European Journal of Pharmaceutics and Biopharmaceutics 177 (2022) 81–88

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

Rational and practical considerations to guide a target product profile for patient-centric drug product development with measurable patient outcomes – A proposed roadmap

Sven Stegemann [a,*], Liz Sheehan [b], Alessandra Rossi [c], Andrew Barrett [d], Amrit Paudel [a,e], Abina Crean [f], Fabrice Ruiz [g], Massimo Bresciani [h], Fang Liu [i], Zakia Shariff [j], Margarete Shine [b], Christel Schmelzer [k], Anne-Marie Pense-Lheritier [l]

[a] Institute for Process and Particle Engineering, Graz University of Technology, Inffeldgasse 13, 8010 Graz, Austria
[b] SRL, Office of Technology 2-44, Western Gateway Building, University College Cork, Ireland
[c] Department of Food and Drug, University of Parma, Parco Area delle Scienze 27/A, 43124 Parma, Italy
[d] Drug Product Design, Pharmaceutical Sciences, Pfizer, Discovery Park House, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK
[e] Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria
[f] SSPC Pharmaceutical Research Centre, School of Pharmacy, University College Cork, Cork, Ireland
[g] ClinSearch, 110 Avenue, Pierre Brossolette, 92240 Malakoff, France
[h] CMAC Technology and Innovation Centre, University of Strathclyde, 99 George Street, Glasgow G1 1RD, UK
[i] Department of Clinical, Pharmaceutical and Biological Sciences, University of Hertfordshire, College Lane, Hatfield AL10 9AB, UK
[j] School of Pharmacy, Aston University, Birmingham, B4 7ET, UK
[k] Welfenstrasse 14, D-55218 Ingelheim, Germany
[l] Ecole de Biologie Industrielle, 49 avenue des Genottes, 95895 Cergy Cedex, France

ARTICLE INFO

Keywords:
Patient centric
Drug development
Drug product design
Target product profile
Acceptability
Medication errors
Effectiveness
Compliance/adherence

ABSTRACT

The increasing awareness of acceptability and usability of pharmaceutical drug products by the patient as a key quality requirement continues to drive need for integrating patient centric drug product design into the pharmaceutical development process. The complex matrix of multiple drug product related decisions during the early drug development process often limits patient-centric drug product (PCDP) design options in the final commercial drug product development phase. To integrate the specific needs and perspectives of patients into drug development and product design process, a rational approach integrated into the complex development matrix is required from the start and weighs product development decision options accordingly. The aim of this work was to develop a roadmap for PCDP design in a multidisciplinary approach that leads to better usability, adherence and acceptance of the drug by patients via early integration into the development matrix. The proposed rational approach is based upon regulatory requirements and lessons learned from pediatric and geriatric drug development.

1. Introduction

Due to progress in pharmacotherapy and the resulting variety of therapeutic options, as well as the social development towards increasing personal responsibility and individuality, the role of the patient and care giver ecosystem has steadily evolved. From a rather passive role, patients are more and more taking an active part in the decision-making process as they are the most critical factor in the implementation of therapy and physicians increasingly implement shared decision making on the therapeutic approach [1]. Without the active and continued contribution of the patient, the product might not be taken properly and hence therapeutic outcomes are likely to be sub

* Corresponding author.
E-mail addresses: sven.stegemann@tugraz.at (S. Stegemann), lsheehan@srlresearch.com (L. Sheehan), alessandra.rossi@unipr.it (A. Rossi), andy.barrett@pfizer.com (A. Barrett), amrit.paudel@rcpe.at (A. Paudel), a.crean@ucc.ie (A. Crean), fabrice.ruiz@clinsearch.net (F. Ruiz), massimo.bresciani@strath.ac.uk (M. Bresciani), f.liu3@herts.ac.uk (F. Liu), christel-schmelzer@gmx.net (Z. Shariff), mshine@srlresearch.com (M. Shine), christel-schmelzer@gmx.net (C. Schmelzer), am.lheritier@hubebi.com (A.-M. Pense-Lheritier).

