ФАРМАЦЕВТИЧНІ НАУКИ

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THE PHARMACEUTICAL QUALITY REVOLUTION

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Pharmaceutical products are patient-oriented. If they had a deficient quality they might put live at risk. Ensuring their quality is not, however, a straightforward task and this is why different approaches have been used along the way. This article analyzes them and shows how our present approach, if well implemented, is very effective in ensuring quality.

Methods. *This article analyzes the current pharmaceutical quality system as described by international guidances in the light of practical experience gathered by the author as an international GMP-consultant.*

Result. *Nowadays we have come to understand that as quality is a global concept in terms of time and of requirements, it has to be assured in a global way too. This is why quality assurance is a permanent process that starts during the development of a product and goes on during its manufacturing life. Manufacturing should be performed within a pharmaceutical quality system which ensures GMP compliance. Decisions should be science and risk-based. Products and processes are monitored by means of critical variables.*

Conclusions. *The approach followed in the 21st century for ensuring quality is very effective and allows for a progressive reduction of the level of quality risk. However, this quality system is either comprehensive or there is no quality*

Keywords: *Continual improvement, Critical Process Parameter (CPP), Critical Quality Attribute (CQA), Knowledge management, Lifecycle, Pharmaceutical Quality System (PQS), Quality by design (QbD), Quality risk management, Quality Target Product Profile (QTPP), Supply chain*

Фармацевтична продукція орієнована на пацієнтів. Застосування препаратів сумнівної якості може виявитись небезпечним для життя. Проте забезпечення їх якості є непростою задачею, і тому в цьому напрямку використовуються різноманітні підходи. У представленій статті наведений їх аналіз та оцінка, яким чином представлений нами підхід при належному впровадженні може виявитись достатньо ефективним у забезпеченні якості.

Методи. *У представленій статті наведений аналіз сучасної системи якості у фармації, описаної міжнародними настановами у світлі практичного досвіду, зібраного автором як міжнародного консультанта з питань належної фармацевтичної практики.*

Результати. *У теперішній час нам доводиться зрозуміти той факт, що, оскільки якість є глобальним поняттям з точки зору часу і вимог, вона також повинна бути і глобально забезпечена. Саме тому забезпечення якості є безперервним процесом, що починається з розробки продукту та триває протягом його виробництва. Останнє має здійснюватись у рамках фармацевтичної системи якості, яка забезпечує дотримання вимог належної фармацевтичної практики. Рішення мають бути науково обґрунтованими та з урахуванням можливих ризиків. Продукти та процеси контролюються за допомогою критичних змінних.*

Висновки. *Запроваджений у 21 столітті підхід із забезпечення якості є достатньо ефективним та дозволяє поступово знизити рівень ризиків якості. Проте дана система якості або має бути комплексною, або виявиться не ефективною*

Ключові слова: *безперервне вдосконалення, параметр критичного процесу, критична властивість якості, управління знаннями, життєвий цикл, система якості у фармації, дизайн якості, управління ризиками якості, профіль якості цільового продукту, ланцюг постачання*

1. Introduction

Quality is a must for any product or service and this is particularly true for medicinal products which being patient-oriented should be sure and effective. Two different approaches have been consecutively used to achieve this objective. The first one which might be called "analyzed quality" relied on the analysis of the finished products for ensuring their quality. The second one which might be denominated "manufactured quality" was introduced about the middle of the 20th century and it focused on appropriate manufacturing. This was obtained, firstly, by the introduction of GMPs (Good Manufacturing Practices) and, secondly, by the implementation of validation. Although both approaches contributed to improve the quality of drug products they had evident shortcomings. This is why a new way of considering this problem has been introduced at the beginning of the 21st century. This new approach that we might denominate "designed quality" gathers former experiences and provides a comprehensive frame for ensuring quality.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

The analytical approach to quality is inadequate because of the intrinsic limitations of the methods of analysis (unsure detection of unexpected contaminations, reduced sample size) [1] and because in case of non-compliance of the finished product corrective measures are difficult to implement. This is why in the 1960s GMP (Good Manufacturing Practice) was introduced. At the beginning GMP texts were concise [2] but they have progressively grown. The intended aim was to diminish the chance of failure by controlling the elements which might put quality at stake. Quality accidents could be prevented by keeping under control the chain of events that might lead to them, as shown in Fig. 1.

GMP is in fact "compulsory pharmaceutical common sense" and as such it has an evident limitation, it provides general rules not directly-linked to the products. This is why validation was introduced [3]. As a matter of fact, validation is product-linked and thus it increased the efficiency of GMP in ensuring quality. The validation of a process consisted in repeating it several times according to the approved procedure and following it accurately. If the process produced successfully a product meeting specifications it could be inferred that successive batches prepared following exactly the same procedure would also yield a compliant product. In order to keep drifting under control revalidation and change control were introduced.

Fig. 2 shows the differences in approach between "analyzed" and "manufactured" quality.

In the first approach starting and packaging materials were analyzed to confirm that they met specifications and, often, some in-process controls were also performed. However, it was the analysis of the finished product that decided its fate.

In the second approach were maintained the same kinds of analysis than in the first one, but three important items were added: GMP quality measures, validation, and process monitoring (including here personnel, equipment and utilities). The fate of the finished product is determined on the basis of in-process control, in-process monitoring and the analysis of the finished product.

Be that as it may, validation, even if complemented by revalidation, was a time-limited process and it is evident that a time-limited process cannot ensure efficiently the quality of a time-extended process.

