UDC 658.562

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DAME STRATEGY. A NEW APPROACH TO ENSURE THE QUALITY OF PHARMACEUTICALS

The joint application of ICH guidelines Q8, Q9 and Q10 allows for the development of the DAME strategy in order to ensure the quality of the pharmaceuticals, both new and legacy. This article describes in detail how to develop and implement it.

Ключові слова: Quality by design (QbD), quality target product profile" (QTPP), critical quality attributes (CQAs), critical process parameters (CPPs), real time release testing (RTRT), process analytical technology (PAT).

FORMULATION OF A QUESTION

In the 21st century we have to change our minds...

Although Good Manufacturing Practice (GMP) is not going to be neither significantly changed nor increased, the American initiative of "GMP for the 21st century", adopted by the ICH as the "Quality new paradigm" (Brussels, 2003), supposes a modification:

- Of its frame of application, as it proposes an integrated quality system covering the whole life-cycle of the products;
- Of its interpretation, as it indicates that decisions should be technically based and prioritized in relation to risk;
- Of its approach, as it defines that quality cannot be manufactured and controlled unless it has been previously designed;
- Of its mode of use, as it points out that, when considering products within their whole life-cycle, discontinuous actions (all/nothing) have no sense and have to be substituted by continuous ones (verification and continual improvement, knowledge management, CAPA system, etc.).

... And this supposes a great opportunity

Notwithstanding the fact that pharmaceutical industry has started the 21st century submitted to important economical pressure, derived from the reduction of the profits, and that, traditionally, any modification regarding GMP tends to result in an increase of costs, there are acceptable reasons to consider that the initiative of "GMP for the 21st century" offers a good opportunity, among other things,

- To update information and to take advantage of the knowledge gathered by personnel;
- To increase the efficiency of process control;
- To substitute traditional validation tasks by a practical system of process monitoring;
- To facilitate decisions by means of risk management;
- To improve performances during audits or inspections, by being able to justify objectively the points of view;
- To exchange a great deal of analysis by monitoring;
- To transform the organization of the unity into a better one.

Let us then analyze how we can do that!

REVIEW OF PUBLICATIONS

In the 21st century the quality of the products is ensured by the joint application of GMP, of the ICH guidelines (Q8, Q9 and Q10) of the program "Quality new paradigm", and of an integrated pharmaceutical quality system along the whole life-cycle of a product.

ICH guideline Q10 describes the main elements of a "Pharmaceutical Quality System – PhQS", applicable to the whole life-cycle, but adapted and proportionate to each of its stages. Even if by now it is not compulsory to have this system, it is evident that its implementation supposes an improvement. Although the description of the characteristics of this system is outside of the scope of this article, it is worthwhile to point out:

1st that it is applied both to raw materials (APIs) and to pharmaceuticals;

2nd that the scopes of application of the PhQS and of GMP do not coincide in their entirety, as PhQS covers also the stage of development, whereas GMP just covers the production of investigational pharmaceuticals to be used in clinical trials.

3rd that whereas GMP only specify in a very general way the responsibility of the senior management of the company regarding the quality of the pharmaceuticals, the PhQS establishes clearly these responsibilities. This is an important difference because it hinders the existence of differentiated spaces, "technical" and "managerial", lacking the adequate communication.

4th it has several differentiated elements,

– "Process performance & product quality monitoring system";
– CAPA (corrective and preventive actions) system;
– Change management system;
– Management reviews.

5th as well as two "enablers",

– Knowledge management;
– Quality risk management.

THE PURPOSE OF THE ARTICLE

The development and implementation of the "process performance & product quality monitoring system" requires a global approach, because it affects all the stages of the life-cycle and because it has to take into account all the actors which might affect the quality of the products. Quality, or to be more precise, the elements which make it possible and ensure it, are designed during the stage of development of a product, are monitored during the production and are evaluated globally. To do this, we propose to use the DAME strategy. Its name is an acronym derived from "Definition, Approval, Monitoring and Evaluation" and it is based on the life-cycle.

As it is evident that to develop and to apply a PhQS is a subject of enough importance to be considered in a separate way, here we will limit ourselves to provide some general orientations regarding this subject:

– Normally it is better not to be too ambitious and start in a simple way. If necessary, it will be always possible to make things more complex;
– It is possible to start by developing and implementing the PhQS in parallel with the existing system. Then drafts will be progressively improved and they will be applied only when their operability will be positively established;
– It is possible to develop step by step and independently its different aspects (e.g., CAPA, risk management, etc.);
– The errors of the past have to be avoided. It is necessary to be clear and concise. If a document is not understood by the persons supposed to use it, it is good for nothing. Often the use of charts and sketches contributes to facilitate comprehension;
– Structures have to be the simplest possible and responsibilities have to be clearly defined and outlined.