https://doi.org/10.1016/j.ejpb.2022.06.006
Received 20 May 2022; Received in revised form 12 June 2022; Accepted 13 June 2022
Available online 17 June 2022

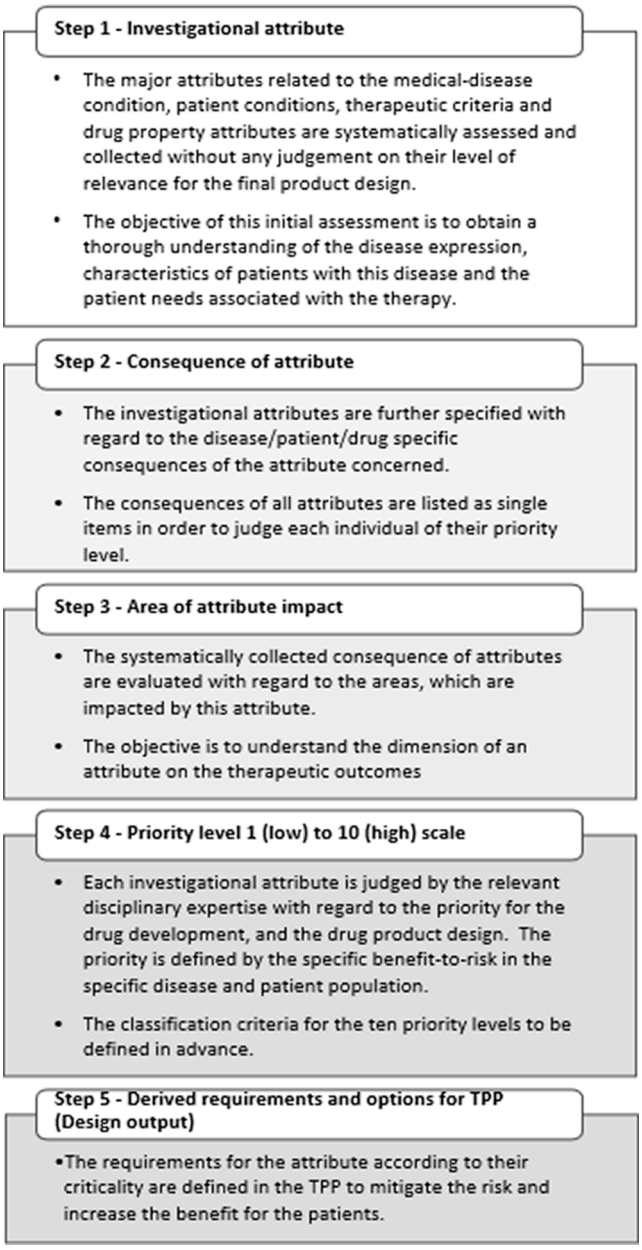

Fig. 1. Steps in the Roadmap to define the important patient needs in the development of the Targeted Product Profile (TPP).

optimal.

The provision of safe and effective pharmaceutical drug products to be used and administered by the patients, care givers and healthcare professionals have to fulfill a number of important criteria to display the best benefit-to-risk profile. Besides the efficacy and safety of the drug compound, which is essential for the clinical outcome, the finished pharmaceutical drug product needs to be of high quality and stability, affordable cost, accessible as well as acceptable and usable by the end user. Over the past decades, evidence is emerging on the importance of the acceptability and usability of pharmaceutical drug products and the contribution this might have to non-adherence, medication errors, other medication related problems and undesired therapeutic outcomes. While the problems in dealing with existing pharmaceutical products are well described [2 –4], our knowledge regarding optimal drug product design and the implementation of patient-centric drug product design [5] within existing regulatory/clinical guidelines remains very limited [6–8]. However, there is increasing scientific and regulatory research on the patient perspective throughout the development process of new therapies [9,10] including acceptability and usability of the drug product. These issues have already been recognized for the pediatric patient population, but are equally acute for other patient populations such as geriatric or multimorbid patients [11].

