

# Product Quality Lifecycle Implementation (PQLI) Keynotes from EU regulators

*Agence française  
de sécurité sanitaire  
des produits de santé*



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# Contents



- Warning
- The starting points
- The development of ICH guidance
- EU regulators vision on ICH
- Industry vision on ICH
- Shared vision on ICH ?
- Regulatory flexibility ?
- EU regulators concerns
- Changes for EU regulators
- Conclusions

# Warning



This presentation should contain ideas and sentences which could irritate the audience .....

The authors are perfectly aware of this danger and are terribly sorry with all caused inconveniences.

But they think that it could contribute to feed free and positive discussions between industry and regulators.

We hope to be successful and have a very good PQLI Berlin meeting.

Emer, Susanne, Jean-Louis, Ian and Jacques

# The starting points ....



- ICH discussions in July 2003 (Brussels) for agreeing a consensus vision : “Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science”
- From this vision, elaboration of new ICH guidance :
  - ✦ Q8 : Pharmaceutical Development (step 5) plus ICH Q8 R (still ongoing before step 2),
  - ✦ Q9 : Quality Risk Management (step 5),
  - ✦ Q10 : Pharmaceutical Quality System (step 2).

## The starting points ....



- FDA's initiative on Pharmaceutical Quality Systems for the 21st century which interfered with ICH strategy. This initiative was presented as containing new concepts and ideas. Six dimensions were assigned to this initiative, some of them really not new at the EU level :

- ✦ Risk based orientation : "Risk" concept mentioned 90 times and in 20 documents in EU GMP legislation and guidance, also used frequently in EU (8). In addition "unless otherwise justified" concept frequently used in both GMP and Quality guidelines,

# The starting points ....



- FDA's initiative on Pharmaceutical Quality Systems for the 21st century :

- ✦ Integrated quality systems orientation : EU GMP guide already mentioned this concept for IMP and finished products,

- ✦ International cooperation : EU concluded MRA with third countries, opened to WHO and PICS (sharing of information on competent authorities and manufacturers, Rapid Alert System on quality defects, ....).

## The development of ICH guidance



- Strong involvement of EU resources : EC, EMEA, MS. EU regulators are committed to fostering innovation.
- Q8 with famous DS and still more famous QbD :
  - ✦ Are these concepts really new or formalization of existing concepts ?
  - ✦ Can we present QbD for years without an agreed definition of this concept ?
  - ✦ Can we talk about “regulatory flexibility” when specifications of the DS are agreed in the Marketing Authorisation ?

- Q8 and its first (?) baby Q8R :
  - ✦ For clarifying QbD ....
  - ✦ To exemplify QbD through illustrative examples (focus on one dosage form only as a starting point)

- Q9 which is unique as for industry **and** regulators :
  - ✦ Harmonised implementation within the EU (e.g. Q9 implementation group at the EMEA level for GMP related matters or working group of assessors),
  - ✦ Is optional but is not an open door to think that the EU legislation could also be optional,
  - ✦ Already assessed by EU GMP inspectors with some good experiences and also lot of bad .....

# The development of ICH guidance



● Q10 which should be the perfect tool for the good implementation of Q8 and Q9 :

