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GOOD MANUFACTURING PRACTICE: A NEW APPROACH FOR THE 21ST CENTURY

This article describes and analyzes the new approach on good manufacturing practice (GMP) derived from the application of ICH guides Q8, Q9 and Q10. Its practical consequences for the pharmaceutical industry are also evaluated.

Key words: ICH quality guidelines, pharmaceutical quality system, risk management, knowledge management, continual improvement.

FORMULATION OF A QUESTION

Although pharmaceutical industry is considered, by its own personnel, but also by the personnel working in other industrial branches, as a very advanced one, supposed to use the most performing technologies, lately quite a number of experts have started to express serious doubts about that. They have underlined the lack of innovation in the pharmaceutical industry and the very conservative attitude among its personnel. They have also suggested that this cannot be justified on the account of the particular characteristics of the pharmaceuticals and of the regulation that applies to them.

This state of mind has led the American FDA to launch in 2002 an initiative on «GMP for the 21st century», relying on:

- Risk management.
- Politics and standards based on science.
- Integrated quality systems.
- International cooperation.
- A strong protection of public health.
- An increased innovation (quality and innovation are related).

REVIEW OF PUBLICATIONS

International cooperation as stated in the initiative of FDA has been concretized by means of ICH. This organization publishes guidelines belonging to four categories («Guidelines QSEM»):

- Q – «Quality»;
- S – «Stability»;
- E – «Efficacy»;
- M – «Multidisciplinary».

In the first of these categories are published the guidelines which develop the initiative of «GMP for the 21st century»:

- Q7 – Good manufacturing practice guide for active pharmaceutical ingredients
- Q8 – Pharmaceutical development
- Q9 – Quality Risk Management
- Q10 – Pharmaceutical Quality Systems
- Q11 – Development and Manufacture of Drug Substances (chemical entities and biotechnological / biological entities)

Note: Although ICH Q7 guideline preceded the American initiative, it can be put into the group, as it develops GMP for active pharmaceutical ingredients (APIs) and thus, it contributes to tighten control on pharmaceuticals.

The proposed changes tend to draw the pharmaceutical industry closer, as far as it is reasonable, to other branches of industry:

- By allocating resources and taking decisions related to the level of risk;
- By increasing the robustness of pharmaceuticals as a result of a scientific design;
- By developing quality all along the lifecycle;
- By controlling production in real time;
- By implementing a pharmaceutical quality system;
- By managing knowledge;
- By introducing the concept of continual improvement;
- By proposing the same rules of behavior for everybody, authorities and industry.

Q7 – «GMP for active pharmaceutical ingredients»

This guideline has turned into reality the old desire of extending GMP to starting materials too. It is true, that by now only APIs are concerned and that its extension to excipients remains always very problematic, as often the percentage of these substances which is used in the pharmaceutical industry is very low.

