Implementation of Patient Reported Outcome Measures (PROMs) in QbD based formulation development in ophthalmology

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Abstract: *Development of drug delivery systems for chronic disorders needs a complex thinking in order to ensure the quality of the product. A multidisciplinary approach of pharmaceutical technology, regulatory and behavioral sciences on the basis of the Quality by Design methodology can be a proper tool for this to handle formulators', patients', and also doctors' needs in therapy planning in case of chronic ophthalmologic disorders. According to the present state-of-the-art", patient perceptions are collected in the form of the "Patient Reported Outcome Measurements" during the clinical trials, but no feedback is given to the formulation development in order to take these aspects into consideration when designing a new product. This work aims to link the key performance indicators from patients' point of view to the pharmaceutical development and show a new approach to product development by evaluating the patient and formulator aspect as critical quality attributes within the classical Quality by Design workflow. This study can be the basis of the formulation design and development of a new ophthalmic formulation as it revealed the patient critical needs and requirement.*

Keywords: Patient Reported Outcome, Ophthalmology Disorder, Early development and formulation, QbD

Introduction

Patient Reported Outcome Measurements

According to competent authorities (European Medicines Agency (EMA) and Food and Drug Administration (FDA) the term Patient Reported Outcome (PRO) is an umbrella nomenclature, which covers single and multi - dimension measures as well in connection with the general health status of the patients, satisfaction with the treatment, adherence to the treatment, symptoms and Health Related Quality of Life (HRQoL) [1,2]. In addition, PROs evaluate all the subjective perceptions of the patients, obtained directly from them [3]. These feedbacks offer information to the health care team to find the possible intervention for health status improvement, to develop the individualized therapy and also could be useful for the researchers or academics during the early development process [4,5]. Patient Reported Outcome Measurements (PROMs) are performed mostly via self-reported questionnaires. Generic and disease specific questionnaires are used for detecting PROs [6]. Importance of PROMs are documented, in the field of clinical trials are used in several years [7]. The competent authorities require to use PROs for the authorization of a new pharmaceutical drug or a new indication. HRQoL of life presents a specific subset of PROs. The definition of HRQoL based on the World Health Organization's (WHO) health definiton is: *„a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity"* [8].

Almost all chronic disorders mean life long treatment for the affected patients. To adapt for a long term therapy and the life style changes is quite a big challenge, and patient adherence to treatment and the persistence in long term, are essential for a successful therapy. Based on this fact, it is important to take into account the patients perceptions from the very beginning at the early development phase, to fulfill the Patient Centered Care and the ensure the HRQoL. According to the World Health Organization's (WHO) Quality of life Questionnaire (WHOQoL) the influencing factors are divided into 4 domains: (1) Physical health (e.g.: mobility, pain and discomfort, work capacity), (2) Psychological (e.g.: negative, positive feelings, religion, personal beliefs), (3) Social relationships (e.g.: social support, sexual activity), (4) Environment (e.g.: financial resources, transport, freedom) [8]. These dimensions are covering all relevant factors of HRQoL and could be useful to separate the influencing factors from the patients' point of view.

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Formulation aspects of ocular drug delivery systems

Development of an ocular drug delivery system is a great challenge in the field of pharmaceutical research and development, as human eyes are indispensable for normal daily activities. Therapy of ocular diseases is a complex task due to the complex anatomical and physiological barriers, patient-compliance and the unique physicochemical attributes of several active ingredients (API) applied in ophthalmology. Eyes are made up of two anatomical segments, the anterior segment is from the cornea to the lens, while the posterior segment contains the lens, vitreous humour, retina, sclera, and the optic nerve. The human cornea consists of five layers: the lipophilic epithelium, Descemet's membrane, the hydrophilic stroma, Bowman's layer and the lipophilic endothelium. Lipophilic agents can permeate through the epithelium by passive diffusion, while the diffusion of hydrophilic drugs is restricted because of the tight junctions of the epithelium layer. Meanwhile the thickest layer of cornea, the stroma is hydrophilic, therefore the diffusion rate of lipophilic API is slower there, while hydrophilic compounds can pass it freely. For optimal transcorneal permeation, a balance is needed in the lipophilic-hydrophilic characteristics in case of the given drug delivery system. Physiological barriers, which are formed by the complex anatomical structure, defend the eye from external agents. Tear film includes a lipid layer, water and mucin, which protects conjunctiva and cornea. Cornea and conjunctiva also act as a barrier, which mainly restrict the penetration of API to the anterior tissues. Blood Aqueous Barrier is partly permeable for compounds with low molecular weight. Because of the tight junctions of retinal blood vessels and retinal pigment epithelium, the Blood Retinal Barrier blocks the drug penetration from systemic circulation, application of oral and intravenous dosage forms are limited, because large doses are needed for proper healing, which results not targeted presence of API and increase the possibility of unwanted side-effects. Moreover, the anatomical blockade, reflex mechanisms (blinking, increased lachrymal secretion) are induced after any external stimulus, therefore the precorneal elimination accelerates the drainage of applied formulation from the ocular surface [9,10].

Considering the mentioned restrictions in ocular drug delivery, ensuring optimal and successful therapy is an exceptionally hard challenge. In the case of chronic diseases of eye, the target of therapy is mainly the posterior segment. Nowadays, invasive routes like, intravitreal and subconjunctival injections are the most conventional methods, although non-invasive innovations are published to reach the posterior segment, besides the therapy of ailments at the anterior segment of eye. Topical administration is the most favourable self-applicable method, which does not need expert assistance. Mainly eye-drops, inserts semisolid formulations and contact lens are used As dosage forms [11].