✦ Derived from ISO norms which will facilitate implementation,

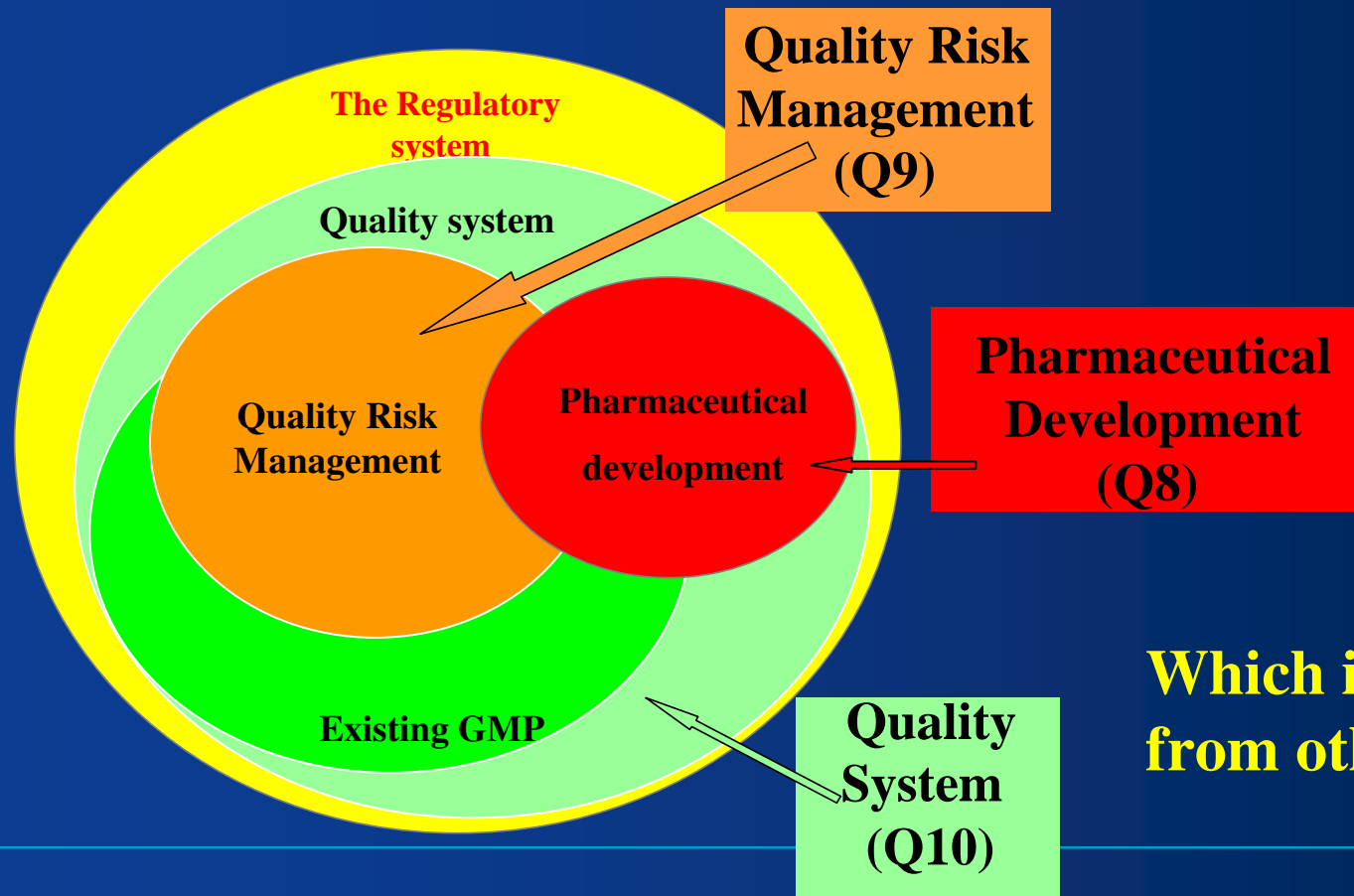
✦ Is not based on science .... ,

✦ Should be carefully considered as it concerns all the lifecycle of the products : implementation should be difficult at certain stages ....