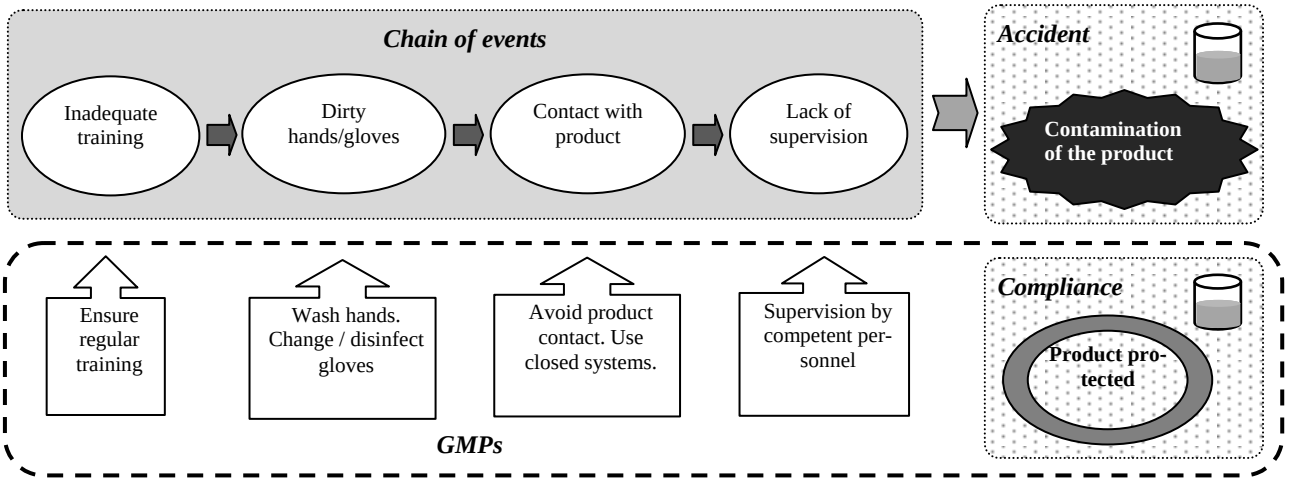

Fig. 1. GMP as a tool for preventing accidents

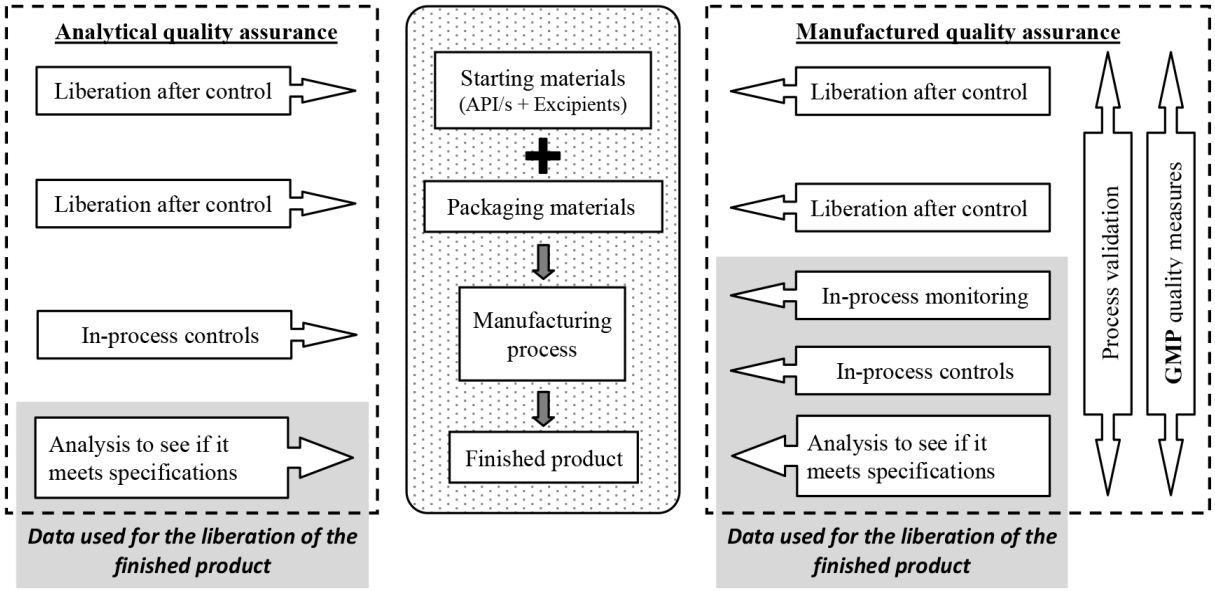

Fig. 2. Quality assurance in the 20th century

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author

Bearing all this in mind, American FDA in the beginning of the 21st century established the bases for a new quality approach to pharmaceutical products which was called "GMPs for the 21st century" [4]. This initiative gathered the experience gained with the application of GMP during the second half of the 20th century and proposed to follow a new approach aimed at filling the gaps left by the application of GMP such as:

– Limited consideration of the particularities of each product;

– No room for improvement (knowledge on products and processes kept "frozen" after obtaining the authorization for commercialization);

– Lack of risk assessment;

– Lack of a comprehensive quality system;

– Poor application of science on GMP-matters;

– Quality assurance limited to commercial manufacturing;

– Validation performed as a limited operation in terms of time and batches;

– Quality ensured by the repetition of processes as validated;

– Although pharmaceuticals are produced to be used by patients, these were not considered to play any role;

– Neither lifecycle nor supply chain were taken into consideration as such.

The use of the preposition "for" in the name of the FDA's initiative ("GMP for the 21st century") showed that the intention was not transforming GMP, but applying it in a different way, that is:

– Risk should be assessed to better understand and monitor products and processes;

– Decisions should be GMP- and science-based;

– Quality should be designed to be afterwards monitored by means of critical variables;

– A pharmaceutical quality system should provide the frame for the application of the quality assurance policy;

– Quality is comprehensive and as such it requires a lifecycle and a supply-chain approach;

– Continual improvement is possible and necessary and can be attained by diminishing the level of quality risk;

– Knowledge is the basis on which quality is build. This is why knowledge on products and processes has to be acquired, maintained and updated, as necessary;

– Validation is a process that starts with the development of a product and continues during its whole life. The objective should be having each batch "validated" (concomitant validation) [5, 6].

This new approach to quality that came to be defined as "designed quality" gained world-wide acceptance when it was adopted by the International Conference on Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use (ICH) and afterwards by other parts such as the WHO or ANVISA (Brazil).

Although approaches were slightly different (FDA proposed applying GMP in a different way, whereas other parts considered it as an updating of GMP by including new chapters) the intended result was the same: a new quality paradigm and a patchwork of new or reinterpreted elements to be applied together with existing GMP in order to better ensure quality.

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

It is important to consider that quality is obtained as a consequence of the implementation of GMP plus all the other above-mentioned elements. This vision of designed quality means that if any element is missing then the picture is imperfect: quality is either comprehensive or is not achieved.