After administration, the drug has to pass the hydrophilic tear film barrier. From the precorneal area the elimination of eye drop is through the nasolacrimal drainage to the systemic circulation. The possibilities for permeation pathway from the tear film are the corneal and non-corneal routes. In the case of corneal pathway, the drug meets the layer formed by lipophilic corneal epithelial cells. Penetration of hydrophilic molecules are limited there, meanwhile lipophilic active ingredients permeate easily by transcellular passive diffusion. Under the epithelial multilayer, the hydrophilic stroma restricts the permeation of lipophilic drugs. The lipophilic endothelial monolayer is permeable for macromolecules, compared with the epithelium. The conjunctival scleral (non-corneal) route is the other possible permeation pathway after passing the tear film barrier, where the permeation of active ingredient mostly depends on the molecular weight. To reach the posterior segment, the formulation needs to pass the complex anterior segment. The opposite directional secretion of aqueous humour also limits the permeation. Using novelties like cyclodextrins, liposomes, nanoparticles, nano lipid carrier systems, polymer micelles and mucoadhesive polymers can overcome these difficulties [12–16].

Considering the fact, that eyes are one of the most sensitive organs in human body, the applied formulation must meet the physiological requirements. Preparation must be done in aseptic environment, sterility of dosage form must be ensured during the therapy and parameters like pH, osmolality, surface tension and viscosity must be optimized to avoid side-effects [12,17,18].

Application of the Quality by Design methodology in product development

The Quality by Design (QbD) approach of the developments is generally used in the pharmaceuti-

cal industry and its application was forced by the regulatory authorities. The QbD method realizes a modern quality management thinking, as it is a risk and knowledge based systemic and holistic development model, described in ICH Q8 (R2), Q9 and Q10 documents [19,20,21]. It focuses on profound preliminary design, taking into consideration of all stakeholder's needs and requirements from the initial step. The stakeholders are: the patient, the pharma industry and the regulatory authority and they have different requirements for having finally a product with proper quality, safety and efficacy profile [22–25]. The steps of a QbD based product development include the following:

1. Definition of Target Product Profile (TPP) and its quality indicators (Quality Target Product Profile, QTPP). This usually comprises therapeutic requirements and other quality demands (e.g. dissolution profile, stability aspects, etc.).
2. Identification of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) which have critical influence on the desired final product. The selection of the CQAs and the CPPs should be based on previous scientific experience and knowledge from relevant literature sources.
3. Risk Assessment (RA) is a systematic process of organizing information to support a risk decision and is the key activity of the QbD based methodology. RA can be initial, repeated and final and RA results help to aim attention on the most critical influencing factors and avoid profitless efforts in later phases of the development process.
4. The next steps of the QbD approach are: the Design of the Experiments (DoE) based on the RA results, performing of the experiment and establishment of the Design Space (DS), the control strategy, and finally considering the possibility of the continuous improvements from the whole process point of view.

The challenges in case of the pharmaceutical formulation of an ophthalmic product, associated with special characteristics of the eye, and the crucial effects on the patients, suffering from chronic eye disorders gave the basic to determine these two different stakeholders' expectations and needs from their own point of view. There are a lot of standardized technological parameters which cannot be altered just because the patients are unsatisfied with the product or with the therapy but also couple of these parameters could be changed according to patients' perceptions and expectations. The research team hypothesized that determination of these factors could provide feedback to researchers for improving the formulation procedure. Implementing patients' aspects to the early development process granted the think of Patient Centered Care from the beginning and ensure the way to improve HRQoL and Patient adherence to treatment.

Based on these facts, the main aim of the research work was to improve the development by means of the QbD based methodology. This tool compares the patients' aspects and expectation to researchers' aspects, and also handles the pharmaceutical technology parameters in case of an ophthalmic product on a risk-based approach.

Materials and Methods

Evaluation of Patient Reported Outcomes

The PROMs were selected according to those chronic ophthalmic disorders, which can be treated by means of eye drops (glaucoma, chronic dry eye syndrome). Based on the evaluation these measures were selected based on the influencing factors which are crucial for the improvement of HRQoL in case of patients affected by chronic ophthalmic disorders, mentioned above [26–35]. These factors were classified according to HRQoL's dimension of WHO.

Definition of the QTPP and the Knowledge Space Development

QTPP forms the basis of the product development design. It is a prospective summary of the quality characteristics of the product that ideally will be achieved which include patient-relevant product performance and regulatory based professional requirements. The QTPP selection was based with careful planning and consideration the relevant needs and special requirements in chronic ophthalmic disorders. This collection and systemic evaluation of the influencing factors is called as "Knowledge Space Development" [21]. The defined QTPP contains the following elements: 1. eye discomfort (itching, redness, smarting, tearing, dryness, irritation, swelling) 2. anxiety 3. daily routine 4. health literacy 5. social support 6. work capacity.

Determination of CQAs

The identification of potential CQAs means the se-

lection of those characteristics which influence the final product's performance and quality. These critical quality parameters were defined from patient outcomes point of view.

The following CQAs were selected: 1. Life-long therapy 2. Topical administration route 3. Dosage form (eye drop) 4. Local effect 5. Dissolution profile (residence time) 6. Device to the administration 7. Microbiological stability 8. Physicochemical stability.

Determination of CPPs

CPPs come generally from the production method. In this special case the targeted observation process aimed the Medical Product Application.