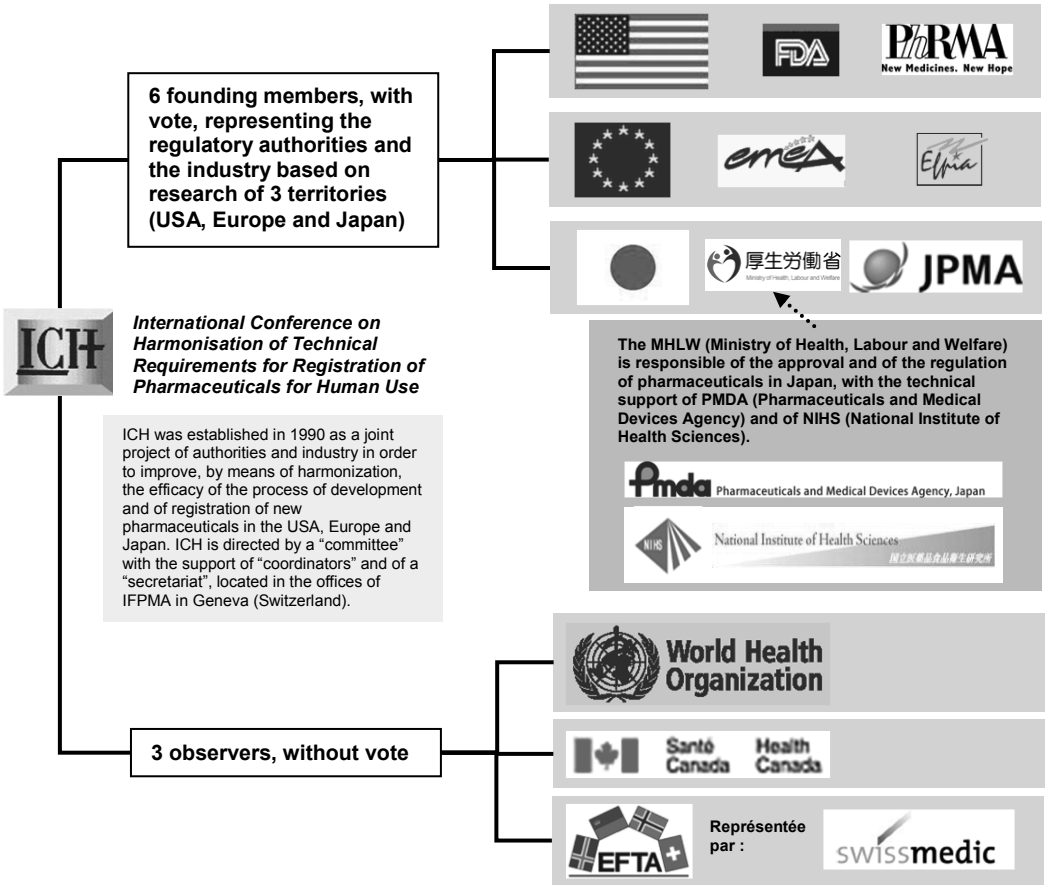

Figure 1. *Organization of ICH*

The contents of this guide are even more updated than traditional GMP, because it is more recent.

Aspects deserving to be underlined

- It contains indications on the scope of application and provides information regarding the starting point from which GMP have to be applied to the process of fabrication of the API.
- Supply chains of starting materials are particularly prone to globalization. To face this problem the guide includes a chapter on agents, brokers, traders, distributors, etc.
- It handles products obtained by culture/fermentation and products for clinical trials too.

Q8 – «Pharmaceutical development»

The goal of pharmaceutical development is conceiving quality products and manufacturing processes capable of producing consistently products with defined characteristics.

This guideline introduces and describes a new approach in order to obtain products with the intended quality. Exactly as it was said that quality cannot be analyzed but it should be manufactured, now it is stated that quality cannot be manufactured if it has not been conceived beforehand.

Aspects deserving to be underlined

- It describes how quality can be designed. Thus, quality is derived from true knowledge, based on science, of products and processes.
- A powerful element in order to conceive quality products is the determination of their critical control points and their monitoring in order to keep them within their acceptance ranges. Or, if the necessary studies on the interaction of these critical quality parameters and attributes are carried out, by the determination of a design space (DS).
- By applying «process analytical technology» (PAT) it is possible to ensure quality in real time.

Q9 – «Quality risk management»

This guideline offers a systematical approach for quality risk management and constitutes a baseline or reference document to be used independently or as a complement for other.

It supplies orientation on the principles and tools of risk management and to the scopes of application as well.

Aspects deserving to be underlined

- It describes the process of quality risk management.

Body	Situation
ICH	**Q7** (initially it was codified as Q7A) **Good manufacturing practice guide for active pharmaceutical ingredients**. Approved: 10/11/2000.
USA (FDA)	Approved: August 2001. (Published in the Federal Register, Vol. 66, No 186, 25 of September, 2001, Pages 49028 - 49029).
Europe (EMEA)	Approved: November 2000 (CPMP/ICH/4106/00). July 2001: Annex 18 to European GMP. October 2005: Annex 18 becomes Part II of European GMP. July 2010: Revision of preface.
Japan (PMDA)	原薬ＧＭＰのガイドライン Approved: 2/11/2001 PMSB Notification № 1200