Considering the complexity of the matrix of a new drug product development, the intrinsic physico-chemical and pharmacological properties of a drug compound, the variety of different patient characteristics and needs, the existing regulatory and industrial requirements as well as the timely access for patients to effective new therapies, the integration of patient-centric pharmaceutical product design remains a major challenge [8,12]. In addition, the multiplicity of different stakeholders, tasks and deliverables, the need for scientific evidence of patient-centric drug product development and design as well as the lack of regulatory guidelines, are challenges for cross-disciplinary discussions and joint research. To overcome these barriers, a pragmatic, rational, and stepwise process commonly agreed between different stakeholders and development organizations is required. One such approach is suggested in this paper. Since each drug development program is specific to the disease, the drug compound and the intended patient population, the process considered must be general in nature to serve as a RoadMap. It must be able to justify the scientific approach taken during development of the patient-centric drug product, including the rationale for product design decisions and associated risk mitigation during the early development stages and scale-up. While there are probably no solutions to all problems yet, a better solution can be developed for every product, through a RoadMap that will improve the product design by qualified assumptions to support decision making without compromising equally important quality requirements of the final drug product, its approval and patient access. The RoadMap can also be applied in life cycle management to further improve the product design or better serve additional patient population.

This publication is intended to serve as a proposal for a RoadMap towards patient-centric drug product design to stimulate further input and scientific discussions with other experts and stakeholders across all disciplines.

2. Methods

The Patient Centric Medicine Initiative (PaCeMe) is a multidisciplinary stakeholder group of academic and industrial individuals with specific expertise covering various aspects of drug development and the interface of patients with their medical products.

After reaching consensus that the complexity of the subject as well as the development matrix of a new drug product will require a case-by-case approach, it was acknowledged that it would not be possible to provide a single, generally applicable RoadMap. However, there was consensus that a RoadMap can be developed that provide a logical framework and process to steer identified patient needs towards inclusion into PCDP development and design. For the RoadMap development, the following preliminary considerations were defined:

- Leverage prior experience and work done in similar field (e.g., product development and clinical supplies in pediatrics, geriatrics)
- Use of available information related to patient characteristics and needs in disease or discipline specific guidelines, documents or publication (screening of literature and regulatory guidance)
- Follow the principles of a rational, meaningful and practical approach, taking into account the feasibility of implementation
- Define knowledge gaps, methodological limitations, and issues with qualification and quantification of results to be addressed in future research
- Assure all stakeholder inclusion and users involvement in the RoadMap for product development and life cycle