In this patient focused theoretical research the selected CPPs are: 1. Storage (temperature), 2. Regimen (frequency of the administration), 3. Device applicability 4. Long-term stability, 5. Long-term sterility, 6. Application without decreased vision 7. Hygienic circumstances, 8. Mobile application (alarm system).

Risk Assessment

The RA was performed using Lean QbD Software (QbD Works LLC., Fremont. CA, USA, qbdworks.com). According to the design of the software, the connections between QTPP elements, the CQAs and CPPs were thoroughly evaluated. The interdependence between QTPPs and CQAs, as well as between CQAs and CPPs was structured and evaluated one by one, then rated on a three-level scale. This scale reflects the impact of the parameters' interaction on the product as high (H), medium (M) or low (L). The probability of the occurrence of the critical factors was also estimated using the same three-grade scale. As the output of the RA evaluation, Pareto diagrams were generated showing the ranked parameters according to their critical effect on the aimed product.

Ishikawa diagram

The Ishikawa, cause – effect, or fishbone diagram is a widely used quality improvement method. Ishikawa diagram illustrates possible causes of a problem and in sorts ideas into categories. According to the expected effect, all the factors can be summarized and grouped as inputs or causes. It is advised to form 4-6 major cause categories and based on these, the minor causes are classified [36].

For the visualization of the selected influencing factors in case of CQAs and CPPs, Ishikawa diagrams were set up as well.

For determining the influencing factors as CQAs in case of a chronic ophthalmic disorder (effect), four major causes were selected according to WHO's HRQoL classification: (1) Physical Health (2) Psychological (3) Environment (4) Sociological Relationship.

To achieve the optimal ophthalmic formulation (the effect for selecting CPPs), the next dimensions, causes were determined: (1) Stability (2) Formulation (3) Efficiency (4) Active Ingredient (5) Preparation (6) Patient Adherence.

Results and Discussion

This research work evaluated the key intervention possibilities in chronic ophthalmic disorders from the patients' point of view for finding the increasing point of the adherence in this life - long treatment needing situation.

First, the QTPPs were identified, as follow: patients who suffer in chronic eye disorder and need life-long therapy, the aimed administration route was topical, and the selected dosage form was the solution (eye drop). The expected effect was a local effect and an intermediate dissolution of the active ingredient is needed, as the residence time on the eye is limited to the physiological environment and state. The device was also the element of the QTPP, as it should protect the formula and helps in preservation of the microbial and physicochemical stability. The long-term protection of the microbial and physicochemical stability has financial advantages and helps in the every-day life of the patient if the medicinal product has no special requirement for storage, handling etc. So, the QTPP elements were: (1) Life-long therapy (2) Topical administration route (3) Dosage form (eye drop) (4) Local effect (5) Dissolution profile (6) Device to the administration (7) Microbiological stability and (8) Physicochemical stability (Table I).

It should be note that there are some essential requirements of the QTPP if the target dosage form is a solution, namely an eye drop. These essential quality requirements are strictly regulated by the physiological needs of the topical application and the researchers have to meet the pharmaceutical standards. These are: (1) pH (2) Viscosity (3) Osmolality (4) Surface tension. However, these factors were not part of the RA because one and all would mark with "high" impact without refer-

Table I *The selected QTPP elements, their target, justification and explanation*

QTPP element	Target	Justification	Explanation	
Therapeutic indication	Chronic eye disorder	Globally more than 253 million people suffers vision impairment	Therapeutic indication is a suggested QTPP by the ICH Q8	**Investigated in the RA of this study**
Target population	Patients, who need life-long therapy	Life-long therapy determined the patents' everyday life, decrease the HRQoL and leads to non-adherence patients' behavior	Target patient group is a suggested QTPP by the ICH Q8 in the clinical settings	
Administration route	Topical (eye)	The topical use avoids systematic effects and drug-drug interactions. Administration of drug by avoiding first-pass-metabolism, Blood Retinal Barrier and Blood- Aqueous Barrier. Expert competence is not needed for application	The route of administration has to be evaluated as a QTPP according to the ICH Q8 guideline	
Dosage form	Solution (eye drop)	Local irritation is decreased permeability of drug is increased, compared with suspension formulations	Dosage form is an essential QTPP element by the ICH Q8	
Site of activity	Local	Local effect is usually a general requirement of products for eye treatment. It is influenced by the solubility properties of the active pharmaceutical ingredient (API), the mucosal adsorption and wettability.	It is critically related to the quality, safety and efficacy of the medicinal product. Being a QTPP is a therapeutic requirement	
Dissolution profile	Immediate release	Immediate effect is usually a critical expectation for locally administered products. The residence time of the formula is limited on the surface.	It is critical from the patients' point of view	
Device	Proper to eye administration	Easy application, dose reproducibility are the main requirements. It is also linked to the microbial stability of the product.	It is critically related to the application safety and product quality	
Microbial stability	Long term microbial stability	Antimicrobial stability is essential in ocular drug delivery, considering of sensitivity of human eyes	It is critically related to the application safety and product quality	
Physicochemical stability	Long term physicochemical stability	It is critically related to the efficient and safe application of medicinal product	Default quality requirement	
pH	pH=7-9 pH=5-9	pH= 7-9 (optimal) pH= 5-9 (acceptable, not painful)	Default quality requirement	**Not investigated in the RA (strict regulated factors)**
Viscosity	30mPa*s	Should be under 30 mPa*s	Default quality requirement	
Osmolality	300mosm/kg	Should be close to isotonic level	Default quality requirement	
Surface tension	43mN/m	Surface tension of tear is about 43 mN/m. It should be similar in the product because of optimal spreadability and therapeutic effect	Quality requirement	