Figure 2. *History of ICH Q7 guideline*

Organisme	Situation		
ICH	**Q8** **Pharmaceutical development** Approved: 10/11/2005	**Q8(R1)** **Addition of an annex (13/11/2008)**	**Q8 (R2)** **Includes the initial Q8 (Part I), the annex (Part II) and also some clarification and the description of the principles of "quality by design»**
USA (FDA)	Approved: May 2006 (Published in the Federal Register, Vol. 71, No 98, Monday, May 22, 2006)		November 2009 (Published in the Federal Register, Vol. 74, No 109, Tuesday, June 9, 2009)
Europe (EMEA)	Approved: May 2006		June 2009 CHMP/ICH/167068/04
Japan (PMDA)	製剤開発に関するガイドライン Approved: 1/9/2006 (PFSB/ELD Notification N° 0901001)		---

Figure 3. *History of ICH Q8 guideline*

- It provides information on the methodology to be used in risk management.
- It enumerates potential applications of quality risk management.

Q10 – «Pharmaceutical quality system»

This guide describes a modern quality assurance system, complementing GMP. Although it is based on ISO 9000 systems, it has been specifically conceived in order to face the particular needs of the pharmaceutical industry.

Aspects deserving to be underlined

- It describes both «risk management» and «knowledge management» as «enablers».
- It involves senior management and defines its responsibilities.
- It considers continual improvement (both of the system and of its performances).
- The system proposed by the guideline comprises all the lifecycle, from development to the product discontinuation, across technological transfer and production.
- It takes into account the management of the purchase of materials and outsourcing.

Q11 – «Development and manufacture of drug substances (chemical entities and biotechnological / biological entities)»

This is a guideline under development (a draft was released in 2011) intended to be the equivalent of Q8 for APIs.

THE PURPOSE OF THE ARTICLE

The implementation of this new approach on GMP is not an easy task. As in any change there are many doubts, both regarding interpretation and application. In order to face this problem ICH has created a task force (ICH Q-IWG: Quality – Implementation Working Group), in which authorities and industry cooperate in order to shed light on the uncertain points and propose practical solutions.

Organisme	Situation
ICH	**Q9** **Quality Risk Management** (Approved: 9/11/2005)
USA (FDA)	June 2006 (Published in the Federal Register, Vol. 71, No 106, pages 32105-32106, June 2, 2006)
Europe (EMEA)	January 2006 EXT/24235/06 March 2008 (Annex 20 to European GMP)
Japan (PMDA)	品質リスクマネジメントに関するガイドライン 1/9/2006 (PFSB/ELD Notification n° 0901004)

Figure 4. *History of ICH Q9 guideline*

Body	Situation
ICH	**Q10** **Pharmaceutical Quality Systems** (Approved : 4/6/2008)
USA (FDA)	April 2009 (Published in the Federal Register, Vol. 74, No 66, pages 15990-15991, April 8, 2009)
Europe (EMEA)	July 2008 CHMP/ICH/214732/07 (Possibly it will become annex 21 to European GMP)
Japan (PMDA)	医薬品品質システムに関するガイドライン 19/2/2010 (PFSB/ ELD Notification No. 0219-1 & PFSB/ NCD Notification No. 0219-1)

Figure 5. *History of ICH Q10 guideline*

Let us then analyze the main changes proposed by these ICH guides:

1st – A new quality paradigm

Quality is developed and monitored using a scientific approach all along the lifecycle of the product / process within a quality management system.

The three ICH guidelines, Q8, Q9 and Q10, should be implemented conjointly in all the stages of the lifecycle and can be used both by the regulatory bodies and by the industry.

A robust pharmaceutical quality system, with an appropriate risk and knowledge management, ensures quality during the entire lifecycle.

According to ICH Q8 guideline «quality by design» (QbD) can be defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

By saying «quality by design» it is emphasized that quality only exists if the product/process has been developed in a scientific way, that is, by establishing and understanding all the factors on which depends quality. Without that, quality will not exist, even if there is an increase in monitoring and analysis. In order to control quality it is necessary to create it previously.

2nd – Design space

It is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. The quality risk management approach will ensure its robustness (severity, impact on the attribute, probability of presentation, capacity of detection of significant variations).

