Inspiring, Informative, Insightful – 2018 ISPE Europe Annual Conference

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As one of the most influential conferences in the pharmaceutical industry, the ISPE Europe Annual conference. The event this year was a total success – inspiring, informative and insightful.

Key features of the conference: The topics on 'facility of the future' and 'pharma 4.0' presented innovative concepts and approach, which enlightened me with new ideas. The regulatory talks interpreted the regulation from inspector's perspective. A perfect balance of speakers from manufacturing, equipment supplier and consultancy provided information on – execution and implementation on manufacturing site, latest technology and development on equipment, and solution from SMEs in specific area.

The conference focused on 4 major areas:

- **Facility of the future and aseptic process**
- **Pharma 4.0**
- **Data Integrity**
- **Mass Serialisation**

Every of the above is a hot topic in the industry and each could be a vast discussion and study. They seem independent, but entangled to a great extent. Thinking of the future of the industry, starting from manufacturing process, which is the core of a facility, Continuous Process could be the answer. To enable the continuous process, a higher level of automation should be achieved, together with agile implementation of PAT technology, which leads us into the discussion of Pharma 4.0. One of the critical enablers of Pharma 4.0 is Data Integrity by Design – the new paradigm for the industry.

At the conference, views and ideas were shared by regulatory from EU, UK and US. Glad to have Russia regulatory presented as well. Also a presentation was given by Russian GEP under the Serialisation track, regarding the new legislation on anti-conterfeiting. Could it be a further emphasis on the possibility of mandatory implementation of serialization in Russia, which has been postponed early this year?

Regulatory talks were given on various topics, as well as a Q&A session on the updated Annex 1 which has drawn great attention ever since the concept paper approved in 2014. Though regulations vary to certain extend on different subject, the fundamental is all built on **science and risk basis**. It was emphasized multiple times through the conference. The regulations should be considered as a guideline document, how to interpret and implement should be based on the manufacturer's process, should be based on science and should be based on risk management and risk mitigation. Interestingly, there was a comment on the Annex 1 revision that if the wording 'should' to be replaced by 'must'. Response from the regulatory addressed the same point: regulation is a guideline rather than mandatory requirement, hence the word 'must' is to be avoided.

Here is a sample of the hot topic and discussion you missed:

The new Annex 1 specified that **entry into the Grade A area by operator** should be minimized by facility, process and procedure design.

Does it necessarily mean NO operator in the grade A zone? Or it could be justifying if the uni-directional air flow is coming from the upstream of equipment and operation while operator is at the downstream of equipment and operation, hence there's no interruption of the grade A airflow hence no risk posed to the sterility.

Another example, filter **PUPSIT** (**P**ost **U**se **P**ost **S**terilization **I**ntegrity **T**est) is always a pain in the real life, you wouldn't be the only one questioned if there's a chance to avoid it. The regulatory is not saying a definite no, but, there has to be a scientific way to prove it.

Also, if your process involves the **stopper height detection**, what the alarm limit is set? A lot of us might say 1mm. But what's the scientific rationale behind it? That would be the question from the regulatory.

Working in a manufacturing environment myself, it's not an entirely alien situation that we 'borrowed' experience from other sites from the network or our neighbor down the road. It is time (if not too late) for us to trully understand our process, to really develop the rationale, to really bring things down to the science and risk basis. It is what ISPE Singapore Affiliate can help you to achieve with our various technical working groups and our ever-growing knowledge network.

We'd recently launched new series of 'Technical Tuesday', as a place and event to study the selected subject, to collect industry benchmark, to share SME's input. The objectives are to provide the industry an engineering tool or decision tree to guide you through the decision making based on your process and condition. There wouldn't be one simple answer to any engineering question, even not the regulation.

Question asked on the conference: **what environment background is required for Isolator/RABS**.

You should know by now that regulators were expecting a risk assessment done as it will depend on a number of variables, i.e. Isolator type, if a negative Isolator is involved, then the background should be higher than D etc..

All the updated regulations emphasized on new technology, i.e. Isolator, but does it necessarily mean that we must upgrade our facility and/or our operations onto a new level? Our industry is conventionally conservative, in my opinion. In the past years, how many cases we've seen potentially over-engineered. Of course it has all from the good intention for quality and patient's safety. But again, we will have to go back to the very basic – risk assessment for your own process and operation.

What's your interpretation of a facility of the future?

New technology, is not to be limited by the regulation, but driven by Safety and Quality improvement as much as Cost efficiency.