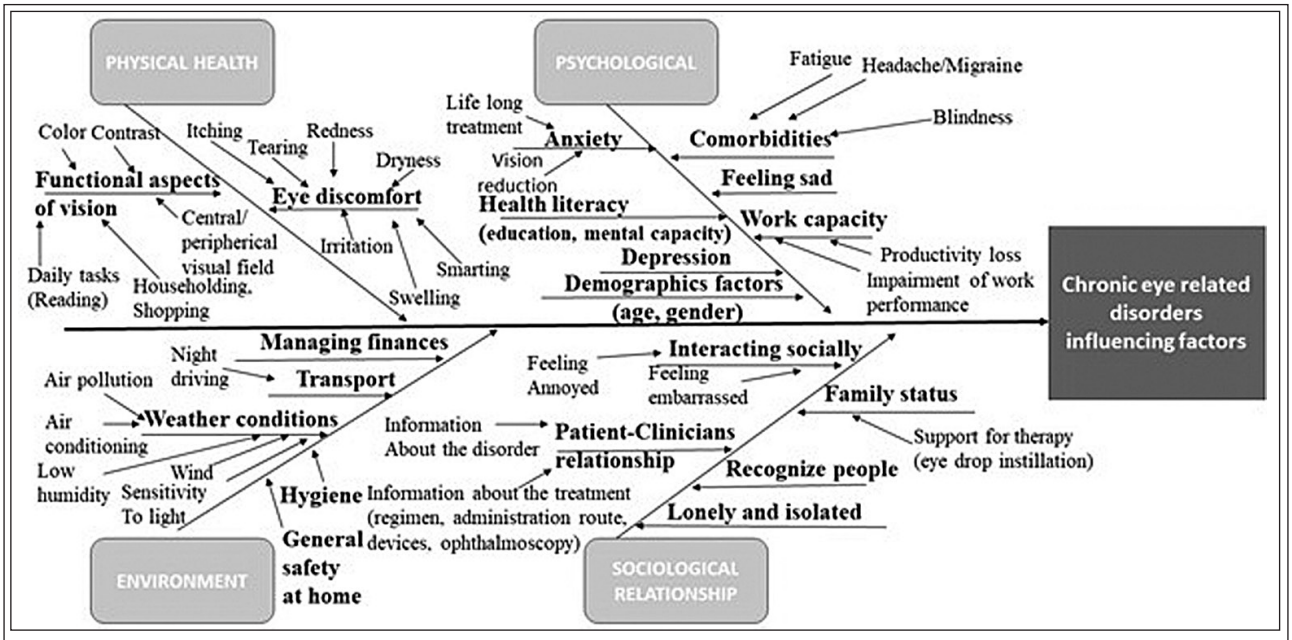

Figure 1 *Ishikawa diagram of influencing factors related to the chronic eye disorders*

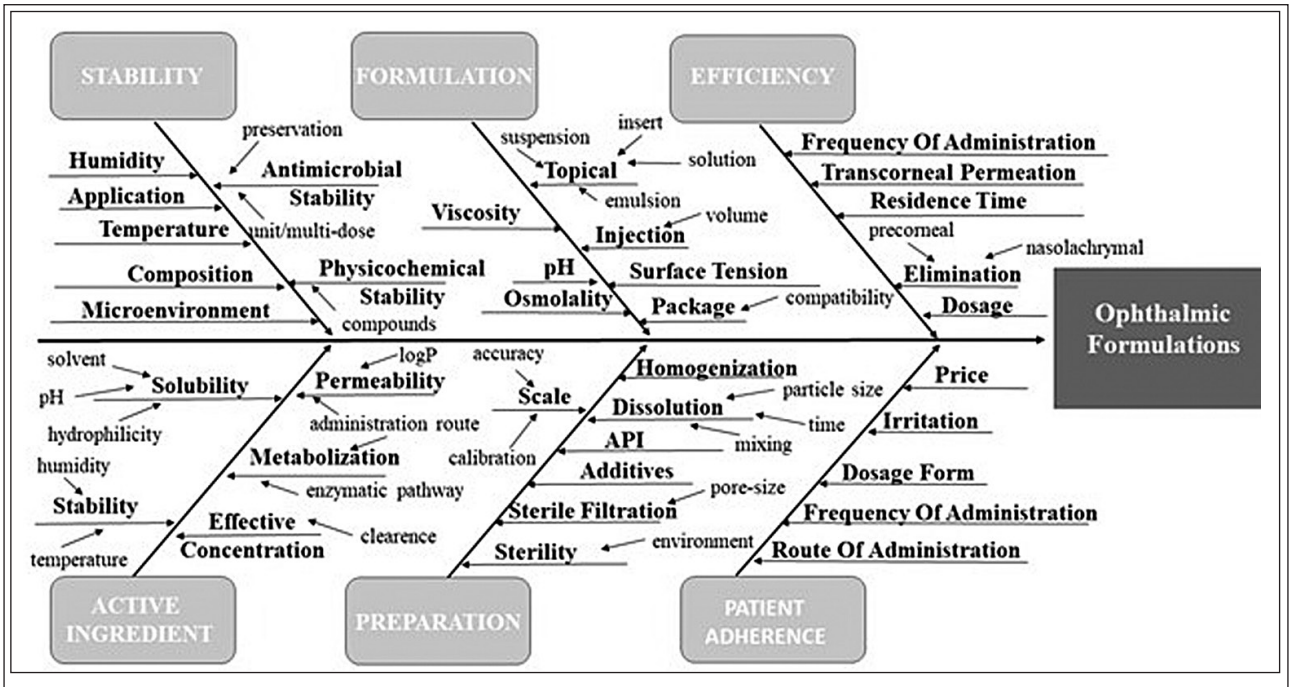

Figure 2 *Ishikawa diagram of influencing factors related to the ophthalmic formulation development*

ence to have or not have connection to selected CQAs and/or CPPs. If these parameters would be part of the assessment mentioned bias in the results. All relevant QTPPs are visualized in the following table (Table I).