Thus, the new quality approach of the 21st century is much more complex than the previous two used in the

20th century not only because, as previously said, it has included both of them, but also because it comprehends the whole life-cycle of products and the complete supply-chain during commercial manufacturing.

All the same, this complexity is not surprising if we consider the intrinsic complication of quality assurance and, as often happens, difficult objectives cannot be attained without some effort. Besides, as it is described further on, this new quality approach is highly successful.

5. Formulation of goals (tasks) of Article

This article describes in a practical way the components that have to be assembled to build a modern quality frame. These components are described taking into account the practical experience of the author in pharmaceutical laboratories.

6. Statement of the basic material of the study (methods and objects) with the justification of the results

Quality in the 21st century can be seen as a patchwork of multiple components that work coordinately within the frame of a pharmaceutical quality system [7].

These components (GMP & Science, Risk management, Lifecycle, Quality by design, Knowledge management, Supply chain, Validation, Continual monitoring and improvement) are represented in Fig. 3.

Quality can be effectively assured by the coordinated and permanent application of all these elements. This might seem rather complex, but it is evident that if in a manufacturing unit many different processes are being continuously performed a system ensuring their quality should be continuous and wide-ranging too.

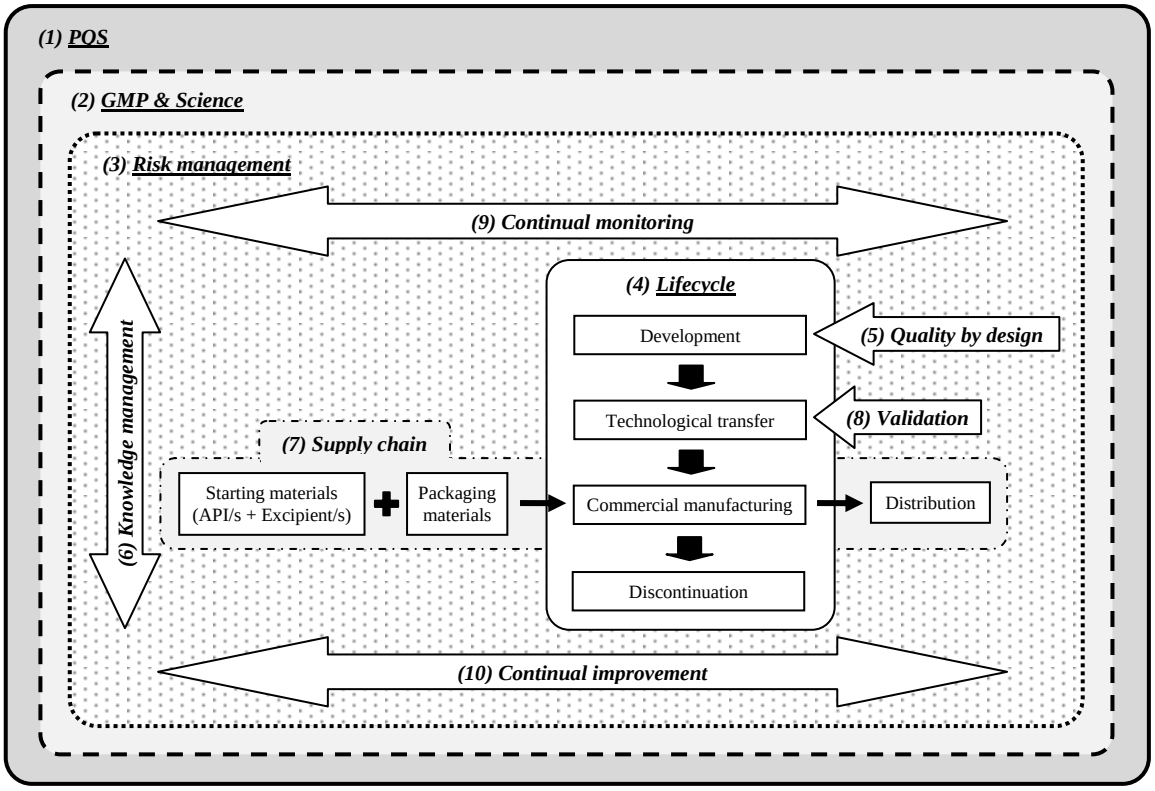

Fig. 3. Quality assurance in the 21st century: the patchwork of quality

(1) PQS

The Pharmaceutical Quality System (PQS), as described in Guideline ICH Q10, inspired in the ISO 9001 norm, is a quality system adapted to the particular needs of the pharmaceutical industry [7]. As such it comprises all the measures and actions which are taken in a company to ensure quality by the application of GMP.

The PQS is the frame which determines how to apply, how to monitor and how to supervise the application of GMP. Besides, the PQS completes GMP on some practical aspects which ensure its application, for example:

– GMP states that quality is everybody's responsibility and defines key posts in a manufacturing unit but there is not a mention on "leadership" and experience shows that this is an essential point in any organization. This is why PQS states that the final responsibility regarding quality matters (i. e. GMP application) corresponds to the senior direction of the organization. Practice shows that without the support of the direction in terms of guidance and resources implementation of GMPs is impossible.

– The implementation of a PQS requires the development of a quality policy and organization expressed in the "Quality Manual" and in the "Declaration on quality policy". These provide the frame for the application of GMP.

– Although GMP provides extensive information on documentation, the PQS completes it in terms of coordination and management.

– For historic (or maybe, to come closer to the facts, for pragmatic reasons) GMP was initially applied

to the manufacturers of finished medicinal products and afterwards to the making of active pharmaceutical ingredients (APIs) [8, 9]. Although originally by finished medicinal products were understood those pharmaceuticals that had been approved by the regulatory authorities to be commercialized, later on investigational pharmaceutical products were included too [10]. However, development of medicinal product was not considered by GMP. Instead, the PQS comprehends all the stages of the lifecycle of a product, from development to discontinuation. Fig. 4 shows the respective scopes of GMP and of the PQS as shown in Guideline ICH Q10 [7].

