



European Commission  
Pharmaceuticals Unit, Brussels  
[SANCO-gmp@ec.europa.eu](mailto:SANCO-gmp@ec.europa.eu)

European Medicines Agency  
Compliance and Inspection, London  
[ADM-GMP@ema.europa.eu](mailto:ADM-GMP@ema.europa.eu)  
[QWP@ema.europa.eu](mailto:QWP@ema.europa.eu)

## Revision of the Guideline on Process Validation

Dear Madam or Sir,

On 25 February 2010 the Committee for Medicinal Products for Human Use (CHMP) & Committee for Medicinal Products for Veterinary Use (CVMP) published a Concept Paper on the Revision of the Guideline on Process Validation. This revision's goal is to implement modern aspects ("enhanced approach") to move towards a "continuous process verification". The deadline for comments ended on 31 May 2010.

In the meantime the FDA finalized a Guidance for Industry Process Validation: General Principles and Practices in January 2011. This Guidance was intensively discussed in the industry.

However, the European requirements with regard to Process Validation are in motion. On one hand it seems to be obvious that a new understanding with regard to process validation on the basis of process understanding is "state of the art" today. On the other hand the current requirements defined in Annex 15 to the EU GMP Guide and in the current version of the Note for Guidance on Process Validation do not yet reflect this approach.

Therefore the ECA and the European QP Association initiated a survey to evaluate the view of the European Industry with regard to Process Validation. With this letter we would like to forward to you the results of the **most comprehensive survey ever performed on this topic**. Please find the results of the survey below.

We hope that the information provided in the letter will support the EMA and the EU Commission in the finalization of the revised requirements on Process Validation.

### Summary:

To understand the current practice and the view of the European Industry a survey was conducted in September 2011. More than 500 professionals provided their input to the survey – single questions were skipped by some of the respondents, though.

The result relative to the first question asking for the respondents' background showed that the large majority came from medicinal products manufacturers (more than 50%), followed by respondents from API manufacturers and companies manufacturing both medicinal products and APIs (each 25%). Some additional respondents – not fitting into these categories – came from medical device manufacturers, consultants, vaccine manufacturers or food manufacturers. These "Others" only represent a single digit percentage, though. Three of those answering further came from the regulatory area.

### Details

Surprisingly, many respondents (86,5%) agree with the statement that it would be necessary to modify the current validation requirements – which are mainly based on the 3 batch model – to a more scientific approach and process understanding. A clear "No" was expressed by only 6,3%.

**Vice Chairman:**  
Vacancy due to untimely death  
of Daniel Scheidegger in  
September 2011

**Advisory Board Members:**  
Richard Bonner  
Independent Consultant  
(Vice Chairman)

Matt Moran  
PharmaChemical, Ireland  
Dr W. Schumacher  
F. Hoffmann-La Roche, Switzerland