After the previous and profound QTPP determination cause-effects diagrams (Figure 1, 2) were set up for the visualization of the most relevant influencing factors.

As it can be seen in Figure 1, a chronic eye disorder affects every aspects of patients' everyday life. Hard to compare the single effects according to their severity on patients' life. According to this fact was summarizes all parameters which could cover every part of the affected patients' life. If some of these factors damaged, supposed to lead ineffectiveness in the ophthalmic therapy.

The formulation aspects can be seen in the form of an Ishikawa diagram in Figure 2. The diagram shows the influencing factors related to develop-

QTPP – CQA

CQA	QTPP	(H) Life-long therapy	(H) Topical administration route	(M) Dosage form (eye drop)	(H)Local effect	(M) Dissolution profile (residence time)	(H)Device to the administration	(H) Microbiological stability	(H)Physicochemical stability
Eye discomfort	28%	High	High	Low	Low	Low	Low	High	High
Anxiety	14%	High	Medium	Medium	Low	Low	Low	Low	Low
Daily routine	12%	High	Low	Low	Low	Low	Low	Low	Low
Health literacy	13%	Medium	Medium	Medium	Low	Low	Medium	Medium	Medium
Social support	16%	High	Medium	Medium	Low	Low	Medium	Low	Low
Work capacity	18%	Medium	Medium	Low	Low	Low	Low	High	High

CQA – CPP

Process	CPP	Drug Product Application Process							
		Storage (temperature)	Regimen (frequency of the administration)	Device applicability	Long-term stability	Long-term sterility	Application without decreased vision	Hygienic circumstances	Mobile application (alarm system)
CQA		17%	30%	9%	6%	6%	21%	21%	12%
Eye discomfort	28%	Low	High	Low	Low	Low	High	High	Low
Anxiety	14%	Low	High	Medium	Low	Low	Medium	Low	Low
Daily routine	12%	High	Medium	Low	Low	Low	High	Low	Medium
Health literacy	13%	High	Medium	Medium	Medium	Medium	Low	High	High
Social support	16%	Medium	Medium	Low	Low	Low	Low	Medium	Low
Work capacity	18%	Medium	High	Medium	Low	Low	High	Low	Medium

OCCURANCE

CPPs	CPP Occurence	CPP Severity	CPP relative occurence	Occurence/ Severity
1. Storage (temperature)	High	17%	20%	1.22
2. Regimen (frequency of the administration)	High	30%	20%	0.68
3. Device applicability	Medium	9%	7%	0.79
4. Long-term stability	Medium	6%	7%	1.18
5. Long-term sterility	High	6%	20%	3.54
6. Application without decreased vision	Low	0%	2%	-
7. Hygienic circumstances	High	21%	20%	0.98
8. Mobile application (alarm system)	Low	12%	2%	0.19

Figure 3 *Results of the interdependence rating between CQAs and QTTPs as well as between CQAs and CPPs together with the occurrence of the CPPs*

ment of ocular drug delivery systems, although all of the interactions are difficult to represent with this method. Stability, efficiency, patient adherence, composition and preparation are considered as the main groups of the diagram.

The previous visualization of the cause and effects relationships presented in the Figure 1 and Figure 2 helped in identification of the potential critical factors. So, the next step was the selection of the CQAs, based on the Figure 1. As there are originally determined and regulated critical factors (pH, viscosity, osmolality, surface tension), those critical quality factors were determined in this study as CQAs which could be modified according to patients' expectations and perceptions. The selected CQAs are "*patient focused*" quality attributes in our present case.

The identified CQAs were the following: (1) Eye discomfort (Itching, Tearing, Redness, Dryness, Irritation, Smarting, Swelling) (2) Anxiety (causing

by life-long treatment and the vision reduction) (3) Daily routine, like householding, reading, shopping (4) Health Literacy, which is determined by education level and current mental capacity or status (5) Social support, first of all family members and friends (6) Work capacity, which could resulted as productivity loss or impairment of work performance.

The physical aspects like eye discomfort essentially influence the whole life, causes pain and overall physical disharmonies, which leads to negative attitude in some cases and could expand in psychological problem like, anxiety or depression. For people whose do not have vision problem, really hard to imagine that even performing the daily routine tasks have lot of difficulties, takes more time and could leads to misunderstanding, like patients do not recognize a familiar person or a family member, pay in the shop with wrong bank note or cannot find what they wanted to buy. These causes humiliation and presume that these patients will not leave their home after a while, especially if this come in younger ages. Besides, probable the problem will state at home as well. To perform the household or cooking will be more difficult. If the hygiene of the house is not enough sufficient, patients do not want to invite friends or family members, which reduced their social life. The situation is a little bit easier, if there are some family member or friends who can support the life of the affected, but unfortunately many patients are alone and do not have any support. The vision impairment affects not just private life but labour life as well. There is no work which can perform correctly without good vision. The loss of productivity and the reduction of the work performance from one side improved in negative feelings and from the other side in the long run could causes the loss of the work, which means lower monthly income and life quality reduction. For managing every kind of treatment crucial the patient's personal equation. The usual heath literacy belongs to a successful therapy output. If patients are not in adequately educated and also do not want to understand due to lack of interest in their own therapy, will not keep the defined treatment, loss some dose or overdose themselves, or do not use the device adequately, like the eye drop bottle, which is the determined device in our case.