DAME strategy, intended to ensure the quality of the products during their entire life-cycle, is developed in parallel to the life-cycle of the product.

It does not, of course, aim to duplicate the work performed by the departments in charge of the different stages of the life-cycle of a product. Its objective is to ensure that the necessary information exists and that it is used in an appropriate way. Consequently, the DAME strategy can be applied to new products and to existing (legacy) products.

Creating a new medicinal product in the 21st century supposes not only to establish a pharmaceutical form, a formula, a manufacturing procedure and a few specifications, but also design a

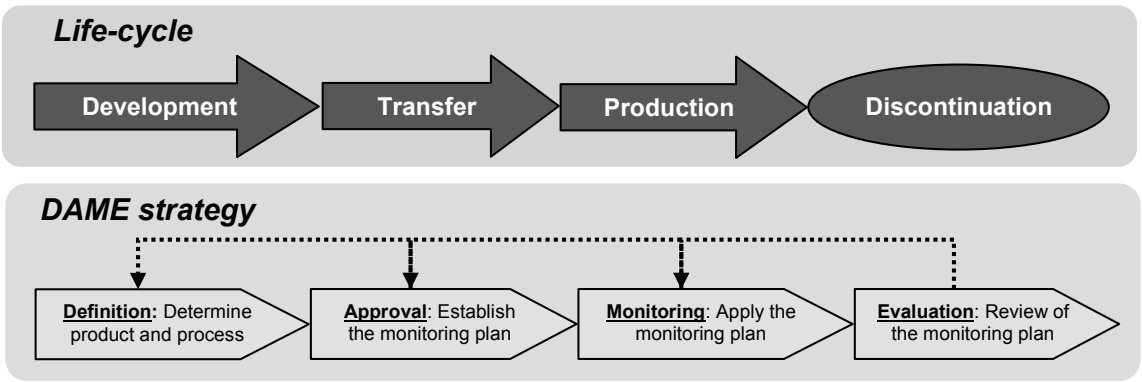

Figure 1. *DAME strategy*

quality product. "Quality by design" (QbD) is 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. (ICH Q8(R2)). In other words, a product should be developed in a way allowing acquiring enough knowledge to produce it with warranty of quality.

General presentation of the DAME strategy

1st step: Definition

Product profile

The starting point of development is the definition of the desired quality profile for the product or "Quality Target Product Profile" (QTPP), which can be defined as a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8(R2)), that is:

- Pharmaceutical dosage form;
- API and dose (or APIs and doses);
- Specifications which provide security and efficacy;
- Aspect and proprieties;
- Characteristics.

The result of development is the establishment of a formula and a manufacturing procedure, but also the definition of specifications for the components (starting and packaging materials) and the products (intermediate and finished).

The characteristics of the finished product have to be related to the proprieties assumed for the raw materials and the characteristics of the manufacturing process. This relation between manufacturing process and product properties should exist as well for the production of the starting materials (for instance, crystallization « particle size) and for the medicinal product (for instance, drying temperature « degradation of active principle).

When determining the relation existing among starting materials, manufacturing process and finished product, it is possible to know its behavior in relation to variations (in the characteristics of raw materials, in the physical and chemical conditions, in the relative proportions of the ingredients, etc.).

2nd Step: Approval

Risk assessment

Both raw materials used for the production of the starting materials, these same starting materials and the pharmaceutical product possess "critical quality attributes" (CQAs). A critical quality attribute is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8(R2)). The CQAs determine if a product is acceptable or not. Consequently, processes are monitored by means of "critical process parameters" (CPP). A critical process parameter is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8(R2)).

The whole of CQAs and CPPs constitutes the critical variables. They are, evidently, identified and their criticality is assessed by means of risk analysis. As usual, the method to be used to perform this analysis is less important than the amount of information at disposal. What counts is that once the dangers have been identified and their associated risk assessed, the critical parameters have been distinguished from those non critical. The first one have to be submitted to monitoring, unless that a change in the process might transform them into non critical. The final result is the acceptance of a residual risk for the quality of the product which is reduced to an acceptable level, by means of reduction or by monitoring. From the three factors determining the level of risk of a danger (severity, probability and detection), in most of cases it is only possible to act on the last two, by improving technologically the process and the capacity of detecting deviations of the critical variables.

Often, for practical reasons, it is necessary to perform the analysis in three phases, in relation with the existing level of knowledge:

- A preliminary analysis, using, for instance, PHA (primary hazard analysis), in order to identify the CQAs and HACCP (hazard analysis and critical control points) to determine the CPPs.
- Afterwards, as more information has been gathered, it is possible to use other methods such as FMECA (Failure Mode, Effects & Criticality Analysis), in order to assess the level of risk of the process.
- Finally, the analysis performed will be revised in order to verify that the implemented monitoring procedures allow for the reduction of residual risk to acceptable levels.

