Powering of process validation

Using Bayesian methods to determine the sampling plan for PPQ

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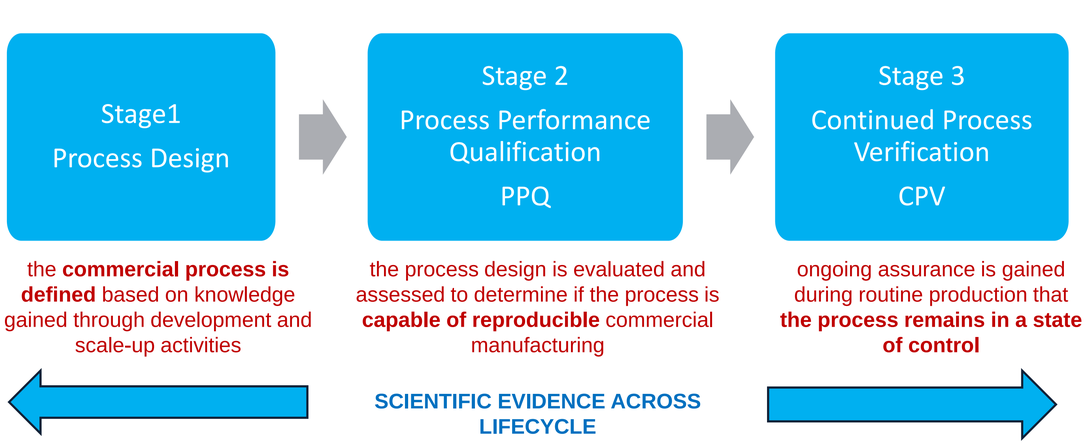
Process validation



Content uniformity

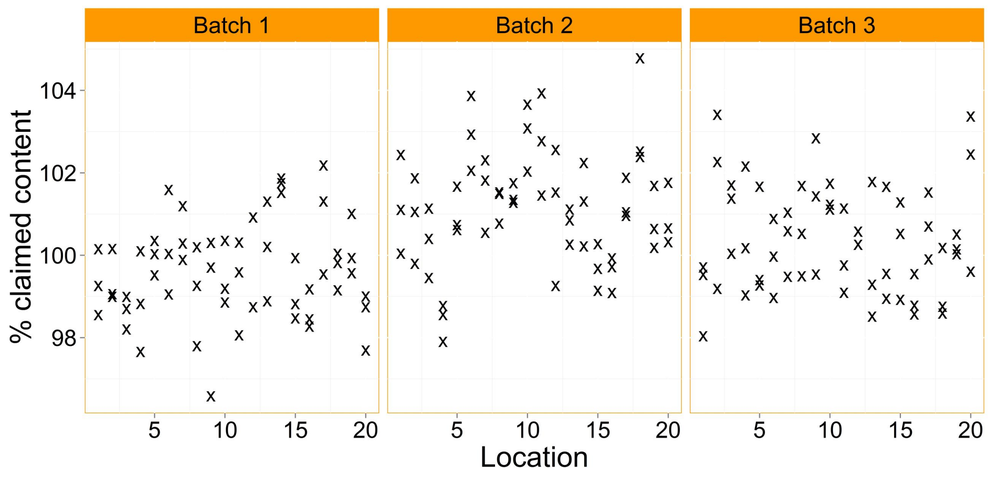
- Content uniformity is the degree of uniformity in the amount of active substance among dosage units
- During tablet press, several tablets are sampled at different time points, called *locations*.
- The following model can be fitted to data

$$Content \sim N(mu, \sigma^2_{residual})$$

With

- *Content*: dosage in % of stated dosage
- $\sigma^2_{residual}$: residual variance
- $mu = intercept + \gamma_{batch} + \delta_{location[batch]}$
- $\gamma_{batch} \sim N(0, \sigma^2_{batch})$
- $\delta_{location[batch]} \sim N(0, \sigma^2_{location[batch]})$