The definition of a design space increases the flexibility in the production, because within it there are no changes. Any movement in the design space and alteration of non critical variables should be managed by the change management system. Only when one goes out from this space there is really a change requiring a modification of the authorization.

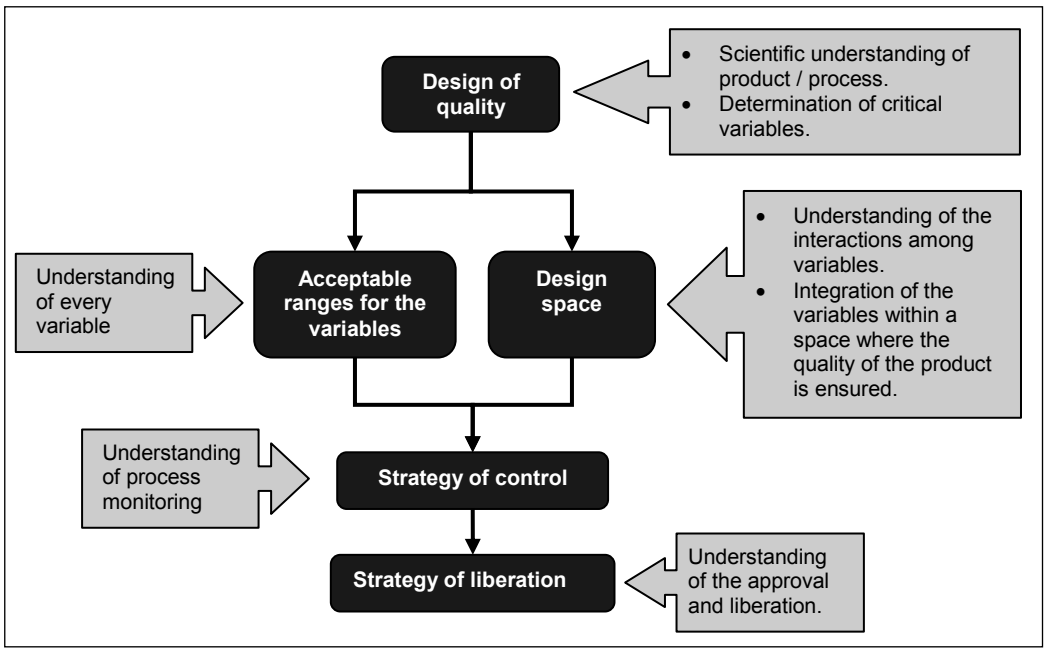

Figure 6. *The new approach regarding quality assurance*

It has to be kept in mind that design space is not compulsory and it can be substituted by the determination of the acceptable ranges for the critical variables.

3rd – Control strategy

It can be defined as a planned set of controls, derived from current product and process understanding that assures process performance and product quality.

Every process and product has its own control strategy, which can have different outlines: in process essays, finish product control, real time release testing (RTRT).

4th – Liberation strategy

It is a consequence of the control strategy. When control is based on analysis, the liberation of the product will be related to the analytical results. When there is a continuous process monitoring with real time information (such as, e. g. by means of process analytical technology – PAT) real time liberation will be possible without final product analysis, following the well-known approach of parametric liberation of sterilized products.

5th – Pharmaceutical quality system

Guideline ICH Q10 proposes a model of pharmaceutical quality system (PhQS) valid for all the stages of the life-cycle.

This PhQS can be applied both to APIs and to pharmaceuticals. It has to be structured and to be adequate for each stage of the life-cycle. It has to be adapted to the particular conditions of each company and to the real situations of every day.

Senior management has to show its commitment with the PhQS:

- By allocating the necessary resources for the implementation and maintenance of the system.
- By demonstrating visible support for the system.
- By ensuring connection among the different functions (quality, development, production, out-sourcing, engineering, purchase).
- B participating in the reviews of performance (of the PhQS, of the processes and of the products).

Although this model of PhQS goes beyond GMP (whereas the PhQS covers all the stages of the life-cycle, the scope of application of GMP does not comprise the development stage, only the manufacture of investigational pharmaceutical products), the regulatory authorities are not intending to create new requirements.