From process and equipment perspective, I'd rank Continuous Process and Single Use among the top trend. On the conference, latest development of continuous processing was illustrated for chemical API, OSD and Bio facilities. Experience shared by Janssen and Pfizer both presented transformation of conventional horizontal layout to a combination of horizontal and vertical layout. In comparison, continuous processing requires higher automation level, less inventory level, less CIP/WIP, easier tech transfer, and gives higher throughput and less CO2 footprint.

From both equipment and process perspective, continuous bio API process would be relatively more complex.

On the upstream side, continuous processing could be achieved by perfusion bioreaction (inevitably dependent on condition and cell line of course). But **continuous downstream process** could be the real

challenge, specifically on chromatography steps judging from the development I've seen so far. The presentation given by Merck Group and University of Vienna briefed their latest research on the downstream processing applying both single use and continuous approach. Basically, the research involved a 3 column system as the continuous capture chromatography step. Followed by a continuous in-line Virus Inactivation step, and single use intermediate/polishing chromatography, virus filtration and UF/DF step.

The very first and probably **key observation** you have comparing the process flow diagram of batch and continuous process is that continuous process involves much less steps hence equipment. This is how your capital cost, batch time, operation cost reduced, while efficiency and throughput increased. In almost all the presentations on continuous process, it's either presented or question addressed on the use PAT as enabler of continuous manufacturing and quality by design. The data collected is not only limited to monitoring the process but also predictive (the predictive control strategy, data enables machine learning). This is one of the cores of Pharma 4.0, the operating model – data to wisdom and knowledge.

Pharma 4.0 it might sound vague and abstract. One concept quoted in the conference made it simple and clear – moving toward Pharma 4.0 is moving from digitization to digitalization. Though it might make some of us think Pharma 4.0 is about automation, in fact, it's the new operation model. This was emphasized throughout the whole conference. Moving from Digitization to Digitalization triggers the transformation of paradigm from 'Quality by Design' to 'Data Integrity by Design', a transformation from 'Process Mapping' to 'Data Mapping'. The 4 elements are the foundation: Resources, Information Systems, Organisation & Process, and Culture. With 2 enablers: Data Maturity and Data Integrity by Design. The presentation on 'Readiness and Maturity for Pharma 4.0', by Uli Kuchenbrod from Vetter Pharma, was of my interests particularly. I believe you'd be the same after hearing all the exiting ideas of Pharma 4.0, next we'd be wondering where to start? The presentation briefed on the impact of Pharma 4.0, available tools for readiness and maturity assessment, maturity approach and model etc.. Basically to decide on the implementation of 4.0, it all came down to a few questions we need to ask ourselves, i.e.: what's your interpretation on Pharma 4.0? Its impacts mean anything to you? Everyone in your organization on the same page? Strategy in place? Tools available? The presentation was comprehensive and informative. It's still a long way to go, ultimately ISPE's vision is to create a generic Pharma 4.0 Value Network Model. The push for 4.0 implementation should be coming down from the management level; a culture of willingness should be established. As well as the right workforce and resource to make it happen. There would be new careers developed around the 4.0, the resources required to integrate information and knowledge from various functions (i.e. process, automation and quality) and make them digitalized. Though digitalization is the future, I would like to highlight that the process is still the fundamental. Pharma 4.0 should be built on the advance of process, equipment and control system.

Some more to offer.

Apart from the presentations, also inspiring were various offline discussion with the SMEs. For instance a talk with David Wolton from SDD inspired me with ideas on the adaptation of process design from stainless steel facility to single use facility.

Another interesting observation, how this industry share the common concerns and questions globally. I.e. how to define the batch size for continuous processing was asked in different presentation. Also concern was raised on Europe conference that regulation required that integrity test on the same filter should not exceed three times however it is very easy to be overlooked hence results in deviation or even FDA warning letter in some serious cases. The same issue was recently addressed in a Sterility Forum in Singapore organized by Sartorius. This issue could be solved with the new version of FIT tester which will

prompt alert on the second failure to recommend the operator to switch to a different FIT method and prompt alarm on the third failure that the max test amount is reached. Hence it's not necessary to go through the entire audit trail. Back to the regulatory talks, it was one of the efforts and achievement to harmonize among regulations globally and to initiate/maintain the mutual recognition between different countries

The End and the Beginning

2018 ISPE Europe Annual Conference has been completed with a great success, it left us with more thoughts, inspiration and questions then what's discussed and presented on the conference. Next we look forward to the 2018 ISPE Singapore Annual Conference in August.