Study of critical variables

When critical variables have been identified (product attributes or process parameters) it is necessary to know which are their acceptable ranges. Also, because it exists or may exist an interdependence among them it is possible to move a step forward and define a "design space" (DS), which is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within

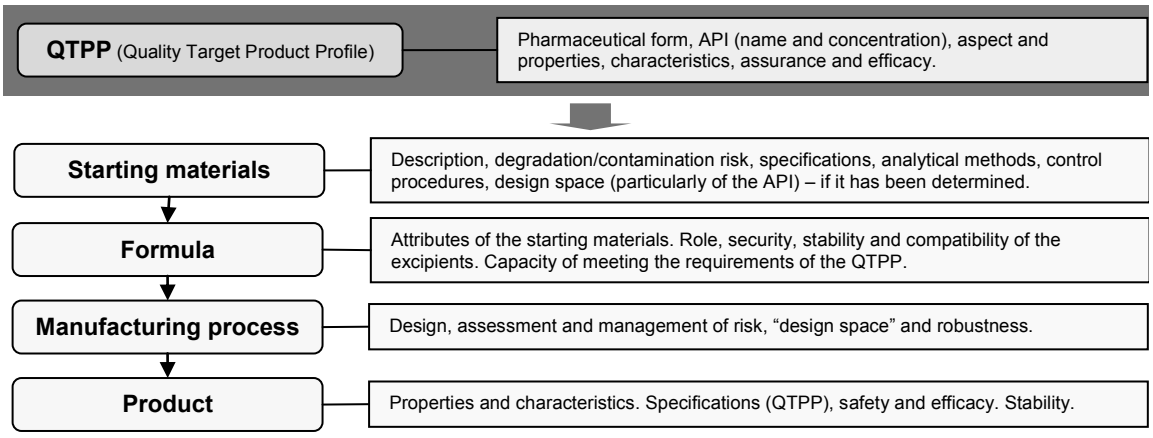

Figure 2. *Product profile*

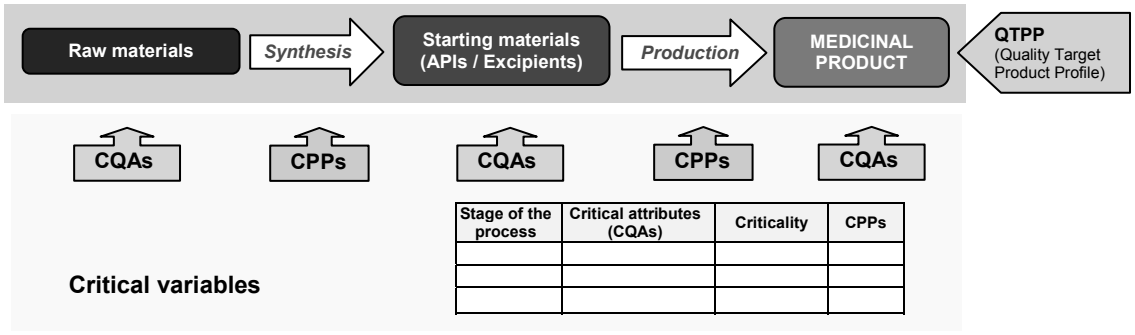

Figure 3. *CQAs – CPPs*

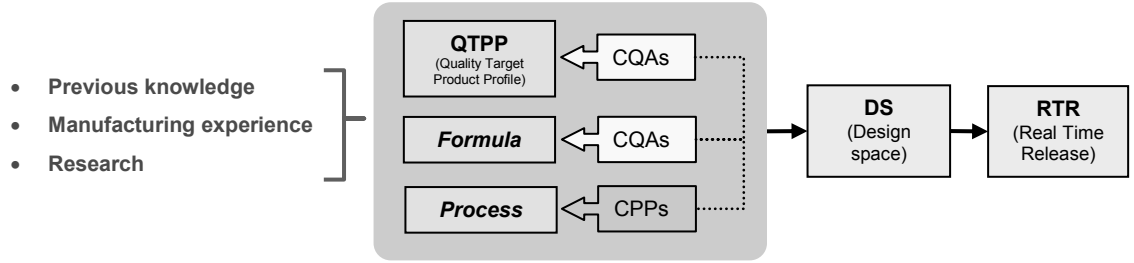

Figure 4. *Quality by Design (QbD)*

the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8(R2)). It is necessary to integrate all the information (input variables, process parameters and final product specifications) in a space where all CQAs will meet requirements and within which the product quality will be ensured. The application of statistical methods (design of experiments - DoE) allows for the reduction of the number of assays which are needed to establish the multifactorial influences of the variables among them. It is necessary to underline that the design space is the result of multivariable assays, which may include both critical and uncritical variables and has to be verified and be operational along the whole scale. The determination of acceptance ranges for the variables alone cannot be considered a design space. Although design space can be represented graphically, the ideal objective is to establish a predictive mathematical model.