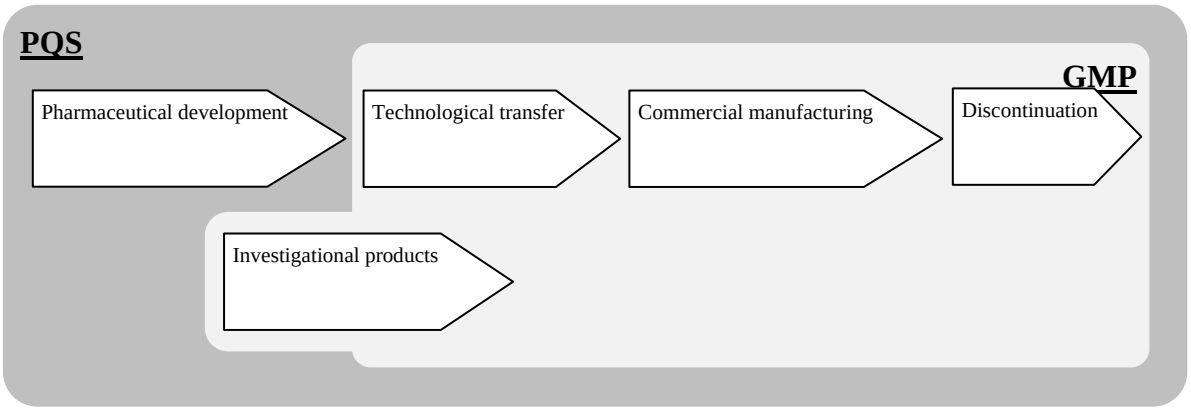

Fig. 4. Comparison of scopes of GMP and the PQS

– The PQS defines four "elements". Although half of them were already considered by GMP (i. e. System of corrective and preventive actions – CAPA- and System of change management, albeit not under these exact denominations), the other half is new (i. e. Process Performance and Product Quality Monitoring System and Management Review of Process Performance and Product Quality) [7].

– The PQS is provided with two "enablers", which correspond to new concepts which did not exist in GMP [7].

– Associated to the Quality Manual a "Process Manual" identifies the processes within the scope of the PQS and defines indicators of performance for them. See below, point (10).

(2) GMP & Science

Good manufacturing practice is the basic rule that explains how to act in order to manufacture quality pharmaceuticals. As such it describes the practices which are recognized as appropriate in their fabrication. It accepts that other approaches might be adequate too, provided that this is proved.

Although basic concepts have remained unchanged since its introduction, GMP is continuously improved in order to provide wider orientation and to include new concepts and areas of knowledge, as necessary.

Even though there is not yet a universally accepted GMP text, all existing GMPs are close enough as to allow for the practical existence of a world-wide pharmaceutical market. GMP provides information on the basic issues of pharmaceutical manufacturing (i. e. personnel, premise, equipment, documentation, operations, validation, etc.) as well as on specific types of products (i. e. sterile pharmaceuticals, blood derived products, etc.).

GMP is a reference norm in audits and inspections and as any norm it is prone to be interpreted or used in a too literal or restricted sense. However, GMP is derived from science and has to be applied as such. It is possible to say that either GMP is scientific or is not really GMP.

(3) Risk management

Risk management is a key element of modern quality management (Guideline ICH Q9 considers it an "enabler") [11]. Its importance derives from its two functions.

Firstly, it allows for the distinction of what it is important and what is not and thus it is possible to apply existing resources in a more useful way. At first sight (e. g. from the quality point of view of the 20th century) it might seem that as quality is an absolute must (i. e. riskless) all necessary resources should be applied everywhere. This is however wrong (or, in other words, it can be proudly affirmed but cannot be turned real). Resources are limited and they cannot be used to obtain matchless results, because this is not possible in our world. What we can really do is using our resources to obtain as better as possible results (i.e. with the lowest possible quality risk).

Secondly, it is extremely important to really understand products and processes. GMP is a given norm and as such many people tend to see them as a kind of "precepts" that have to be applied blindly. This is why the initiative of GMPs for the 21st century insisted on "science-based decisions" and on "risk management". GMPs have to be applied and understood on a background of science and adapted to the real needs. Personnel should analyze their products and processes to be aware of the real hazards and their respective risks (e.g. only if personnel involved in a process analyze it and are aware of why, how and when contamination is harmful and which is the level of risk they will be able to understand in depth what GMP states).

And thirdly, only if we are aware of our level of risk it is possible to introduce improvement seen as risk reduction. Continual improvement is the result of persistent assessment of products and processes in order to

understand the level of risk and to diminish it by introducing new measures (i. e. better training, enhanced monitoring, new equipment/instrumentation, etc.). See point (10).

As shown in Fig. 5 process management is a permanent process composed of four steps.

These steps correspond to the logical phases of a continual process:

– Risk assessment: Products and processes have to be well known and assessed (i. e. risks have to be identified, analyzed and evaluated).

– Risk control: Once risk is known it has to be decided if it is low enough to be accepted or if it should be reduced to be acceptable (Fig. 6). Accepted risk can be communicated to third parts.