1.Historical data from stage 1



2.Fit model on historical data

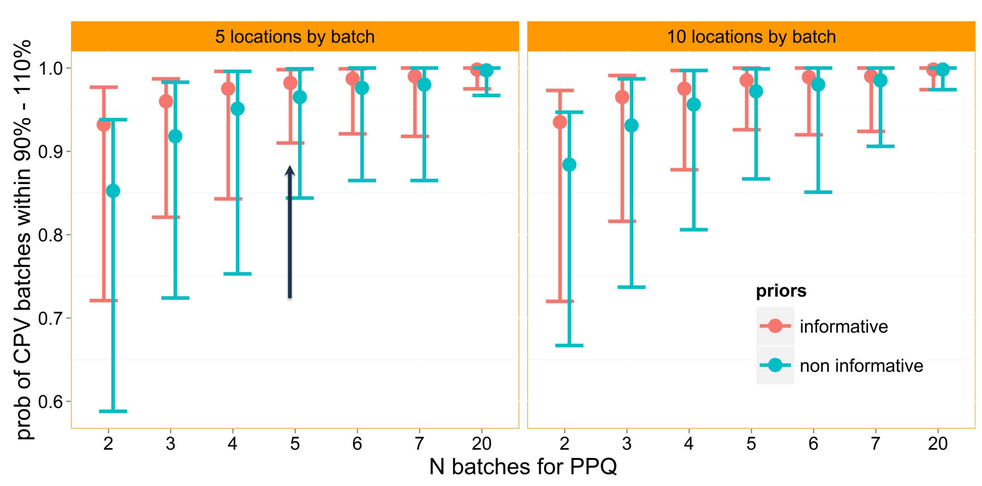
	Median	Lower 95% HPD interval	Upper 95% HPD interval
$intercept$	100.38	97.57	103.29
σ^2_{batch}	2.83	0.04	19.19
$\sigma^2_{location[batch]}$	0.59	0.25	1.01
$\sigma^2_{residual}$	1.10	0.84	1.41

There is a large uncertainty on the random batch variance, because there is only three batches in the data.

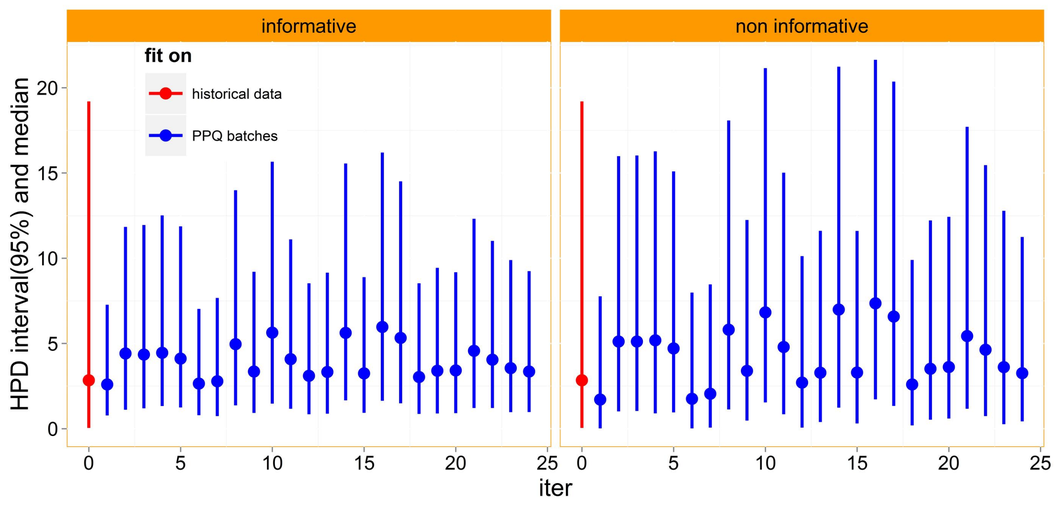
3.Test a sampling plan for PPQ

1. Simulate new batches with a given format (*e.g.* 3 batches with 10 locations and 3 samples by location), as we would obtain during PPQ.
2. Fit the same model on the simulated batches (using or not informative priors, from historical data).
3. Using the posteriors, simulate new batches as we would obtain during CPV.
4. Repeat steps 1 to 3 a high number of time.
5. Compute the probability to pass an acceptance criteria (for example to be within 90 and 110 % of the claimed content).

4. Results



- The plot shows the probability of success to meet the criteria for different PPQ sampling plan.
- Using informative priors improves the probability to meet the criteria, especially when the number of PPQ batches is small.
- Using 5 additional batches, with 5 locations by batch and 3 replicates by location, we can achieve at least 90% of success.
- Important to be able to justify the source of prior information.



- The plot shows the precison of the random batch estimated from the fit on historical data and from some of the fit on the PPQ batches.
- Over the runs, the precision on the estimate is improved.

Conclusions

In order to justify the sample size to perform the PPQ, the natural sources of variability of the process (within and between batch variability) should be evaluated. Obviously, the most variable processes should require more data and analyses compared to the most controlled processes to achieve the same target. Bayesian methods are a usefull tool to evaluate the sampling plan needed to achieve a high probability to meet the specifications during CPV. It also allows gaining power from historical data.