Rudolf Völler  
Regierungspräsidium Darmstadt,  
Germany

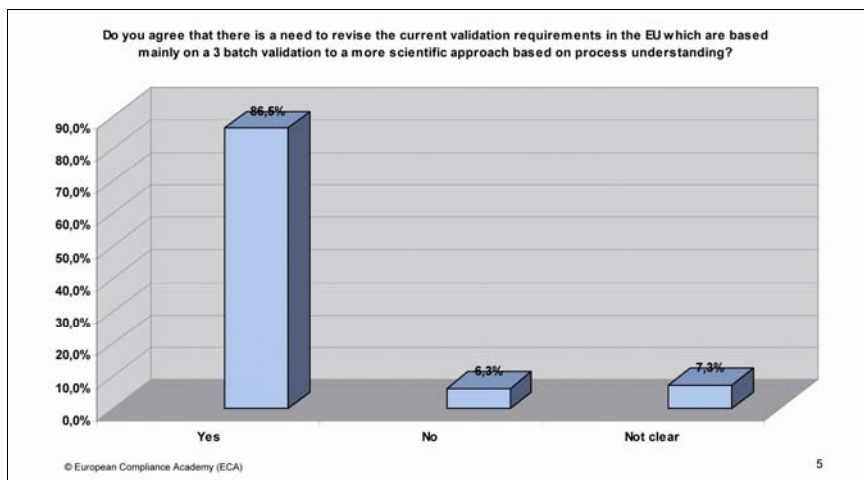
John Taylor  
MHRA, UK

Dr Jean-Denis Mallet  
Switzerland

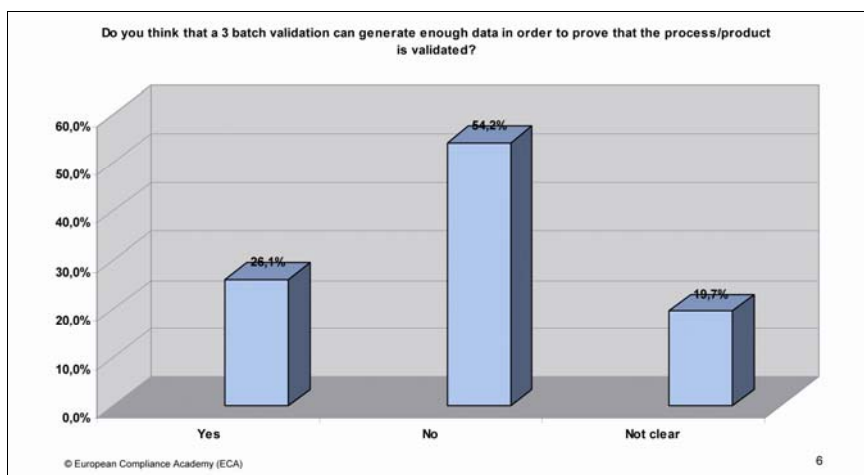
Dr Bernd Renger  
Vetter Pharma-Fertigung GmbH &  
Co. KG, Germany

Dr Boris Pimentel  
DNP (DSM-Nutritional Products),  
Switzerland

Colin Booth  
Oxoid Limited, UK



The opinions with regard to „Data Quantity“ provided by the 3 batch validation varied a bit more. Merely a little more than a quarter (26%) of those questioned believe that this approach generates enough data to show the process’/product’s validity and therefore value it as efficient. However, more than half of the respondents (54,2%) do not agree with this estimation. Noticeable is the group of undecided respondents (20% “not clear”).



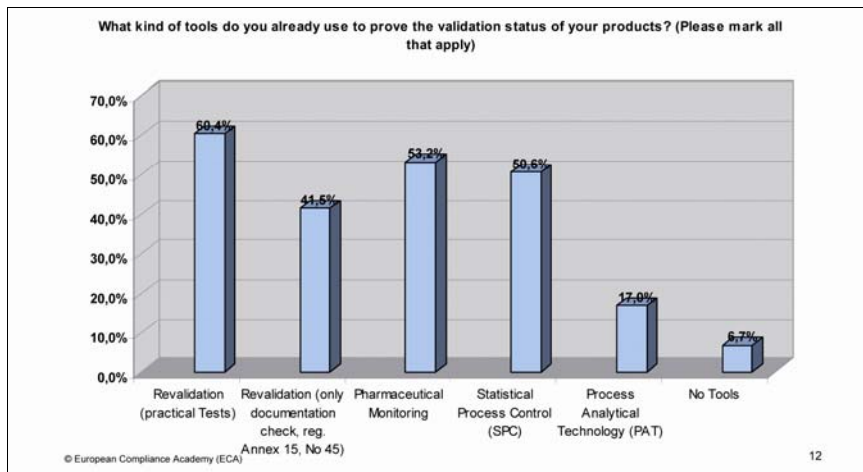
Asked for their estimation of the new FDA Guidance for Process Validation as a basis for a modern approach, almost 57% believe that the Guidance of the US authority would provide a good foundation. Close to 40% have not decided yet, and merely a small part of respondents – 3,4% –thinks that the FDA Guidance would rather not be a good basis. However, only a few from this group specified their opinion: “No clear / Too broad expectations” probably summarizes the single comments the best. Only two participants mentioned “growing expenses” as main reasons for their criticism.