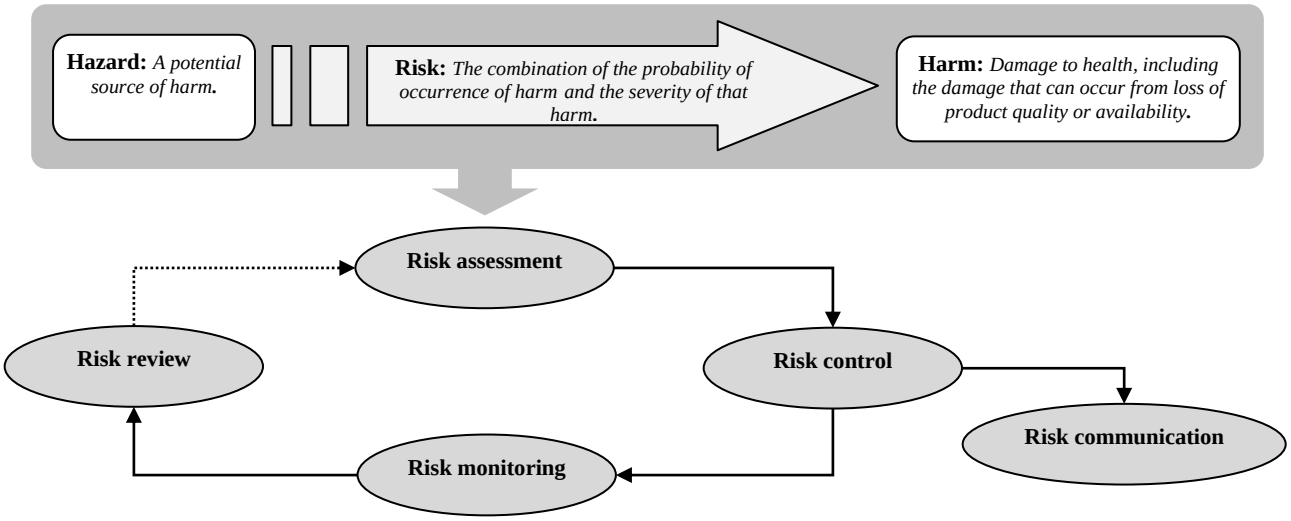

Fig. 5. Risk management

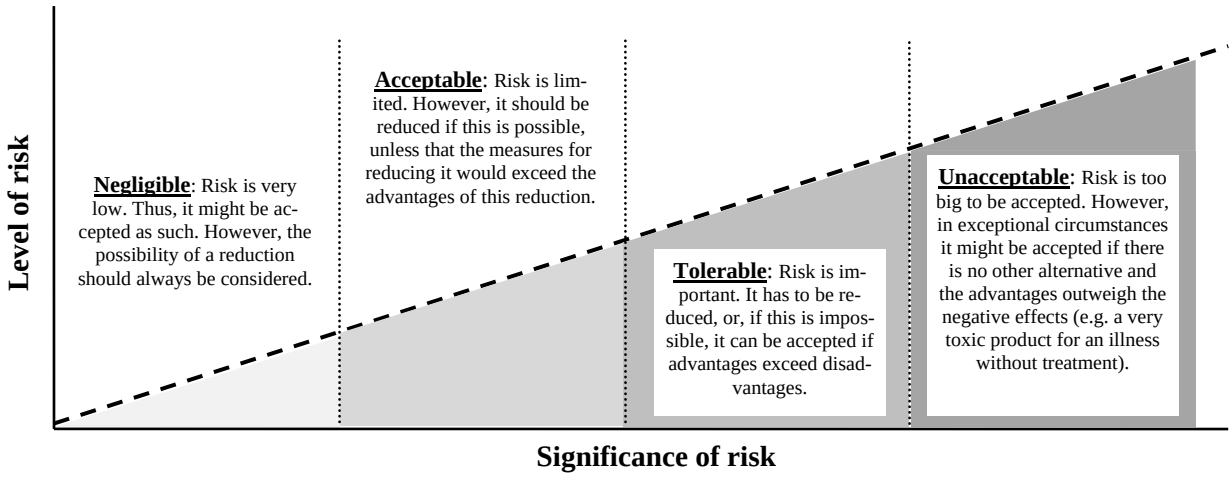

Fig. 6. Significance of risk

– Risk monitoring: Quality risk for products and processes has to be monitored to ensure control on them.

– Risk review: In any case an accepted risk should be reviewed within the frame of continual improvement to see if it can be further reduced.

(4) Lifecycle

As shown in figure 3 the lifecycle of a medicinal product is composed of four stages [12]:

– Pharmaceutical development: The objective is designing a quality product and a process capable of producing it consistently. This stage comprehends all the investigational operations which are necessary to define a product effective and sure enough to be granted approval for commercialization by the regulatory authorities.

– Technological transfer: The objective is transferring the knowledge on the product and on the manufacturing process from the center of research and development to the center of manufacture.

– Commercial manufacturing: This is the stage typically covered by GMP, which traditionally focused on the fabrication of the products (i.e. from the purchase of the starting and packaging materials to the shipment of the finished products). The objective of this stage is obtaining a product meeting specifications, maintaining a state of control on the processes and facilitating the continual improvement.

– Discontinuation of the product: When it is decided not to manufacture a product anymore it is necessary to bear in mind that pharmaceutical manufacturing should be patient oriented. This means not only that drug products should be effective and safe, but also that in case of discontinuation patients should be protected from the unavailability of necessary products. In case of dis-

continuation of a product safety means that while there is product on the market, the necessary procedures are maintained (i. e. batch manufacturing documentation, ongoing stability studies, pharmacovigilance, traceability, etc.)

Although these stages of the lifecycle of a drug product have long been recognized their significance and role in ensuring quality has been largely overlooked. The objective of development is not only designing a formula and a manufacturing process able to be granted marketing authorization, but also designing a quality product and process by knowing and understanding all the factors from which the quality depends (see further on). Nowadays a product which has not been provided with quality during its development cannot be manufactured with quality. This is a very important modification regarding the quality approach of the 20th century. Then quality was defined by preparing detailed master formulae or batch manufacturing protocols [13, 14] and validated by manufacturing with them several batches. Now, it is considered that quality has to be designed before being manufactured [12]. This is easy to understand if we consider that an ill-defined product prepared by a process that is not robust will very unlikely be reliable.

Technological transfer is also very important because it ensures the right transfer of all the knowledge gained during the development to the manufacturing site. It is also essential because it confirms or improves knowledge and because it establishes the bases on which commercial manufacturing will be performed.

(5) Quality by design

Whereas in the 20th century had been spoken of "analyzed quality" and of "manufactured quality" in the 21st century it is spoken of "designed quality". First of all, it is important to bear in mind that these three approaches are not exclusive, but additive. As it has been previously shown, "manufactured quality" did not exclude analysis. The difference was that whereas in "analyzed quality" analysis were basically performed in the finished product and decided its liberation, in "manufactured quality" finished product analysis were just one of the elements (albeit a very important one) which were considered. Liberation of a batch required considering other aspects like the results of in-process, personnel and environmental controls. It was also necessary to ensure that the manufacturing process was realized as validated.

Let us then consider the approach followed in "designed quality". As it was already mentioned, this approach encompasses the whole lifecycle of the product. It starts during the stage of product development, when quality is designed. Guideline ICH Q8 defines "Quality by Design" (QbD) 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 [12].