# EU Regulators vision on ICH

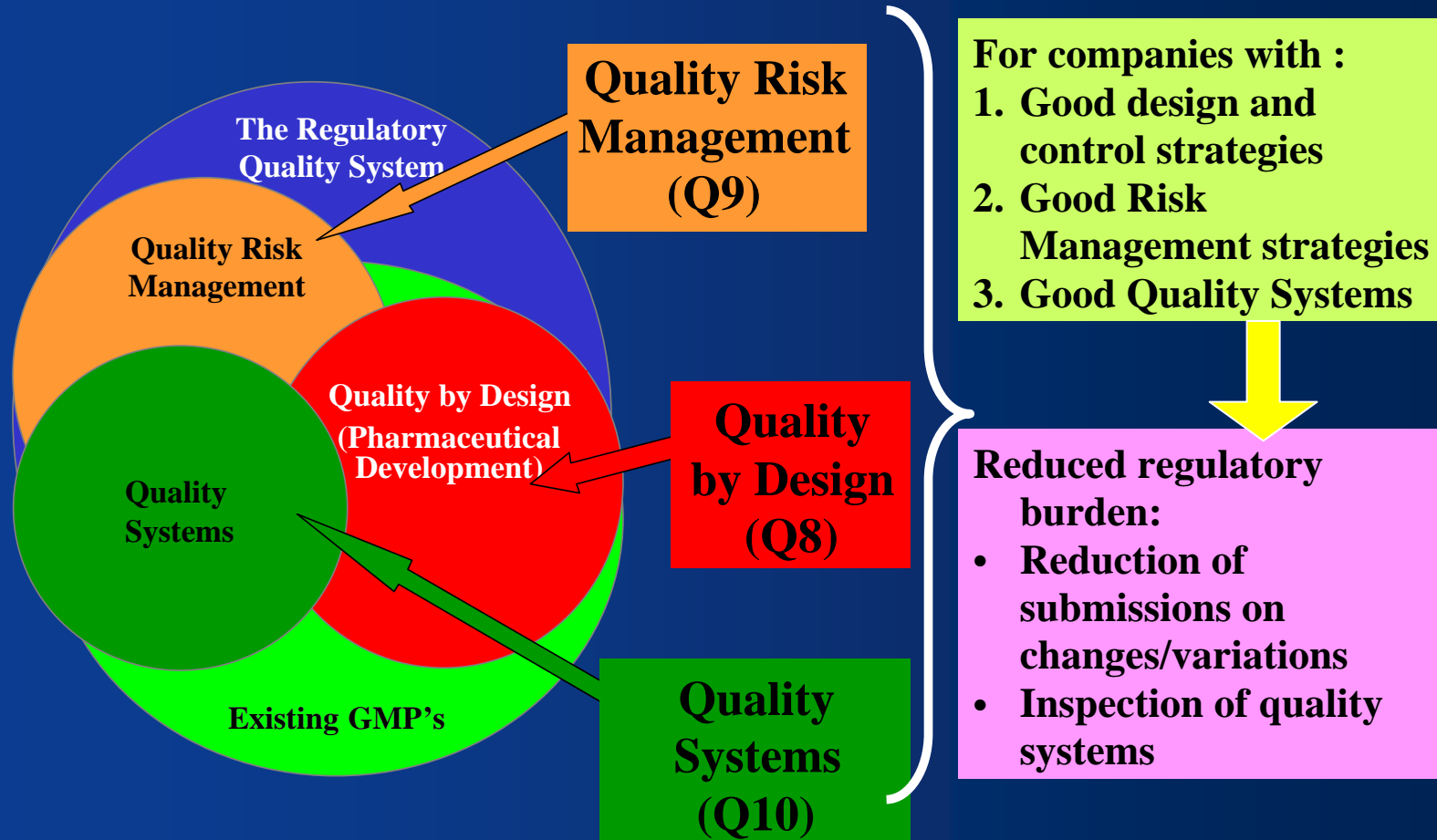


## The EU regulatory point of view on integration of different ICH quality concepts

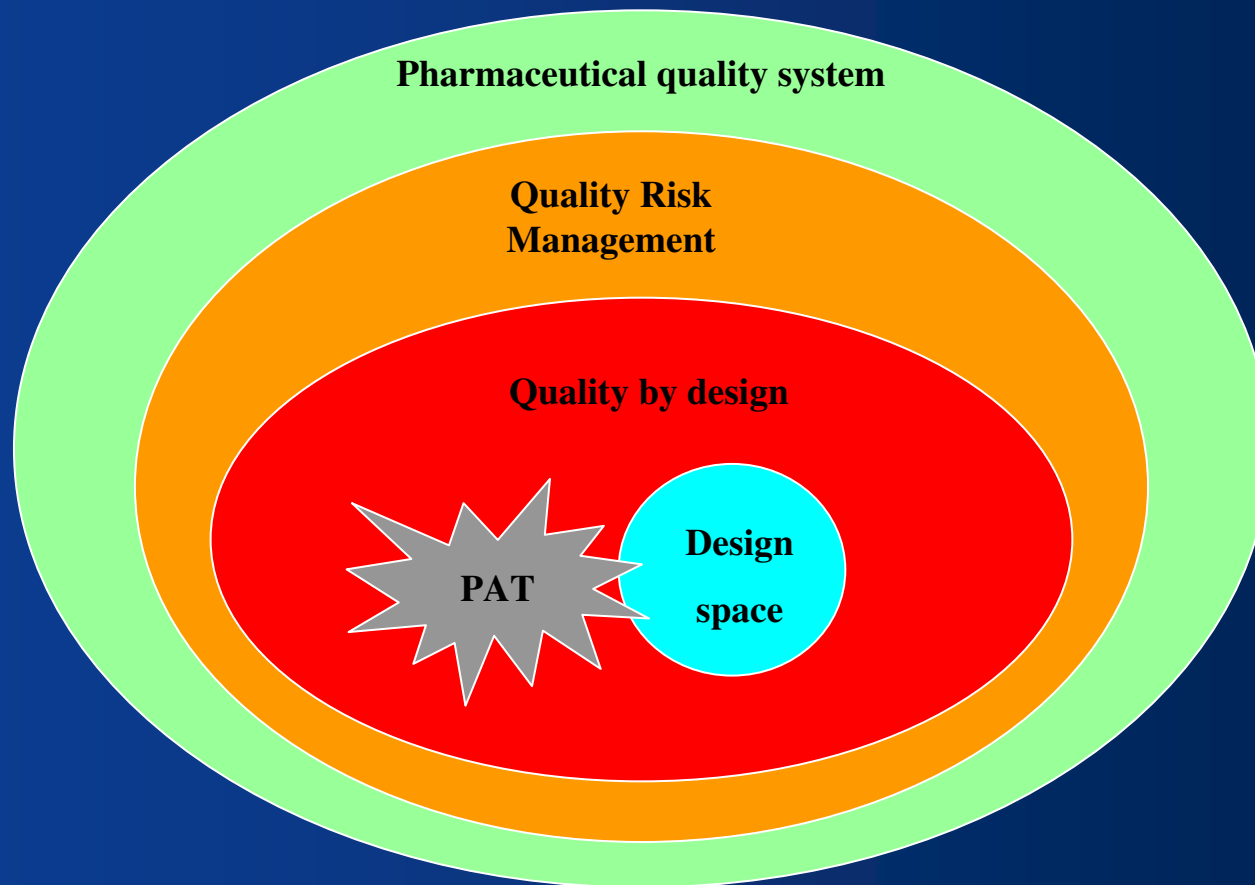


**Which is different from others as ....**

# EU industry vision on ICH



# US Regulators vision on ICH



# US Regulators vision on ICH



# Shared vision on ICH



**Discussions still needed between EU regulators  
and EU industry for obtaining common approach  
and understanding!!!!**

# Regulatory flexibility ?



- Using concepts described in ICH Q8, Q9 and Q10, there are opportunities for “regulatory flexibility” on process and product through information transfer between Industry and Competent Authorities.
- But even this “regulatory flexibility” is very often quoted, nobody knows what it is really .... (example defined in the next slides ...).
- These should be achieved through mutual trust and confidence.