All these factors escalate the problem and destroy the affected patients' entire life.

From the researchers' point of view, first of all the technological parameters determined the production of a drug, which was mentioned above as pharmaceutical standards In this case the production steps of an eye-drop formulation are fixed, the composition and preparation depend on the physicochemical attributes of active ingredients and additives. The final formulation need to meet the strict physiological requirements, such as pH, osmolality, viscosity and surface tension. The preparation must be done under aseptic environment to ensure a sterile product and proper microbiological stability during the storage and the application of the eye drop.

As the product production has severe defined elements in our present study "*the application of the medicinal product by the patient*" was identified as the process, and its critical attributes were identified as CPPs. The enumeration of the selected CPPs are: (1) Storage conditions, e.g. temperature, (2) Regimen, which is characterized by the frequency of the drug application (3) Device applicability, which is determined by the complexity of the drug application (4) Long-term stability (5) Long-term sterility (6) Application without decreased vision – this means the shortest time between the application and the perfect vision capacity to continue the daily routine, (7) Hygienic circumstances, e.g. clear hands, (8) Mobile application, which functions as an alarm system to pay attention to the application of the next dose.

The selected QTPPs, CQAs and CPPs were applied in the initial RA process. In the initial item of the RA the interdependence ratings were performed. The interdependence was evaluated step by step by each pair of the CQA and QTPP element, then by each pair of the CQA and CPP items. The effects of pairs by each other were estimated using the three-grade scale, as the potential effect can be rated as high, medium or low. Figure 3. presents graphically the results of the interdependence rating as part of the RA between QTPP elements and the CQAs as well as the CQAs and CPPs as. The CQAs and CPPs are also presented in Pareto charts (Figure 4), generated by the software, which shows also the numeric data of the selected critical factors and their ranking.

Figure 5 shows the relative severity –relative occurrence diagram. It has four quarters, which present the estimated occurrence and the estimated severity of critical factors related to the application process from the patients' aspects point of view. The most important is the "relative high oc-