As shown in Fig. 7 it all starts by defining the Quality Target Product Profile (QTPP) of the product which is a kind of characterization of the product taken as the basis of design for the development of the product, for example:

– Dosage form and route of administration;

– Intended use and dosage of the API (or APIs);

– Primary packaging materials (container and closure);

– Therapeutic release and pharmacokinetics of the API (or APIs);

– Characteristics (attributes) of the dosage form affecting the release and pharmacokinetics of the –API (or APIs);

– Quality criteria of the product (e.g. sterility, purity, stability and drug release).

– Etc.

Then it is necessary a knowledge in depth of the critical variables of the starting materials, of the manufacturing process and of the product. It is evident that packaging materials should be also taken into account and they might also have critical variables affecting the product (i. e. leachables, absorption, degradation, etc.).

In fact, it is possible to say that the key of development is the identification of the critical variables, either quality attributes or process parameters (Fig. 7). There is a relation between CPPs and CQAs (i.e. if starting materials with given CQAs are processed under determined CPPs, the product will possess defined CQAs. according to QTPP).

Once that these critical variables have been identified their respective acceptable ranges have to be determined. Here two different approaches are possible:

– Individualized study of the variables: In this case for each variable is determined the acceptable range (i. e. the upper and lower values which ensure the quality of the product);

– Multivariable study of the variables which takes into account the existing interdependencies among them. The result of this study is known like "design space" (DS), which is defined in the Guideline ICH Q8 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.

Both approaches are considered acceptable by the regulatory authorities. The definition of a DS requires much more developing work but it has the advantage of allowing some amount of freedom in terms of modification of the variables. Regulatory authorities consider that modifications within the DS are not a change and do not require regulatory approval. By using statistical methods (design of experiments – DoE) it is possible to reduce the number of assays needed to establish the multifactorial influences of the variables among them. Although design space can be represented graphically, the ideal objective is to establish a predictive mathematical model.

The understanding of the critical variables of the process allows for the establishment of a control/ monitoring strategy of the manufacturing process. The objective is ensuring that the finished product will meet the established requirements (QTPP).

Critical attributes are monitored and if they remain within the acceptable ranges or within the DS the process remains under control and its quality is ensured. The process is overseen, step by step, by means of its critical variables.

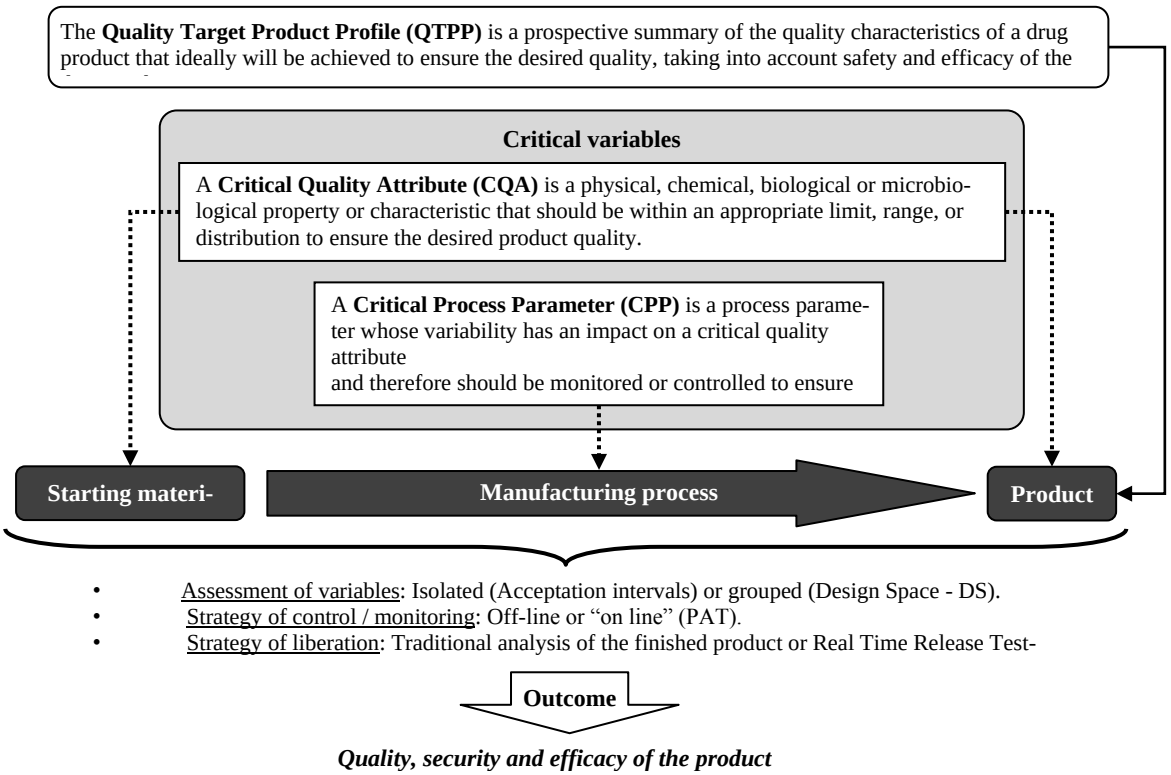

Fig. 7. Designed quality

CPPs can be monitored following different approaches. A simple and traditional one would be taking a sample and measuring/analyzing "off line" a given parameter. A more evolved system would be doing this "on line", provided that the manufacturing equipment is outfitted with the adequate instrumentation. This is known as "process analytical technology" (PAT). This latter approach eliminates the typical problems derived from sampling.

The strategy of control/monitoring is directly related with the strategy of liberation. Traditional approaches relied on "off-line analysis" for the verification of critical variables. With the development of better equipment, instrumentation and analytical methods more and more critical variables can be determined on-line (i.e. particle counting, humidity, identity, etc.) and, consequently, less relevant is the analysis of the finished product. It is evident that if all critical variables can be determined on-line, than further analysis is not necessary and the product can be released as soon as the manufacturing process is finished. This is known as "real time release testing" (RTRT) which can be defined as the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. The "parametric liberation" described in GMP [15] is a type of RTRT.

(6) Knowledge management

Besides quality risk management it composes the couple of enablers defined in Guideline ICH Q10 [7]. It is defined as a "systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components".