Authorities do not require the registration of a design space, neither for new products, nor for the legacy ones. It is only a choice, which is made by the person preparing an application for the registration of a medicinal product. He has to determine and justify the CQAs and CPPs used in the multivariable assays, and also define the extension of the design space in relation to scale, site of production, etc.

Although it is evident that the better a product is known, the easier it is to ensure its quality, it is not less evident that the studies in order to establish a design space suppose an important amount of work and, consequently, they are expensive. Then it is quite logical that questions arise in relation to its utility. Companies which have defined it and integrated it in their registration appliances point out the following advantages:

- Process is more robust;
- The deeper knowledge of the product is translated in a better control and, above all, in a diminution of deviations and rejects;
- A higher flexibility in manufacturing, as it allows for the management of many modifications without being necessary to ask for variations in the registration dossier. It was already mentioned that modifications within the design space are not considered as changes of specifications requiring to be authorized and may be handled by the change management system;
- Increases the confidence in the quality of the product of the regulatory authorities and of other companies;
- The cost of the definition and registering of a design space is compensated by the advantages in terms of reduction of time and resources that it supposes.

It has to be mentioned that although a design space can be applied for new and legacy products and for any type of medicinal product, the choice usually is made for new solid oral forms. And this is, simply, because new products are already developed using this approach and because design space reaches its highest utility when products are manufactured with complex technology and possess CPPs, which can be monitored on line. Parenterals offer a quite different situation, with relatively simple manufacturing processes, but which possess the risk of microbiological contamination as their most critical aspect. It is also possible to develop design spaces for starting materials and very particularly for APIs.

It is then perfectly acceptable to follow a traditional approach and do not apply for a design space. In this case any modification has to be handled in the traditional way.

Control

The control strategy derives from risk management and from process understanding and it aims at ensuring a constant level of quality for the product, aligned with the defined quality profile (QTPP). The control strategy can be defined as a planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

Following the approach of substituting validation by continual process verification, the process is overseen step by step by means of its critical variables. If a CPP within its defined acceptation range ensures the adequacy of a CQA, this opens the doors to the possibility of using a monitoring/measure system of CPPs as a way for assessing the quality of the product, because CPP monitoring equals CQA control. Thus, for example, if studies have shown that there is a correlation between granule size and disaggregation or between humidity and granulate hardness, then it is perfectly acceptable that we monitor one in the place of the other. This approach is acceptable as far as during the development of the product it has been demonstrated that there is a correlation and afterwards periodical essays are carried out to show that this correlation continues to exist.

Thus, control of products can move from the traditional off-line analysis to the real time monitoring by using process analytical technology (PAT). This last approach eliminates the typical problems derived from sampling.

Liberation

The strategy of liberation should follow in parallel the strategy of control. It is possible to choose a traditional approach after analysis of the finished product or, when there is monitoring/measuring in real time (or almost) to liberate it also in real time. The "real time release testing" (RTRT) 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. (ICH Q8(R2)). The "parametric liberation" described in annex 17 to European GMP is a type of RTRT.

The application of automatic systems, like PAT, allows for the liberation of products in real time with all the guarantees, even with more guarantees, than by using the traditional methods, because:

- Parameters which are subjected to monitoring are related to analytical results;
- All critical aspects are controlled;
- All batches are "validated";
- Measures are performed automatically and in real time (when the operation is performed).

Thus, exactly like the final analysis, the control strategy is one of the elements of the liberation of the batch.

It is necessary to keep in mind that, like the design space, the RTRT is just an option, not a requirement. In case of choosing RTRT it will be necessary to define the procedure to be followed in case of failure of the monitoring equipment (for instance, traditional liberation after analysis, use of reserve equipment, etc.; the chosen option should be justified in a scientific way and to be based on risk assessment).

Validation

The objective of validation is providing confidence in the product and in the process and it should confirm the predictive model, by ensuring that the manufacturing process is capable of yielding steadily a product corresponding to the QTPP. According to the current vision this can hardly be obtained by means of a unique and time-limited process. Consequently the traditional validation can be substituted by a "continuous process verification" defined as an alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8(R2)), which is a kind of "concurrent validation", that is a validation carried out during routine production of products intended for sale (Annex 15 to European GMP).

Thus, in order to meet validation requirements it suffices applying the monitoring strategy defined above. The traditional validation protocols are replaced by other one showing that the followed approach ensures that the manufacturing process is capable of yielding a product which corresponds to the QTPP. This strategy is based on:

- Knowledge acquired during the development,
- Data derived from process monitoring,
- Risk assessment,
- Statistical studies of "process capability" which is defined as the ability of a process to realize a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms (ICH Q10).