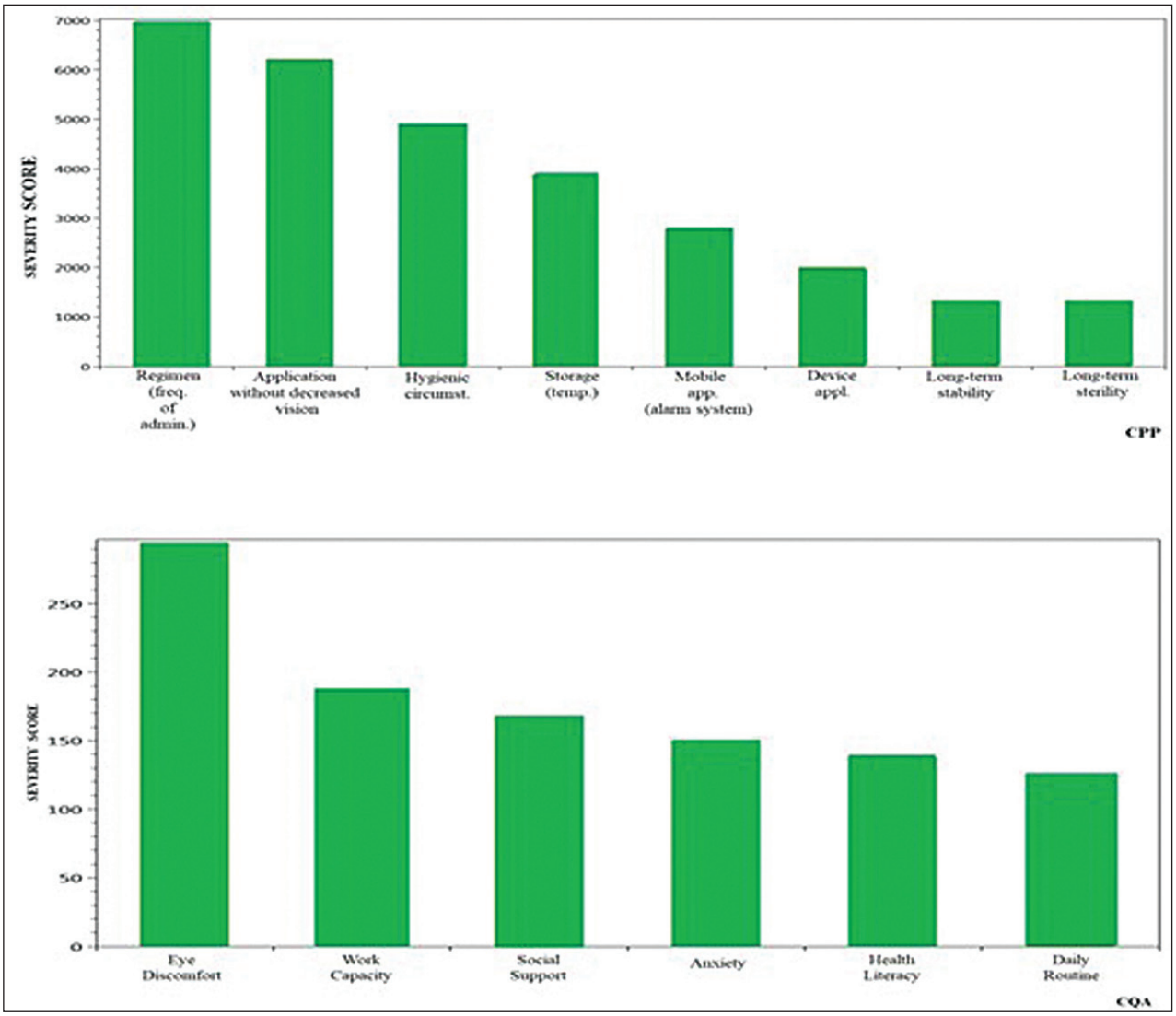

Figure 4 *Pareto charts according to numeric data of CQAs and CPPs*

currence – relative high severity" quarter. In this study this quarter contains the factors like the regimen (the frequency of a product use), the hygienic circumstances (e.g. purity of hands and environment), and the storage conditions (temperature).

Conclusion

Our study delivered up those factors which are crucial from ophthalmic patients' point of view – based on commonly used disease specific questionnaires' items - and are worthy to take into consideration at the early development phase of formulation work. These are the essential elements which influence the pharmaceutical treatment in ophthalmology and are capable to improve the long-term patient adherence to treatment, resulting in an increased HRQoL. Besides, apart from the patients and the researchers, the health care providers, like ophthalmologist, also play crucial role in the treatment selection and optimization. Figure 6 summarizes the partners involved in the ophthalmology treatment. This figure also presages the completion of a further study, because the researcher and the patient aspects were evaluated in this present work.

If the storage condition, the frequency of the drug application and the comprehensive hygienic circumstances are highlighted during the formulation process, for example ensuring with primary wrapper change, or ensuring reduced application frequency, possible to help for patients during with drug application process, which was determined as the critical process in our study. However, our study has some limitations as well, which

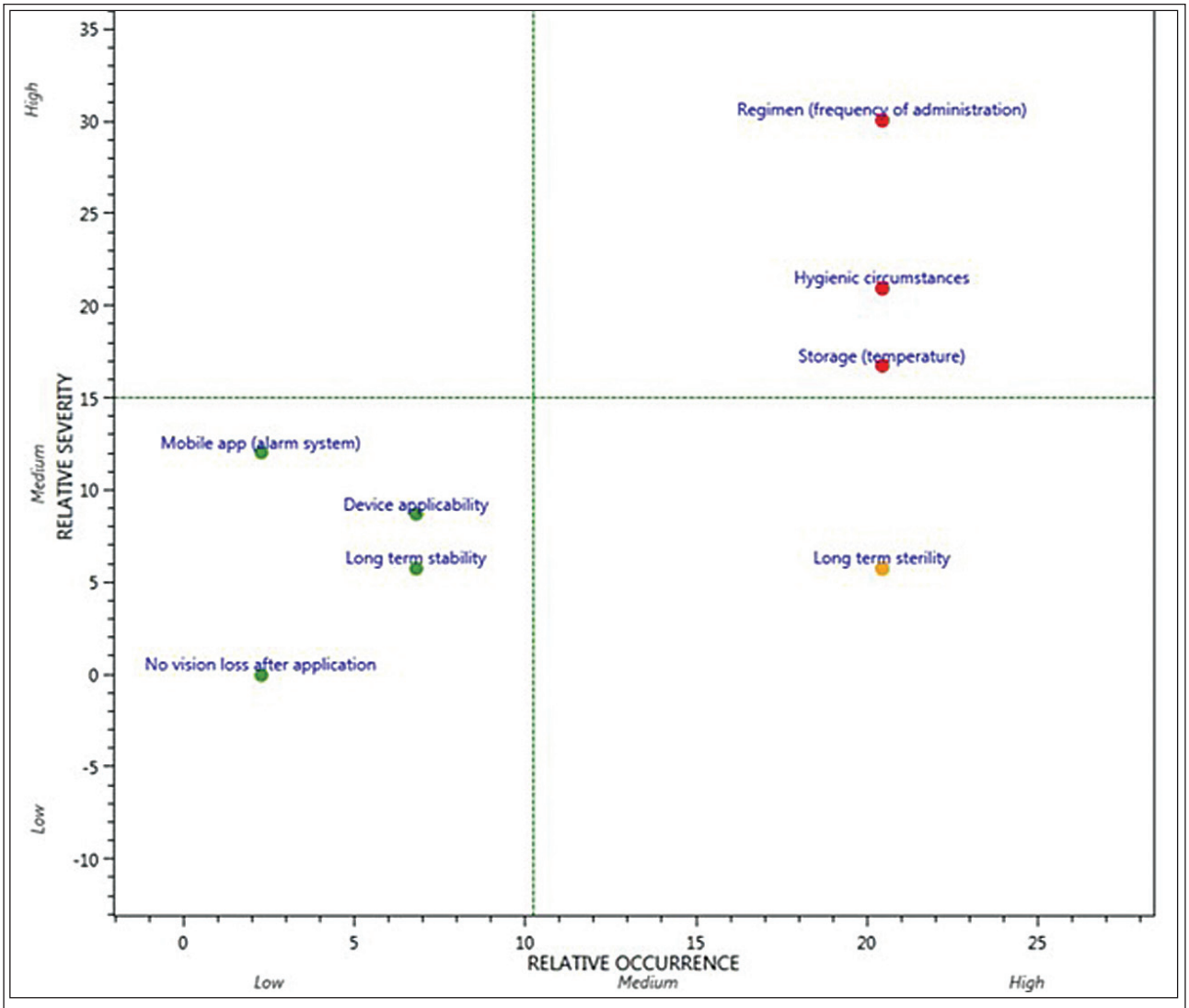

Figure 5 *The application process dependent relative-severity – relative occurrence, based on selected CQAs*

