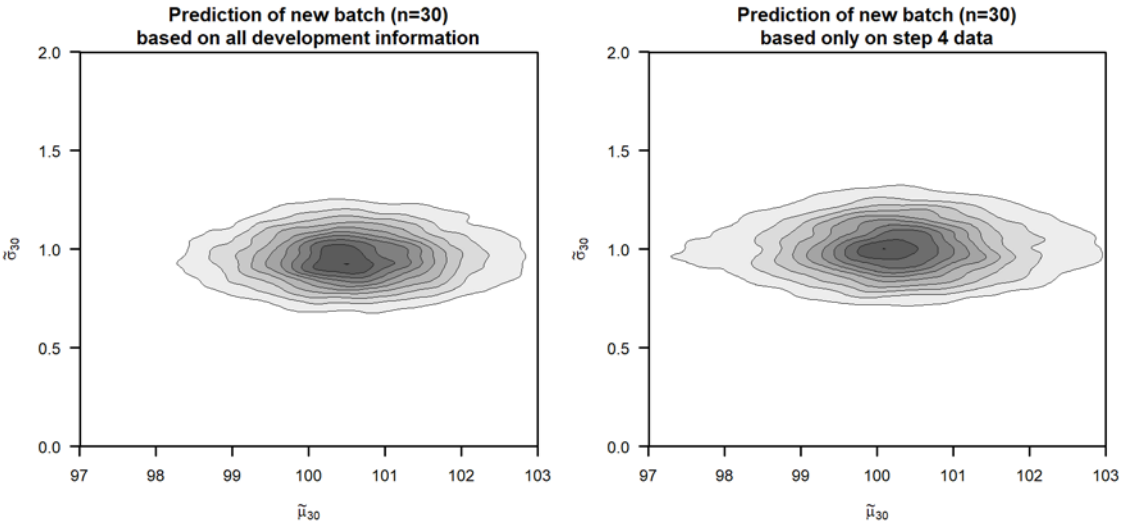

Posterior of step 2
σ
μ


Prior for step 3 and data
individual batch mean/sd
overall mean/sd
70% non-inf. component
σ
μ

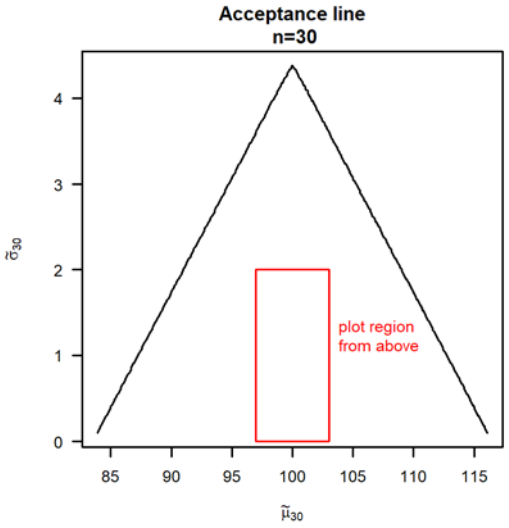

Posterior of step 3
σ
μ



For the go/no-go decision after Step 4 (technical evaluation and transfer to launch site), one new batch of n=30 is predicted from the posterior distribution of μ, σ and τ. The values of the predicted batch are compared to the intended process performance qualification (PPQ) acceptance criterion. The chosen PPQ acceptance criterion ensures with high certainty that batches delivered by the process will pass the content uniformity test with high probability (Schorr et al. 2006, Ph.Eur. 9.5). The actual acceptance range is two-dimensional (see last graph below), and a "go" signal is given if the predictive probability of the new sample staying there is ≥ e.g. 0.9:



The univariate graphs on Slide 3 show that the marginal posterior distribution for μ, after consideration of all available information, is relevantly narrower compared with the posterior distribution based on an uninformative prior distribution before Step 4. The bivariate predictive distributions for a new batch of size 30, based on the full information or confined to Step 4, do still show a difference in μ but it is smaller. No difference is however seen for σ and also for τ (not shown).
The last bivariate graph shows that the predicted range for the new μ and σ is much smaller than the acceptance region, indicating that there is high determinism in the process and pure random variability plays a minor role:



Further references:

Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR: How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Statistics in Medicine 2005; 24(15): 2401-2428

Gelman A: Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). Bayesian Analysis 2006; 1(3): 515-534

Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B: Robust Meta-Analytic-Predictive Priors in Clinical Trials with Historical Control Information. Biometrics 2014; 70(4): 1023-1032

Weber K, Hemmings R, Koch A: How to use prior knowledge and still give new data a chance? Pharmaceutical Statistics 2018; 17: 329-341

Schorr R, Gössl R, Häusler H: Konzepte der Content Uniformity-Prüfungen in den Arzneibüchern einschließlich des neuen, harmonisierten (ICH) Tests. Pharmazeutische Industrie 2006, 68(10):1200-1206

Council of Europe: 2.9.40. Uniformity of dosage units. European Pharmacopoeia, Ninth Edition, 2018; Supplement 9.5: 4055-4057