A suggested developed model for quality losses estimation

The quality of products in general is of great importance in the current time, and its impact on various aspects of life, such as economy, health and welfare of society as a whole is crucial and visible. It is vital to have a deep understanding of the product realization process, including understanding the dynamics under which the product quality changes under the manufacturing conditions and the customer's (sensitivity) ability to recognize changes in product quality. This article aims to develop and modify the Taguchi model to suit the case of pharmaceutical products. The model of pharmaceutical quality loss suggested in this paper can be considered as a combination of the traditional concept of quality model and the Taguchi model, modified to suit the case of the pharmaceutical quality. The suggested quality model can be used to assess quantitatively the quality loss value that is associated with each deviation from the established tolerance zone; and accordingly to enhance the understanding of the pharmaceutical manufacturing process to avoid and prevent the occurrence of such loses of the pharmaceutical quality in the future.

Keywords: quality loss model, pharmaceutical industry, quality management, quality improvement, model of pharmaceutical quality loss.

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Introduction

The quality of products in general is of great importance in the current time, and its impact on various aspects of life, such as economy, health and welfare of society as a whole is crucial and visible. Measuring and reporting the Cost of Poor Quality is a technique that has been used for over forty years in as a tool for advanced continuous quality improvement. The introduction of the new international standard ISO 9001:2015, and emphasis on measurement, and focusing on processes, and its requirement to demonstrate quality improvement, gives new impetus for tracking poor quality costs.

For decades, the quality engineers and pioneers had tried to find a complex definition for the concept of Quality. Each definition of them reflects a different view to quality, regarding one or more of the quality demands. It's possible to consider the definition of the international organization for standardization ISO as a globally accepted definition of quality concept as «Quality — degree to which a set of inherent characteristics fulfills requirement» [7]. The adjective of quality applies to objects and refers to the degree to which a set of inherent characteristics fulfills a set of requirements. An object is any entity that is either conceivable or perceivable and an inherent characteristic is a feature that exists in an object. The quality of an object can be determined by comparing a set of inherent characteristics against a set of requirements. If those characteristics meet all requirements, high or excellent quality is achieved but if those characteristics do not meet all requirements, a low or poor level of quality is achieved. So the quality of an object depends on a set of characteristics and a set of requirements and how well the former complies with the latter1. When considering the quality in the pharmaceutical context it's important to take into account the other dimensions especially the safety and efficacy of the pharmaceutical product to the human organism. Accordingly, the good pharmaceutical product hasn't only an accepted quality level, but also its shouldn't harm the human organism and effective sufficiently to give the needed therapeutic effects to treat the disease [2-4]. ICH Q9 standard defines the quality as the degree to which a set of inherent properties of a product, system, or process fulfills requirements [5].

1. Taguchi loss model

The Japanese scientist G. Taguchi in 1960 expressed the idea that quality can no longer be viewed simply as a measure of compliance with the requirements of design/design documentation. Observance of quality in terms of tolerance limits is not enough. It is necessary to constantly strive to reduce the spread of values even within the established boundaries [9]. The generally recognized definition of quality «finding the parameters of products within the established limits» (see fig. 1) allows to consider that two products differ a little from each other if the parameters of one are inside the tolerance boundary, and the parameters of the other one are slightly outside these limits, the first of them is considered «good», and the