needed further observation and examination. First of all, the collected results need to apply during formulation process in practice and also important to ask the affected patients directly about their opinion to justify our results via self-reported questionnaires. The main aim of this study was to compare the patients' and the researchers' expectations and perceptions to give feedback for early development process via QbD based manner. This QbD based manner was achieved and RA was performed by using all affected parties' opinion. The research work is a method development which needs to be proved by further real-life experiments. However, the work aimed to develop a method which could be used as a basic for practical application. The most important outcome of the research is that if there is a concrete specific chronic eye disorder as a target, by using the QbD approach, the determination of the target product profile and its desired quality is possible in the first step. Then, based on the QTPP and related knowledge from the literature and practice the CQAs and CPPs can be identified. After performing the risk assessment, the design of experiments can be made and later the DoE-based experimental work the will be resulted in the determination of the design space. The information needed to the QbD based formulation-design can originate from the scientific literature and directly form patients via PROMs. In our specific case those questionnaires' items (more specifically the issues which were covered by the items) were used which are the most common regarding to chronic ophthalmic disorders. The presented method helps in systemization of the available information on a risk-based manner. By a further research, patients should be interviewed directly via questionnaires and the responses could be com-

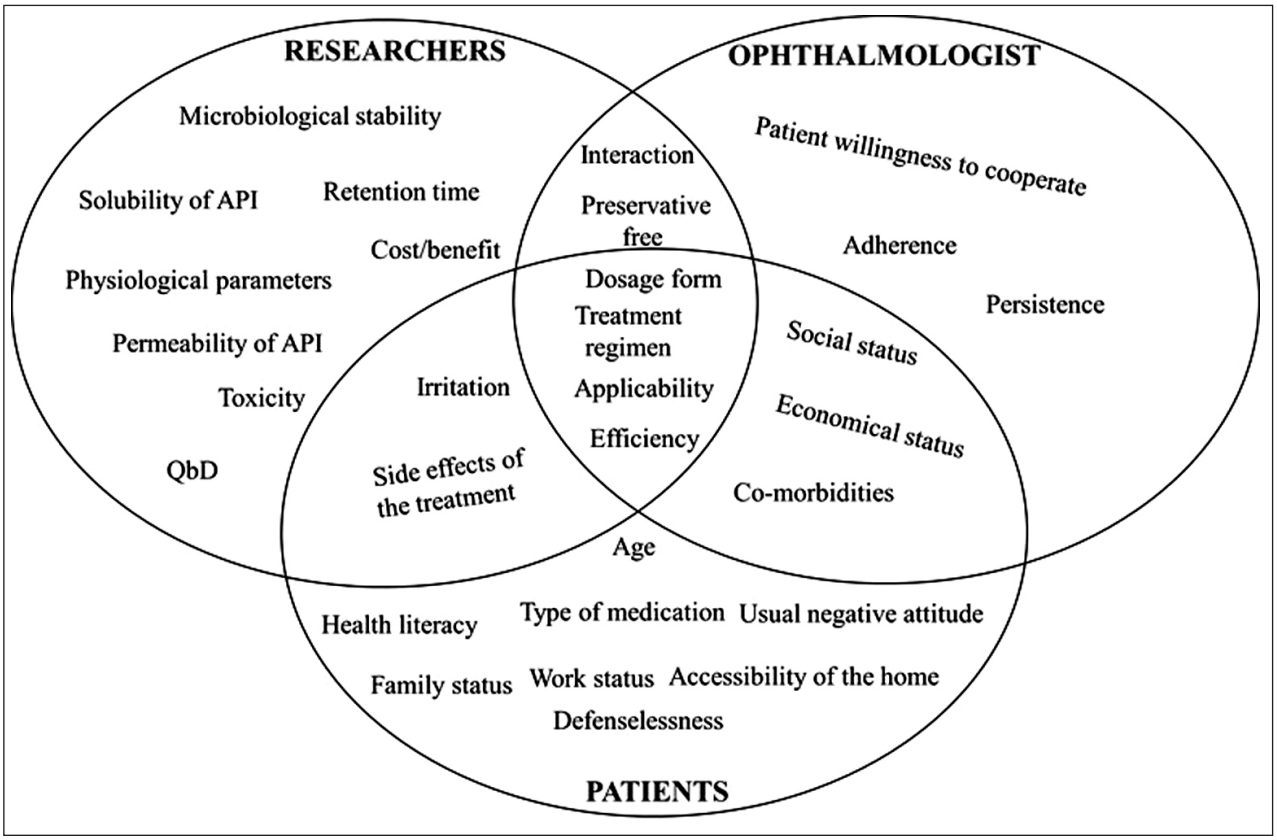

Figure 6 *Presage of all of the concerned parties' expectations*

pared to technologists' and health care providers' point of view as well. The "Patient Centered Care"-approach can be provided from the very beginning, if the patients' needs and requirements are taken into consideration from the design phase of the pharmaceutical formulation and it is built in during the whole development process. In addition, by the presented risk-based method several useful results can be predicted to both of the parties, as this model can improve the satisfaction of the patients and can improve the success of the drug development.

Declaration

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