Although pharmaceutical development allows for the authorization of a medicinal product, it is evident that experience is restricted both in terms of clinical assays and in terms of the number of patients who have used it and this is why unexpected reactions derived from the particular behavior of the product on varied population groups cannot be excluded. Authorized products have a positive risk-benefit balance which has to be confirmed under real conditions. An "increase of knowledge on the product" might change its risk-benefit balance and this is why pharmacovigilance was introduced (Fig. 8). The increase in knowledge of a product is not limited to its behavior in front of different genetic types, but also in relation to its characteristics, to the manufacturing process and to many other matters (in-process monitoring, testing, equipment, etc.). Variables were identified during the development. Some were considered critical, other not and for those considered critical were defined acceptable ranges, but this has to be monitored along the service life. This is why knowledge management is necessary.

Knowledge management can rely on the practical experience gathered by pharmacovigilance, taking into account the differences which exist between pharmacology and pharmaceutical technology. Thus, a knowledge management system can be composed of the following elements:

– A responsible of knowledge management aided by a team, as necessary;

– A communication strategy for gathering information regarding the products;

– A procedure for collating and managing information;

– A knowledge management committee (to simplify matters it can be the same performing Management Reviews);

– Periodical knowledge management committee reviews and reports providing updating on product knowledge;

– A database or master file for preserving the above mentioned information.

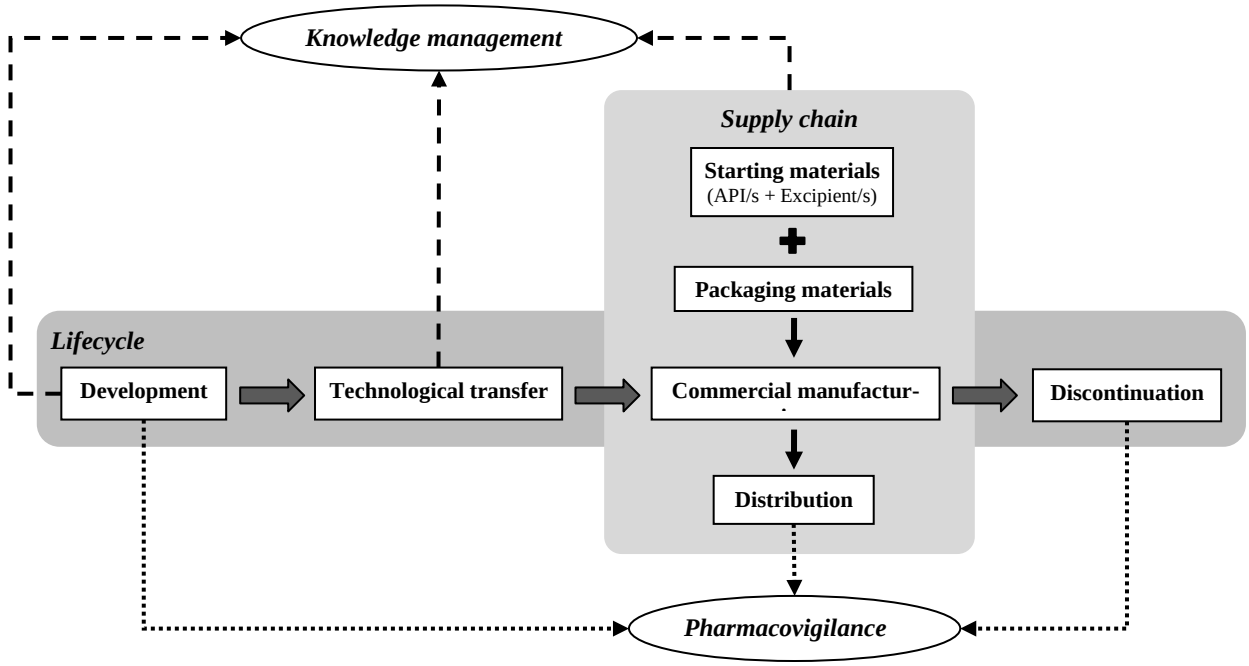

Fig. 8. Knowledge management and pharmacovigilance

The responsible of knowledge management receives information on the products (rejects, recalls, returns, complaints) and on the processes (deviations, out-of-specifications, out-of-trends, comments/remarks) and other topics (monitoring and testing results, equipment performance, etc.) collates them and decides if they are significant or not. Those considered significant are retained as candidates to increase knowledge on the product and to be analyzed by the knowledge management committee. The results of the committee review are summarized in a report, which is distributed for "diffusion of knowledge" and data are filed and become part of the corpus of knowledge of the product. These results may include recommendations of change, as necessary.

(7) Supply chain

Figure 8 shows a supply chain intersecting with the lifecycle. This is an extremely simplified one because in practice a supply chain is much more complex and with many steps and intervening actors. In the past it was not paid much attention to the supply chain because its configuration corresponded to this very simple representation. Starting and packaging materials were purchased from a few well-known suppliers, often not very far-away from the plant where drug products were manufactured. Finished products were sent to a limited number of well-known distributors which supplied pharmacies and hospitals. Recently this simple supply-chain panorama has changed completely. Suppliers are varied and scattered around the world. Manufacturing processes are often outsourced, either completely or partially. Finished products are distributed in a world-wide market. A very complex supply chain is very difficult to keep under control and this supposes, evidently, a high risk of damage for the quality of the products. Let us consider the aspects which should be controlled in a supply chain:

– Suppliers of starting materials and packaging materials;

– Incoming starting and packaging materials;

– In-house manufacturing and analytical processes;

– Outsourced manufacturing and analytical processes;

– Distribution of the finished product;

– Transport conditions whenever they are deemed critical;

– Tampering, falsification, theft, smuggling, etc.

As it was previously mentioned medicinal products should be patient oriented. This means that whatever happens during the supply chain should not affect the quality and security of the product which receives the patient. Or, in other words, what really counts is the quality of the product received by the patient and here an inadequate step in the supply chain can ruin all the efforts made for obtaining a quality product. The worst step in the chain determines the quality of the product. This is why the supply chain has stepped into the first rank among the subjects of preoccupation. Nowadays supply chain can be very complex and they have to be thoroughly monitored to ensure quality.