“Do you think that the approach for new products should be different to legacy/existing products?” Exactly 68% answered with “Yes” to this question, 19% negated it. Almost 13% have not decided yet. Among those considering different approaches as necessary, nearly 75% think that legacy/existing products should be verified through statistical data (e.g. Cp, Cpk). For almost 27% legacy products should not be subject to new requirements. Further comments with regard to optional requirements for legacy products were quite heterogeneous. Five comments can be summarized with the intention to use the APR/PQR as a means for evaluation of legacy products, three respondents recommend the use of SPC for these products. Further, five persons providing

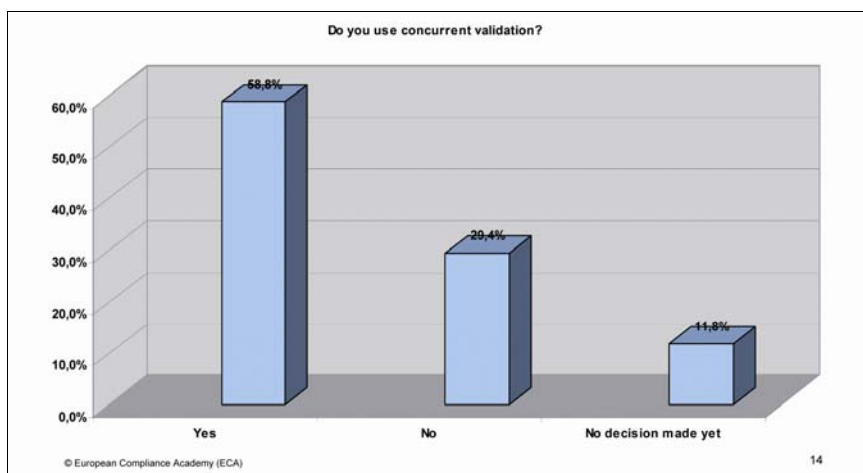
input also plan (re-)validations for large process changes with regard to the manufacture of legacy products.

For the question “What kind of ‘Tools’ do you already use to prove the validation status of your products?” respondents could choose between the answers Revalidation (practical tests), Revalidation (Documentation Check), Pharmaceutical Monitoring, SPC, PAT and No Tools with the option to mark all applying answers.

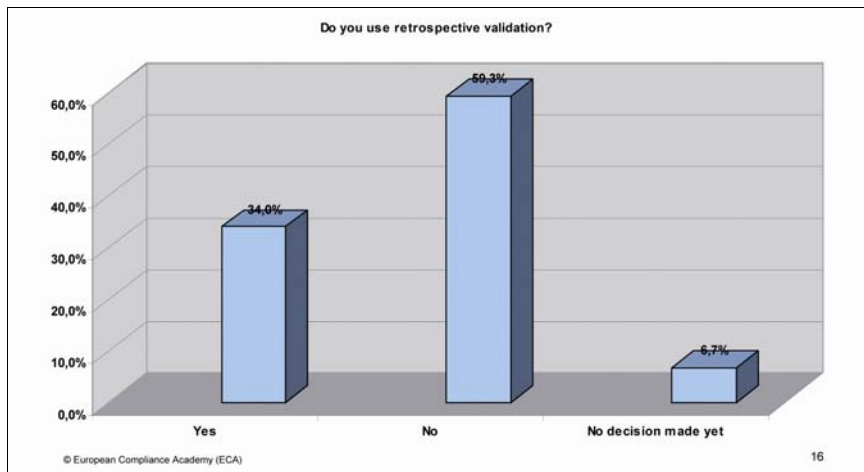
The feedback clearly showed that the pharmaceutical industry likes to take advantage of the width of possibilities. A little more than 50% conduct SPC (50,6%) and pharmaceutical monitoring (53,2%). Some 41% use document check and 60,4% still perform practical revalidation tests. PAT is used by 17%, and 6,7% do not use any tools. These answers were substantiated by 33 additional comments. A large majority (20 comments) recommends APR/PQR. Three respondents mentioned trend analysis.



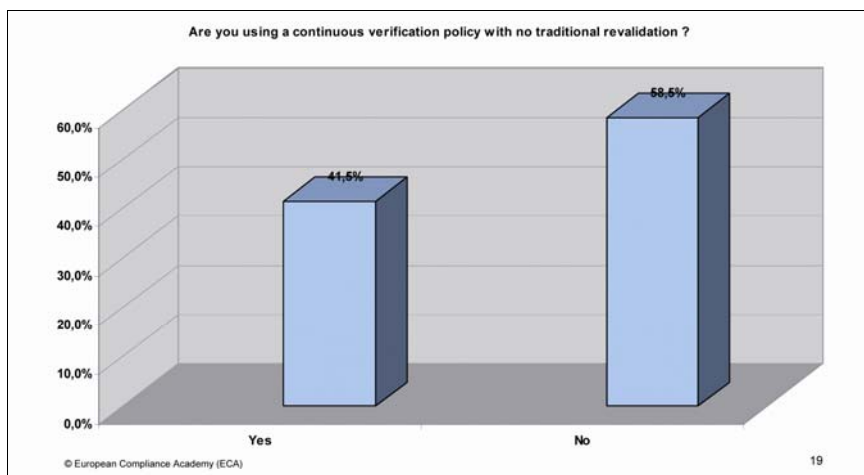
Quite surprising were the results with regard to the question “Do you use concurrent validation?” Nearly 60% answered with “Yes”. Close to 30% (29,4) do not, and almost 12% remained undecided. The number of comments received to the additional question “Why do you use concurrent validation” for those affirming was also surprising (205 comments). This means that 40% of all survey respondents did also provide a comment to this question. A quarter of those (53) noted that they use concurrent validation for small batches or product volumes. Further, 17% (34) use it after slight changes, for 15% (39) “cost and time savings” are the reason for concurrent validation. Finally, seven respondents blame market pressure for this approach.