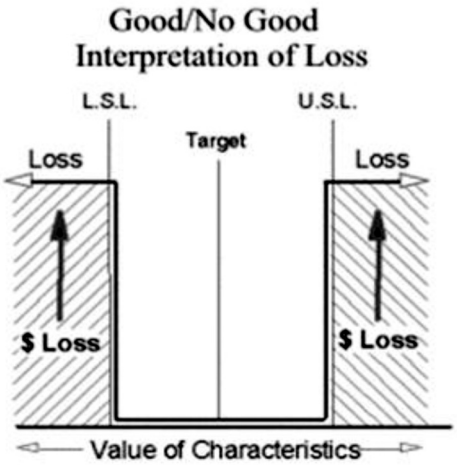

Fig. 1. Traditional approach to product quality

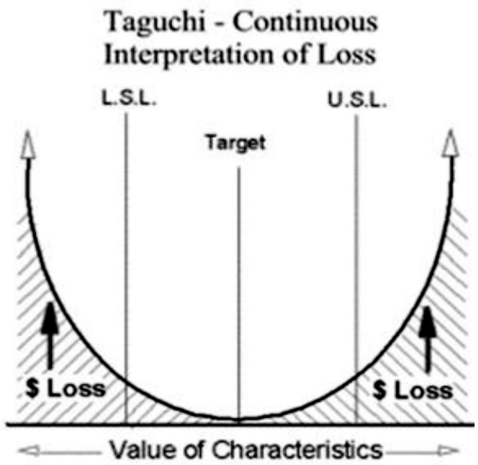

Fig. 2. Taguchi loss function

second — «bad» [1, 12]. Unlike the traditional approach, Taguchi suggests assessing the quality of the amount of damage to society, from the moment of delivery of products (see fig. 2) the less this damage, the higher the quality. However, Taguchi considers the damage to society in a broader context. He associates possible losses with any product falling into the hands of the consumer [13, 14]. In addition, he considers consumer dissatisfaction as a component of these losses, additional manufacturer's costs for warranty obligations, deterioration of the company's reputation, which entails the loss of a part of its previously owned market [6, 11, 15].

2. A suggested quality model for pharmaceutical products

When considering the quality in the pharmaceutical context it's important to take into account the other dimensions especially the safety and efficacy of the pharmaceutical product to the human organism. Accordingly, the good pharmaceutical product hasn't only an accepted quality level, but also its shouldn't harm the human organism and effective sufficiently to give the needed therapeutic effects to treat the disease [2, 3, 8].

The critical to quality attributes of the pharmaceutical products are measured and evaluated according to proofed and validated analytical and measurement methods often explained in detail in the pharmacopeias such as the international pharmacopeia (issued by WHO), USB (United States Pharmacopeia), British Pharmacopoeia, and so on [10]. A pharmacopoeia, in its modern technical sense, is a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society [16]. It constitutes a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances and dosage forms The pharmacopeias establish criteria for quality assessments of the active pharmaceutical ingredient(s) and the excipients and the finished product [4, 17].

The accepted quality tolerance zones are established depending on the bioavailability studies that were conducted in the clinical studies stage and according to this data an acceptance criterion for each quality attribute is defined taking into account the safety, efficacy issues of the pharmaceutical product [9]. Normally, the permitted tolerance for the active pharmaceutical ingredient (API) concentration shouldn't exceed ± 10% of the labeled content of drug substance (i. e., a total variability of 20%: a requirement of 50 mg ± 10% thus means an acceptable range from 45 mg to 55 mg), unless a wider range is proved by a clinical study [8]. The therapeutic effect of the administered dose is thought to be accepted when the quality attributes of pharmaceutical product falls inside the acceptance criteria (between the specification limits). Thus, the quality level of the pharmaceutical product when the quality attribute falls behind the upper specification limit is equal to quality level of the product when the quality attribute falls near the lower specification limit, in other words the quality level of the pharmaceutical product doesn't change (stable) as long as the quality attribute falls inside the specification limits and the therapeutic effect of the dosage form still accepted.

The suggested quality model (see fig. 3) can be considered as a combination of traditional concept of quality model and the Taguchi model to suit the case of the pharmaceutical quality. It is based on the fact that the therapeutic effect of the drug is considered efficient and safe when the critical to quality attributes of the pharmaceutical product meets the pre-established quality tolerance zone. So, in contract to Taguchi quality loss model, in the introduced model the quality level of a pharmaceutical product inside the specification limits is stable and the variation inside the accepted tolerance zone is not perceived by the final customer of the pharmaceutical product (the patent), and the sensitivity of the organism to the delivered drug dose along the accepted tolerance period is the same according to the clinical studies.

The difference in the quality level of the pharmaceutical product between the USL and LSL isn't perceived by the patent and has the drug product still has the same therapeutic effect on the organism hence the CTQ characteristic still meet the specification tolerance established according to the clinical studies. That is, within the specification limits established according to the clinical studies, the quality of the pharmaceutical product is the same as for the lower, the midpoint, and for the upper specification limit.

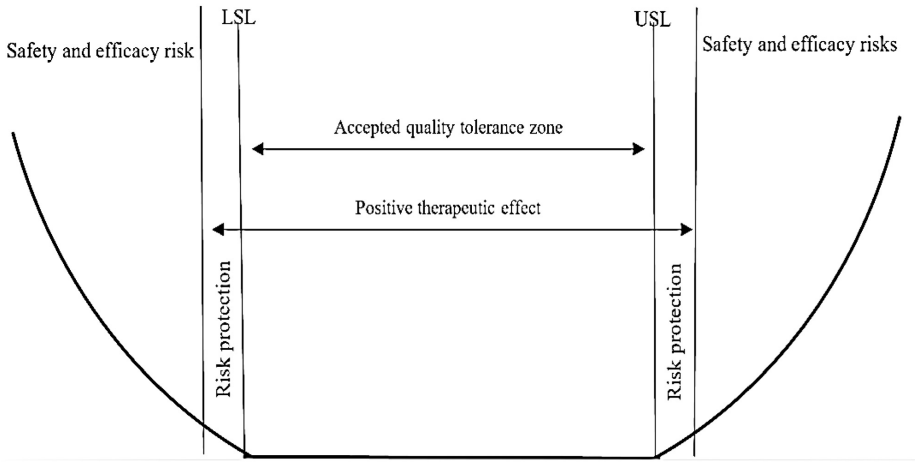

Fig. 3. A suggested model of pharmaceutical quality losses

We highlight three zones:

when x < LSL: QL = $F(x–\text{LSL})^2$,
when x > USL: QL = $F(x–\text{USL})^2$,
when LSL ≤ x ≤ USL: QL=0,
F = (Cost of improper dose)/(Tolerance allowed)2,

where LSL — lower specification limit; USL — upper specification limit; X — the measured critical to quality attribute; F — the cost of improper pharmaceutical dose; QL — the loses associated with improper pharmaceutical product quality.

According to the quality model shown in fig. 3, when the quality attribute (x) exceeds the upper or lower specification limits, the loses associated with improper pharmaceutical product safety and efficacy issues QL value increase dramatically. The associated loses depend mainly on the studied quality attribute, and on the clear determination of the costs of improper quality delivered by the administrated medicine. Such costs may be: harming the company image and compensation of those affected by the bad product, product recalls from the market, harming the reputation of the company, losing the product marketing authorization, etc.

Among the critical to quality characteristics, the content of API in the dosage form is very critical attribute to the safety, efficacy, and the desired therapeutic effect of the drug. When the quality attribute (API concentration) falls next to the upper specification limit, there is a decreasing risk of facing undesired effects (severe side effects) and in several cases may cause a severe damage to the health of the patient and may lead to the death. On the other hand, when API concentration is less than the lower specification limit, the desired therapeutic effect of the drug is not guaranteed and there is a decreasing risk of undesired effects to the health and may lead to danger consequences because of insufficient dose, and may lead to death.

The suggested quality model can be used to assess the quality loss value associated with each deviation from the established tolerance zone. Depending on the studied quality attribute of the pharmaceutical product, the risk of non-conformance to the established quality criteria occurs. The value of the loss associated with the inappropriate quality of the drug varies depending on the size of the violation of the applicable quality standard and the consequences for the manufacturer. An example of this can be the damage to the patient and the legal and financial liability of the drug manufacturer; recovery of defected batches from the market; damage the reputation of the company and its image and loss of market share and so on. The obtained results can be used to enhance the pharmaceutical manufacturing process capability to avoid and prevent the occurrence of such loses of the pharmaceutical quality in the future.

Conclusions

The model of pharmaceutical quality loss suggested in this paper can be considered as a combination of the traditional concept of quality model and the Taguchi model, modified to suit the case of the pharmaceutical quality. It is based on the fact that the therapeutic effect of the drug is considered efficient and safe when the critical to quality attributes of the pharmaceutical product meets the pre-established quality tolerance zone. The model takes into account the concept of pharmaceutical quality and the strict legal and organizational environment of the pharma industry and its need to keep a full and continues compliance to the good manufacturing practices GMP and other governmental legislations. The suggested quality model can be used to assess quantitatively the quality loss value that is associated with each deviation from the established tolerance zone; and accordingly to enhance the understanding of the pharmaceutical manufacturing process to avoid and prevent the occurrence of such loses of the pharmaceutical quality in the future.

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Предлагаемая разработанная модель для оценки потери качества

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Качество продукции в целом имеет большое значение в настоящее время, и его влияние на различные аспекты жизни, такие как экономика, здоровье и благосостояние общества, имеет решающее значение.

Крайне важно иметь глубокое понимание процесса реализации продукта, в том числе понимать динамику изменения качества продукта в условиях производства и способность клиента (чувствительность) распознавать изменения в качестве продукта. Эта статья направлена на разработку и модификацию модели Тагучи в соответствии с фармацевтическими продуктами. Модель фармацевтической потери качества, предложенная в этой статье, может рассматриваться как комбинация традиционной концепции модели качества и модели Тагучи, модифицированной в соответствии с требованиями отрасли. Предлагаемая модель качества может использоваться для количественной оценки величины потерь качества, которая связана с каждым отклонением от установленной зоны допуска; и, соответственно, улучшить понимание процесса фармацевтического производства, чтобы избежать и предотвратить появление таких потерь качества фармацевтических препаратов в будущем.

Ключевые слова: модель качества потерь, фармацевтическая промышленность, управление качеством, улучшение качества, модель потери качества фармацевтической продукции.