It is necessary to point out that the qualification of equipment, as it has been performed until now, is not modified. Notwithstanding it has to be linked to risk assessment and, consequently, limited to the critical aspects.

The analytical methods which are used have to be validated as usually.

3rd step: Monitoring

As soon as the manufacturing procedure, the CQAs and the CPPs have been defined, the routine production can be overseen in a very sure way. It has already been mentioned that the utilization of automatic methods and in real time (PAT) is, evidently, the best alternative. However, in most of cases, this would only be the last stage, of "maturity", after having acquired the necessary experience. Often it will be better starting in a humble way, by identifying the critical variables and defining methods to oversee them, both "on line" and "off line".

The situation of the quality unit (QA / QC) in the application of the DAME strategy does not change, even if it allows for a simplification as a consequence of a sharper separation between "analytical" and "monitoring/supervision" tasks.

Monitoring has to be extended to the gathering of analytical data of commercial batches in order to confirm and, if necessary, correct the predictive model (corresponds the commercialized product along all its life to the product clinically tried in all its critical aspects? Is it stable?).

4th step: Evaluation

Even in "mature" processes, e. g., well known and under control, there is the risk of deviations imperceptible for those who participate in the daily production. It is then necessary a follow-up of the information coming:

- From deviations (CAPA system);
- From variations;
- From the manufacturing experience;
- From complaints;
- From trend analysis of monitoring and testing data;
- From the product quality reviews;
- From the liberation of batches.

Continual improvement will be a consequence of this evaluation, with the objective of reducing variability.

DAME strategy is based on the life-cycle and thus it is also submitted to continual improvement by a double process of increase of information ("feed forward") and of "feedback", so that process parameters may be adjusted during the life-cycle.

Particular case of application of the DAME strategy to an existing product

In this case the application of the DAME strategy would be performed in a progressive way, in relation to the existing amount of information and aiming at a gradual improvement of the system and of its practical implementation.

1st step: Definition

It is evident that the product has already been "defined". Consequently, it will only be necessary to revise the information at disposal. If necessary additional essays may might be always performed. If a baseline definition such as QTPP does not exist, it would be prepared in a retrospective way.