The PhQs possesses two «enablers»:

6th – Risk management

Risk zero does not exist. Consequently every process has its own amount of risk of not possessing the purported quality. Thus, it is necessary to study it in order to know its nature and importance, as this allows for its control and thanks to the continual improvement it can be reduced.

Risks can be anticipated, prevented and controlled by means of a continuous procedure. The level of effort, formality and of documentation should be related to the level of risk.

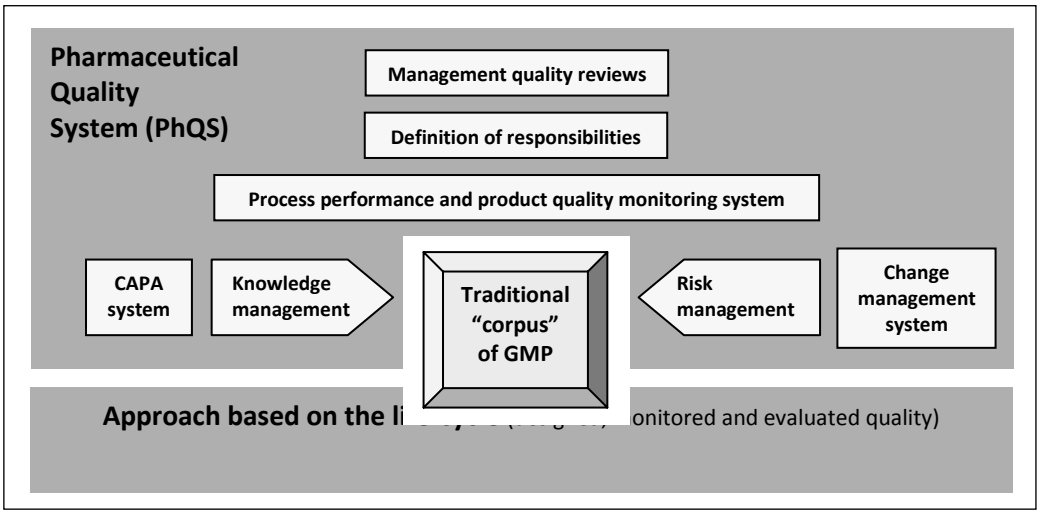

Figure 7. *The Pharmaceutical Quality System (PhQS)*

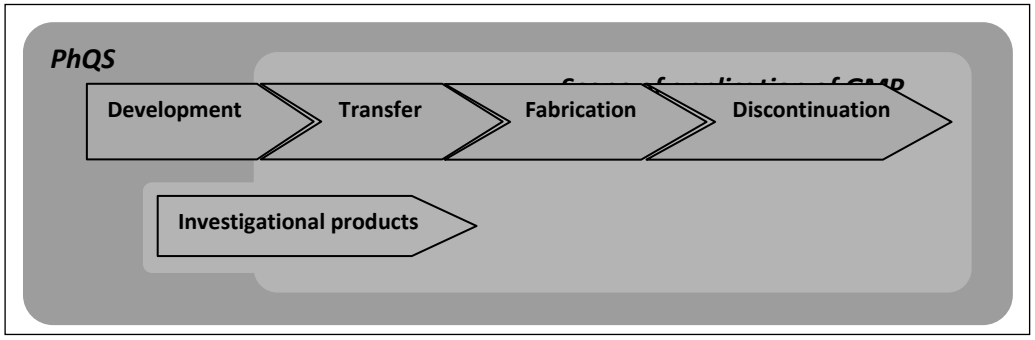

Figure 8. *GMP and the PhQS*

7th – Knowledge management

It can be defined as a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components.

This system handles information valuable for the company in order to put it at the disposal of personnel. Without knowledge, risk management and improvement become impossible.

8th – Continual improvement

While respecting the contents of the registration file, as new knowledge on the products and processes is gathered it is possible to improve control and diminish risk.

All the elements composing the PhQS provide information which can be used to improve the system. Improvement is tightly linked to change management, which ensures that changes will not have unwanted consequences.