Another surprise provided the answers to the question “Do you use retrospective validation?” – which 34% answered with “Yes”. Almost 60% said “No”, and 6,7% were undecided. As for the question before, the number of comments (116 comments) from those affirming the additional question “Why do you use retrospective validation” did surprise the survey designers. After all, that is close to 23% of all participating in the survey. Almost half of those (45%) use the retrospective validation for legacy products. Nearly 20% mentioned to use it for verifying the process, and only four respondents do actually use it in the meaning of a revalidation.



Close to 84% noted that they do have a revalidation policy, a little more than 16% do not. Less than half of the respondents (41,4%) further use a “continuous verification policy” without traditional revalidation, the majority (58,5%) does not.



## Conclusion

The survey yielded some surprises. Surprising was, for instance, the noticeable high number of participants (and also the number of comments). 509 persons providing input truly shows that validation is a topic that bothers the industry. Amazingly clear is also that the industry knows that the “3 batch model” should be modified towards a more scientific approach and process understanding, although a quarter of all respondents still believe that 3 batches can generate sufficient data to show the validity of a process. Vice versa, more than 50% do not believe this. With regard to this specific question 20% were undecided – which also shows some uncertainty.

Whether the new FDA Process Validation Guidance provides a good basis for the new direction for a new validation approach in Europe is evaluated quite differently. 57% believe the new



**Vice Chairman:**  
Vacancy due to untimely death  
of Daniel Scheidegger in  
September 2011

**Advisory Board Members:**  
Richard Bonner  
Independent Consultant  
(Vice Chairman)

Matt Moran  
PharmaChemical, Ireland

Dr W. Schumacher  
F. Hoffmann-La Roche, Switzerland

Rudolf Völler  
Regierungspräsidium Darmstadt,  
Germany

John Taylor  
MHRA, UK

Dr Jean-Denis Mallet  
Switzerland

Dr Bernd Renger  
Vetter Pharma-Fertigung GmbH &  
Co. KG, Germany

Dr Boris Pimentel  
DNP (DSM-Nutritional Products),  
Switzerland

Colin Booth  
Oxoid Limited, UK

direction can be based on the US authority's Guidance, but nearly 40% have not made up their mind. Almost 70% would like to see different regulations with regard to new and legacy products – whereas nearly ¾ recommend statistical data as a tool for the validation of legacy products.

Interesting were the comments with regard to methods for showing the validation status of products. With some 50% SPC and pharmaceutical monitoring were represented equally often. A little more than 60% (60,4%) conduct practical revalidation tests and 40,5% perform document checks.

Statements with regard to the use of concurrent and retrospective validation were particularly interesting. Both are validation types that should rather be an exception. Still, almost 60% noted to validate concurrently, and 34% use the retrospective validation. However, the use is mostly regulation compliant. 25% apply concurrent validation for small batches and/or small product volumes, respectively 17% after (slight) changes. The retrospective validation is mainly used for legacy products (45% of the answers). Moreover, somewhat surprising are the statements by 15% of the respondents who either mentioned to use concurrent validation as a means for cost and time savings or due to market pressure. A revalidation policy seems to exist in most of the companies (> 80%), and more than 40% even have established a “continuous verification policy” – and thus already move towards a modern validation approach.

We hope that EMA and EU Commission can benefit from this data.

Best regards

Dick Bonner  
Vice Chairman and Director Regulatory Affairs ECA  
Advisory Board Member European QP Association