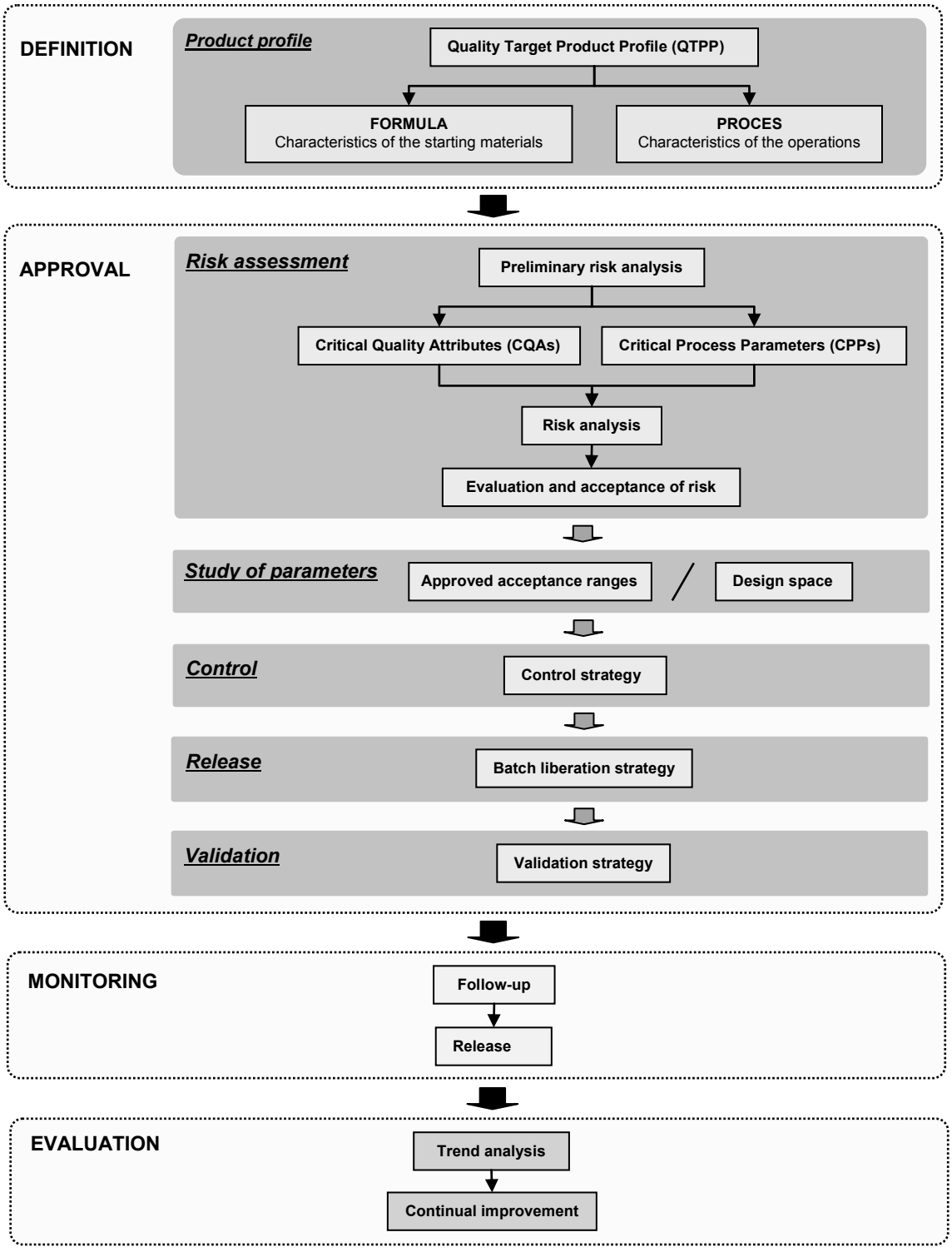

Figure 5. *DAME strategy step by step*

2nd step: Approval

Risk assessment

The critical variables are determined by risk analysis. Even if in this case it is very likely that it exists already the necessary information to perform risk analysis directly in one stage, using, for instance, FMECA, it will often be convenient to follow the three-step method described previously.