Continual improvement can derive from:

Management reviews of the PhQS (measure of the degree of attainment of the quality objectives, evaluation of the indicators of the effectiveness of processes, audits, etc.);

Process monitoring;

Process evaluation;

Etc.

9th – Some differences between the approaches of the USA and Europe

Even if the final result should be the same, there are some differences of approach between both sides of the Atlantic:

While in the USA this change in approach has been clearly expressed, in Europe it appears just as a series of modifications/additions to existing GMP.

In the USA all these modifications are considered as elements of the same puzzle, contributing to the implementation of the new approach. There is not a European equivalent of «GMP for the 21st century» and consequently among the personnel of the pharmaceutical industry the perception of an important global change remains rather misty.

GMP of the USA, mainly 21 cfr parts 210 and 211, just describe basic requirements and thus re-

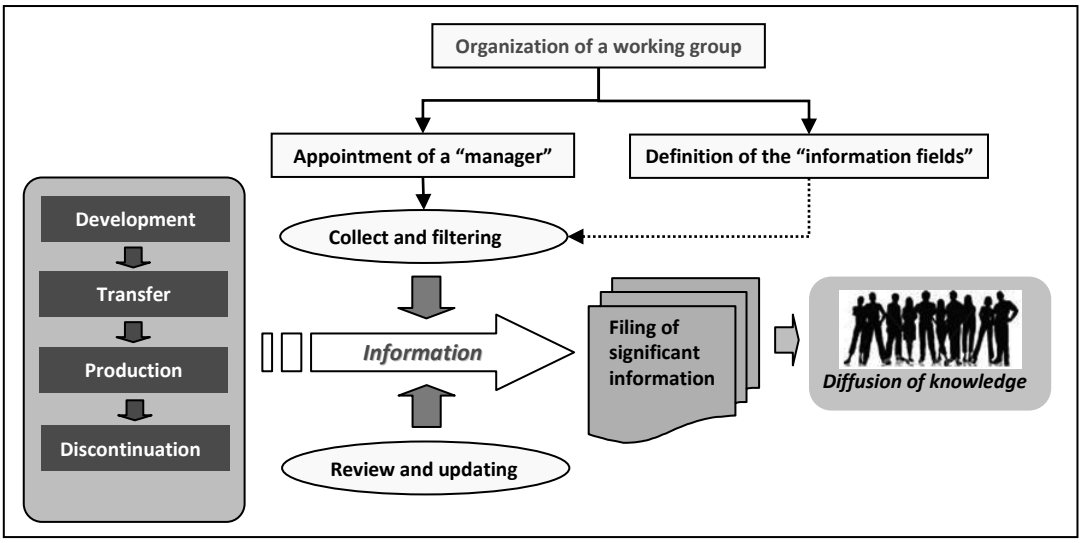

Figure 9. *Knowledge management*

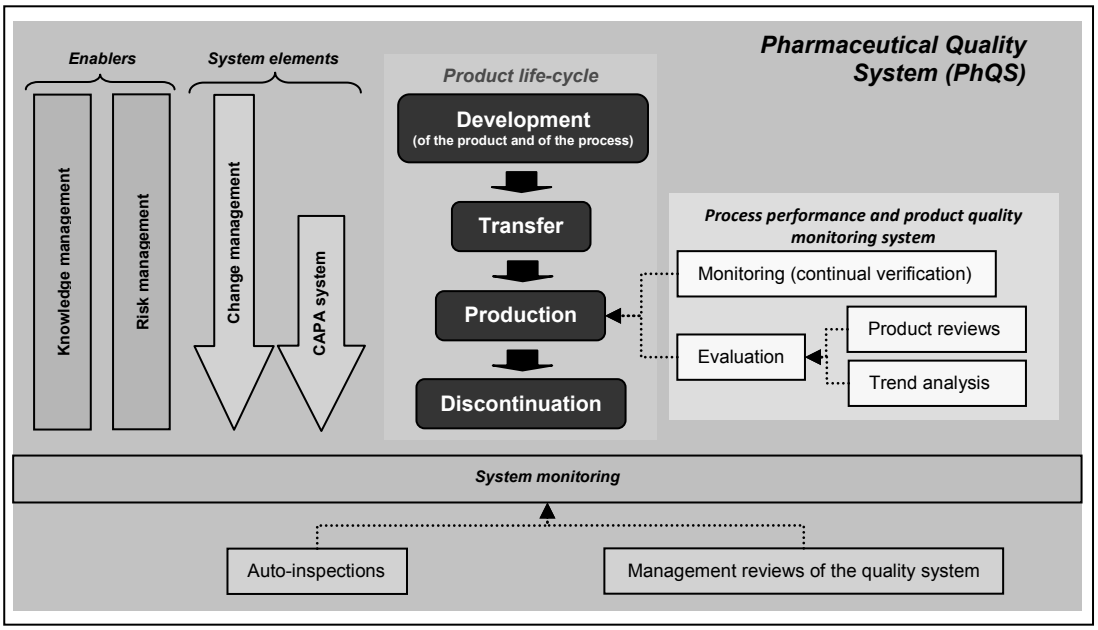

Figure 10. *The control strategy of the 21st century*

main practically unmodified, whereas FDA guidelines, which represent the current point of view of the agency, develop the GMP for the 21st century. In Europe GMP covers both aspects in one guide, which is composed of two general parts and specialized annexes. This implies that European GMP is frequently modified.

RESULTS OF RESEARCH AND DISCUSSION

The inconveniences of the classical system of «quality by analysis» are evident, from both points of view, logistical (results are only known when the manufacturing process is finished and this means that a whole batch can be lost if considered out of specifications) and technical (are collected samples true representatives of the batch?). In the system applied during the second half of the 20th century, and still in use, which is based on «manufactured quality», it is fundamental to develop «the right procedure» which it then formalized as a SOP and validated by the verification of a certain number of batches (usually three). The exact repetition of the process should ensure of a steady quality. Deviations are mastered by means of the change management system and by performing revalidations.