(8) Validation

Processes are validated before commercial manufacturing with the intent of ensuring that they perform as intended. The approach to validation, however, has also evolved in these last years [3, 5, 6]. As it has been previously indicated validation was introduced as a basic element of quality assurance in "manufactured quality". Nowadays it is considered as one of the elements which ensure quality. Validation is a never ending process that starts during de pharmaceutical development of a product when the bases of the product are established, as discussed in point (5). Then during the stage of technological transfer batches are fabricated in the real conditions of commercial manufacturing with the aim of confirming the knowledge acquired in the laboratory of development. It is important to show that a product meeting requirements can be obtained by monitoring critical variables. Subsequent commercially manufactured batches are routinely monitored following this approach. Thus, it can be said that each batch is "validated". The study of trends, not to tell deviations, allows for the detection of drifts caused by imperceptible variations in the items which intervene in manufacturing (i.e. personnel, starting materials, equipment, etc. This is why in the following point (9) is described how processes are permanently monitored by means of critical variables identified during development and verified during the technological transfer.

(9) Continual monitoring

This is a basic element in the present model of "designed quality assurance". As a result of validation it is known that processes can be monitored by their critical variables. Two elements of the PQS (Process Performance and Product Quality Monitoring System and Management Review of Process Performance and Product Quality) are essential to ensure that what was determined during the stage of development and, afterwards, assessed during the stage of technological transfer is maintained all along the way of commercial manufacturing. Any new piece of knowledge acquired during this last stage should be handled by knowledge management and any required change should be treated by the change management system (Fig. 9).

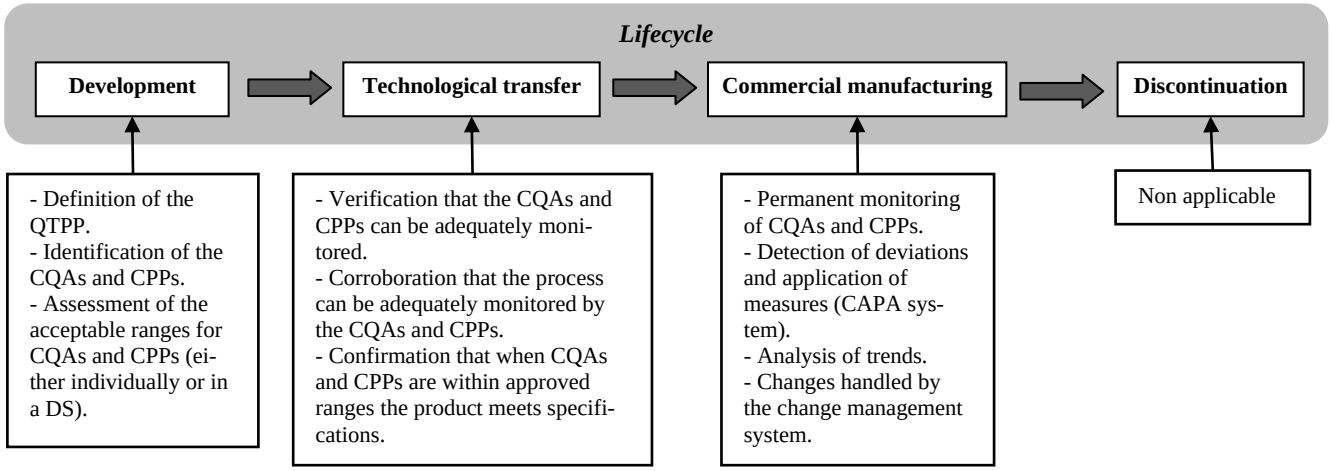

Fig. 9. Continual monitoring

(10) Continual improvement

By continual improvement it is understood the progressive upgrading of the scores of critical variables and indicators.

Critical variables (CQAs and CPPs) should always be within established (after investigation) ranges. Anyway if they show excessive variability or they start to show a given trend (which might lead to an out-of-specification).

Indicators established for the processes identified in the organization, see point (1), are used to assess their performance and to promote improvement. Unlike critical variables indicators are not directly linked to the quality of products or processes but only to performance. Thus, for example, the number of effective units per batch, the number of cases of out-of-specification per year, the number of returned units, the number of batches of starting materials that were not approved, etc.

These results are considered in the management reviews and they are used to draw improvement programs or to assign new resources to a given department by the senior direction of the organization.

7. Conclusions from the research and prospects of further development of this area

Medicinal products are critical. If they have not the intended quality they can put health at stake. Consequently, it has been always considered essential to ensure their quality. Different approaches have been used to attain this goal. Initially it was considered that analysis was enough to detect unsafe pharmaceuticals. When it was evident that this procedure was not adequate it was completed by a more complex system composed of GMP, additional controls and by the validation of the manufacturing processes (supposing that the exact repetition of the processes validated should ensure quality).

Unfortunately at the end of the 20th century it became evident that in order to ensure quality it was necessary a much wider approach. Quality can only be manufactured if previously it has been designed (i.e. "quality

by design"). Nowadays ensuring quality is seen as requiring a global approach. It is the result of the application of a complete patchwork of elements, all coordinated within a quality system. GMP continues to be at the center of the stage, but it has to be applied using a scientific approach. Risk management is a valuable tool in order to know better products and processes and to keep them under a known level of control. Knowledge on products and processes is acquired during the development and maintained by knowledge management. Critical variables and process indicators allow for the validation, the continual monitoring and the continual improvement.

This new approach to quality requires the global application of all the elements of the patchwork. It is important to bear in mind, however, that this model of "designed quality" contains the adequate mechanisms for detection of deviations and for the necessary updating in a controlled way. It is also global because it is applied to the four stages of the lifecycle of a product and to the complete supply chain in order to attain the objective of providing patients with sure and effective pharmaceutical products.

Quality is the result of controlling successfully all the elements comprised within the PQS and the system is prepared to detect any lack of control, but be that as it may the failure of any element puts quality at risk. Quality is global or there is not quality [16].

This global approach to quality can be compared with the music played by an orchestra. You need good musicians, instruments and musical notes, but if you do not have a good conductor the risk of playing out-of-tune is high. In pharmaceutical manufacturing the role of the conductor is played by the senior management. Thus, again: there is quality management (both in terms of Quality Assurance and of Senior Direction) or there is no quality.

As continual improvement is a key component of a modern quality system it is not difficult to imagine that in the next future some of the components of the patchwork will be enhanced, particularly if we take into account that its world-wide implementation will provide increased experience.

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