Study of parameters

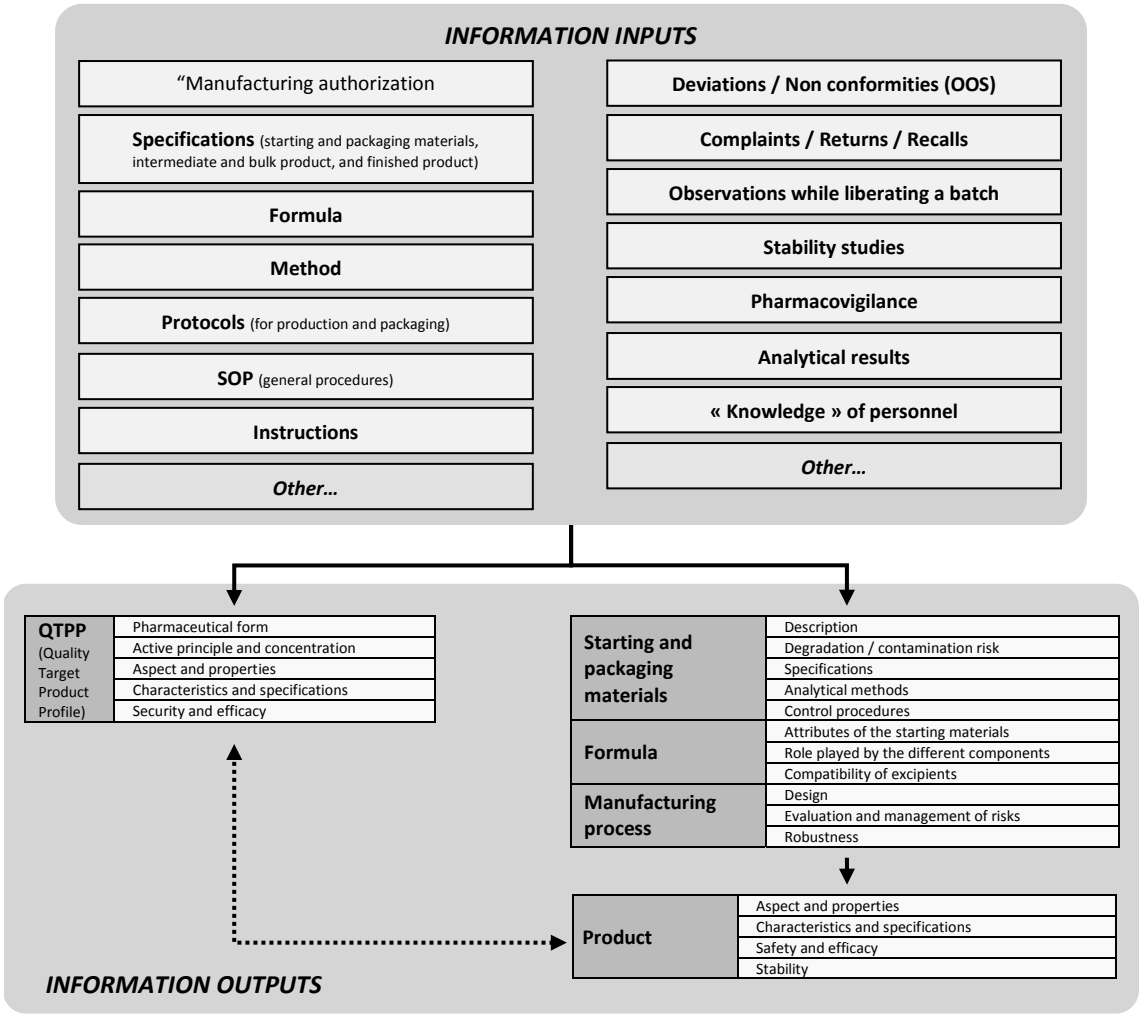

Figure 6. *Definition of the product profile*

Even if the possibility of performing multivariable studies in order to establish a design space remains always open, in most of cases it will suffice with the determination of critical parameters and with the establishment of their acceptation ranges, defined by their alert and action limits.

Control

The monitoring systems for the critical variables will be established. This will also require that there is a written procedure of action to be implemented in case of excursion outside the defined limits.

Liberation

The procedure to be followed for the liberation of the product will be determined.

Validation

Both if the process is validated or not, it is possible either to use the traditional approach, with the required revalidations or take advantage of the fact that by knowing the CQAs and CPPs it is very easy turn to the continual verification of the process. In this case, it is necessary to indicate in the protocol that this is the procedure which is followed and to justify it.

3rd step: Monitoring

It is necessary to explain in writing the approach which has been chosen for the routine overseeing of the critical parameters, according to a defined plan. Periodically commercialized batches will be analyzed in order to verify that everything goes as intended.

4th step: Evaluation

As indicated previously, a system of periodical evaluation of the existing data will be implemented.

RESULTS OF RESEARCH AND DISCUSSION

The coordinated implementation of ICH guidelines Q8, Q9 and Q10 represents an important change, because without modifying the bulk of GMP there is a significant modification in the way they are used, and this allows for a better quality assurance of products. Consequently, it can be applied both to new and legacy products.