# Regulatory flexibility ?



*Pharmaceutical  
Development:  
Quality by  
Design  
Q8*

+

*Quality Risk  
Management  
Q9*

+

*Modern Effective  
Pharmaceutical  
Quality Systems  
Q10*



*Lower Risk Operations  
Innovation and Continual Improvement  
Optimized Change Management Process  
Flexible Regulatory Approaches*

# Regulatory flexibility ?



Based on:

- Mechanistic process understanding
- Consequent application of risk management,
- Development and implementation of DS for each unit operation e.g; fluid bed drying,
- Derivation of the critical to control attributes

Regulatory flexibility is proposed for the following topics:

- Process validation,
- Scale and equipment change
- Site changes
- Real time release

**From Paul Stott, Astra Zeneca**

# EU regulators concerns



From different initiatives (FDA, industry associations, ....) a lot of “new” ideas are emerging and put on the table .... But without upstream information, shared visions and development (discussions focused with US FDA).

Think globally to make other regulators happy !!!

# EU regulators concerns



We can have same concerns as the following example can show ....

## “Provocative Questions” Linking PQLI Topics

### “Four What’s”

- *What is needed to release product?*
- *What is needed to control the process?*
- *What is needed to be measured during/by process?*
- *What is needed for post-approval change?*

From Roger Nosal

# EU regulators concerns



We have stakeholders who are different as for industry :

- The local government,
- The local or EU Parliaments,
- Public opinion,
- EU partners as the EC, the Heads of Agencies network,

who are not familiar with EU rules/ ICH guidelines and use with other decision making process.

# EU regulators concerns



From	To
<b>“Blind” compliance</b>	<b>Science, risk-based compliance</b>
<b>Process validation</b>	<b>Continuous (real-time) quality verification and improvement</b>
<b>Quality by testing</b>	<b>Quality by design</b>

# EU regulators concerns



<b>From</b>	<b>To</b>
<b>Specifications based on process history</b>	<b>Control strategy developed from process understanding and control</b>
<b>End product testing</b>	<b>Real time assurance of quality</b>
<b>Validation through three consecutive batches pre launch</b>	<b>Ongoing validation through routine manufacture</b>
<b>Focus on reproducibility, ignoring variation</b>	<b>Focus on robustness, controlling variation</b>
<b>Processes locked down, changes require review. Less flexibility in lifecycle management</b>	<b>Flexible process allowing continuous improvement</b>
<b>Quality control</b>	<b>Quality assurance</b>

# EU regulators concerns



We are invited to so many different events in the EU or all around the world and available resources are not enough.

We need to identify key partners and events ....

# Changes for EU regulators



- Industry implementing these ICH guidance, EU regulators should change the way for assessing marketing authorizations and their follow-up.
- A good example is the creation of the PAT team at the EMEA level comprising assessors and GMP inspectors.
- Changes in the EU variation regulation including the new proposal to adapt national legislation on variations to the EU legislation (which will make regulator's life easier but parts of industry would not ..... Depending the actual local legislation).

# Conclusions



- First, we hope that you are not feeling this presentation as too negative or pessimistic,
- We are 95% optimistic and 100% positive for discussing and implementing new concepts derived from ICH process,
- We are committed to listen industry and foster innovation. We will,
- We are happy to be consulted and to support initiative as PQLI as far as it is a global and complementary approach to ICH (interaction between the ICH implementation group and PQLI),

# Conclusions



- Industry is not only global companies. It is the duty of the EU regulators to take into account all kind of companies (medium and small size, generics, ....),
- We need to consolidate and share definitions and understandings for being sure that we all will have a global implementation of ICH concepts,
- You need to consider EU regulators available resources to continue. It will be not possible to go further without their support.

# Conclusions



- We need to go in trust and culture change, enhanced two-way trust for :
  - ☞ Clear understanding of the stakeholders needs and options,
  - ☞ Industry/ regulators trust and openness in working together towards the new vision,
  - ☞ Learning together,
  - ☞ Culture change in both industry and regulators to overcome internal conservatism and “silo” thinking. Also we need change management in front of resistance to change, new competences needed, e-access data ....

Thanks for  
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Thank you for your attention