In the beginning of the 21st century the limitations of this model are quite evident. Thus, for instance, the insufficient knowledge of the product neither allows for the assurance of its quality, even if it has been carefully produced, nor for the understanding of the real significance of a deviation from the SOP. This is why, validation is a

much debated subject (is it acceptable to extend the good performance of a limited number of lots to all the lots which are subsequently manufactured?). Furthermore, it has to be born in mind that GMP indicates that to achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management (European GMP, chapter 1).

CONCLUSIONS

The initiative of the FDA on «GMPs for the 21st century» and its development by ICH through its guidelines Q8, Q9 and Q10 propose a new model with an increased quality assurance, because:

- Quality is built and controlled, but also designed (QbD – «quality by design»), and thus, all the elements influencing quality are well known;
- The control on the process is quite real (monitoring = continuous validation) and no more a hypothetic one (prospective validation);
- The responsibility of senior management is well established, even in the area of GMP;
- All the stages of the life-cycle of a product are well linked, and that supposes exchange and use of knowledge («knowledge management»);
- Problems are identified in a proactive way (CAPA system, evaluation, reviews);
- Dangers are identified and their respective risks evaluated and this allows for their control («risk management»).

It is however evident that in order to obtain the purported benefits it is necessary:

- Use in an effective way an approach based on science and risk for the quality;
- Eliminate useless activities in order to «free» resources for the useful activities. This is perfectly possible in fields of activity such as, for instance, qualification and validation, quality control, knowledge management, quality assurance, documentation, etc.

All in all it is necessary to act less and think more = analyze before doing.

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НАДЛЕЖАЩАЯ ПРОИЗВОДСТВЕННАЯ ПРАКТИКА: НОВЫЙ ПОДХОД В ТЕЧЕНИЕ 21-ГО СТОЛЕТИЯ

Эта статья описывает и анализирует новый подход по надлежащей производственной практике (GMP), полученной из приложения ICH, ведет Q8, Q9 и Q10. Оценены практические последствия этого подхода для фармацевтической промышленности.

Ключевые слова: ICH директива качества, фармацевтическая система качества, риски управления, управление знаниями, постоянное усоверше-нствование.

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