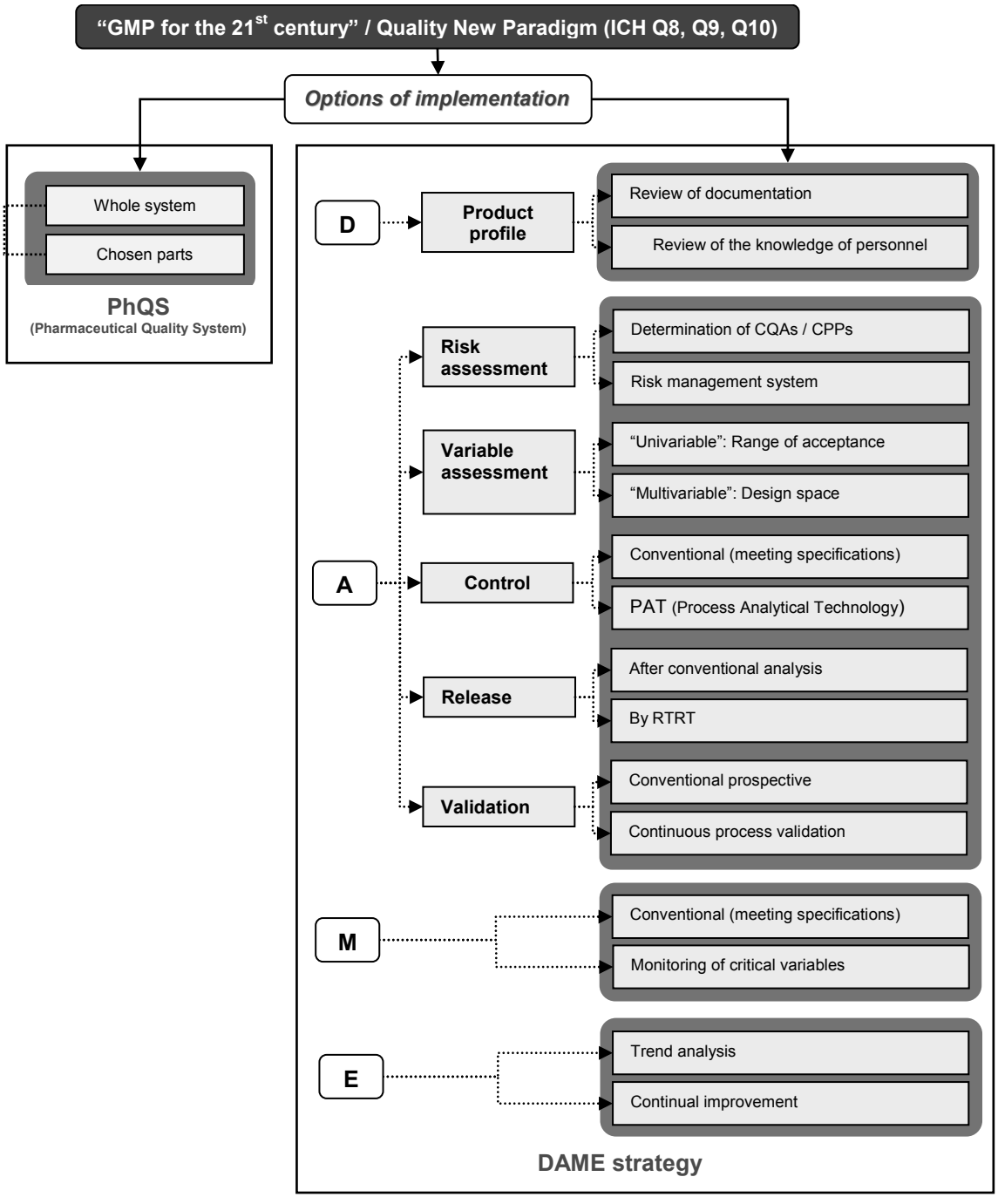

Figure 7. *DAME strategy: Option for its implementation*

The application of current century concepts to last century products offers a great opportunity for improvement, because it supposes an updating of the products with the advantage that the efforts applied to this can be compensated not only by the updating of knowledge, but also, and very particularly by the reduction of costs in validation matters and in quality control.

Within the frame of "GMP for the 21st century" the DAME strategy allows for the application of the new approach for the quality assurance of the medicinal products in a structured and progressive way. In each case it is possible to reach the most convenient extension, as it is summarized in the annexed figure.

DAME strategy in the domain of quality assurance follows a course parallel to the activities of the life-cycle. In legacy products, however, which were authorized and commercialized a certain time ago and, which, consequently have not been devel-

oped according to the life-cycle concept, the DAME strategy allows for the breaking of the vicious circle, by acting as a substitutive and proposing an starting point meeting the requirements of the 21st century.

Even if nothing impedes to apply the DAME strategy in its entirety to legacy products, it is necessary to bear in mind that there are aspects requiring a modification of the manufacturing authorization before its implementation (e. g., RTRT or design space). Consequently in many cases it will be convenient to start by applying it in parallel to the current procedure and substitute it only when it will be well proven and when there is an authorization from the regulatory authorities.

CONCLUSIONS

In the application of the four stages of DAME strategy it will be necessary to take into account the following facts:

1st The review of the existing knowledge about legacy products is not a loss of time, but a way of making the most of them.

2nd The diffusion of information among the different departments and posts in an efficient way is very important and it has to be done in both directions, forwards (from generator to receiver) and backwards (from receiver to generator). Only this way are met simultaneously both requirements of generation and revision of knowledge. The gaps or shade areas between the areas where are performed the different stages of the life-cycle suppose a loss of energy, e. g., of money. This is why it is essential to keep and increase the knowledge on the products along their life-cycle.

3rd The application of new concepts, such as continual improvement, PAT, design space or RTRT, can start in a modest way and progress according to the possibilities. It has to be born in mind that control on the processes can be attained by using the existing technology and that a design space is not a necessary requirement.

4th The introduction of concepts such as continual monitoring or improvement are essential for ensuring the quality of the products and the process performances.

5th It is very important to choose in an appropriate way the first product to which the DAME strategy will be applied (the more "problematic", the biggest seller, the most "strategic", etc.), as it will open the way for the other.

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УДК658.562

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НОВЫЙ ПОДХОД ПРИ ГАРАНТИРОВАНИИ КАЧЕСТВА ФАРМАЦЕВТИЧЕСКОЙ ПРОДУКЦИИ

Документы Международной конференции по гармонизации ICH директива Q8, Q9 и Q10, позволяют развить стратегию DAME для того, чтобы гарантировать качество фармацевтической продукции. В статье подробно описывается, как осуществлять ДМАЕ стратегию.

Ключевые слова: качество проекта (QBD), качественный профиль (QTPP) целевого продукта, критические качественные свойства (CQAs), критические параметры (CPPs) процесса, испытание (RTRT) в реальном времени, своевременная обработка аналитической технологии.

УДК658.562

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НОВИЙ ПІДХІД ПРИ ГАРАНТУВАННІ ЯКОСТІ ФАРМАЦЕВТИЧНІЙ ПРОДУКЦІЇ

Документи Міжнародної конференції з гармонізації ICH директива Q8, Q9 і Q10, дозволяє розвинути стратегію DAME для того, щоб гарантувати якість фармацевтичної продукції. У статті детально описується, як здійснювати ДАМЕ стратегію.

Ключові слова: якість проекту (QBD), якісний профіль (QTPP) цільового продукту, критичні якісні властивості (CQAs), критичні параметри (CPPs) процесу, випробування (RTRT) в реальному часі, своєчасна обробка аналітичної технології.

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Надійшла до редакції:
23.01.2012