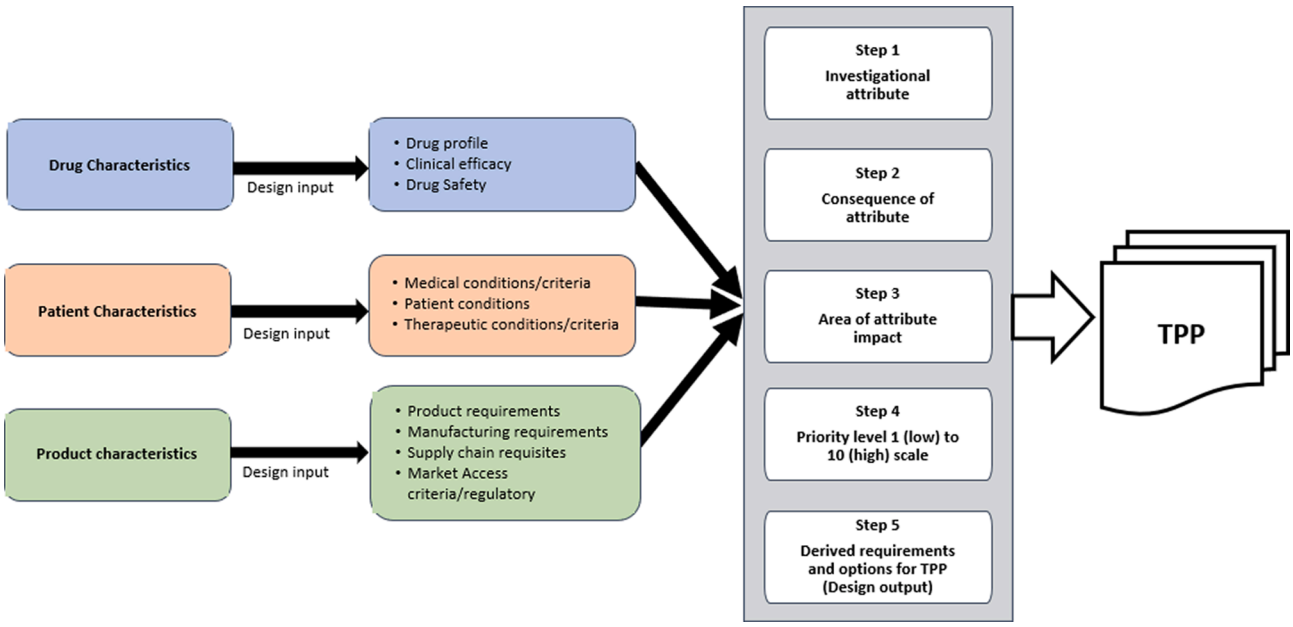

Fig. 2. The various characteristics considered for each step in the RoadMap to define the important patient needs and transfer into the Targeted Product Profile (TPP).

- For practicality reasons, the framework development was limited to oral dosage forms, but should be adaptable and applicable to other dosage forms as well

Based on the preliminary considerations a screening of the literature and regulatory guidance documents relevant to the RoadMap was performed and analyzed. In addition, subgroups were formed to collect insights on (1) patients and therapeutic conditions; (2) acceptability; (3) formulation and manufacturing; and (4) market access and prescribing with a focus on type 2 diabetes mellitus. This information served RoadMap the objective to demonstrate the practicality of the RoadMap as a case study.

3. Results

3.1. Screening of literature relevant to the RoadMap

A screening of the literature identified approaches developed within the pediatric drug product development space. Severin et al described the importance of forming a Pediatric Expert Group within the company to enhance internal collaboration and external collaboration with e.g., research networks, academic institutions and public private partnerships to enhance the quality and efficiency of pediatric medicines development [12]. Sam et al proposed a framework for the development of drug products for pediatric populations. The framework includes considerations for the selection of age-appropriate dosage forms and how to make use of existing formulation approaches and technology to the benefit of the adult populations as well [13]. The WHO and Unitaid published guidance on the clinical and pharmaceutical development of pediatric antiretroviral drugs consisting of 10 modules. Modules 5, 6 and 7 provide useful information about the state-of-the-art knowledge, gaps and potential solutions to assess and achieve acceptability (Module 5), to involve patients and their community (Module 6) and define an appropriate Target Product Profile [14]. Additionally, precompetitive consortia have been established in Europe like e.g. the European Paediatric Formulation Initiative (EuPFI) that aims to resolve scientific, regulatory and technological issues associated with paediatric formulation development [http://www.eupfi.org/] or the European Paediatric Translational Research Infrastructure (EPTRI) which aims to accelerate the pediatric drug development [https://eptri.eu/].

The proposed definition of patient-centric pharmaceutical drug product design describes a 3-step approach. Four different factors were identified as design drivers in the first step (characteristic of disease/condition, characteristic of drug substance/physiology, characteristic of drug therapy, characteristic of drug product, patient characteristics) for which design inputs and design outputs can be described in the second and the third step respectively to guide the drug product development process [5].

Human factor engineering and ergonomic methods for medical device development provide a framework to assess the product-user interface and to assure a smooth and error-free interaction between the product and the user by an iterative design process with direct user involvement [15].

A design process can also be guided by a heuristic problem-solving approach, building on the ability and intuition of the users when interfering with a drug product with the goal of ensuring ease of use without user instructions. A three-step process was proposed, (1) define how the product should be used, (2) identify the most serious challenges of the usage and any resulting complications that must be avoided and (3) identify solutions that support users best while minimizing the cognitive effort required to use the product. The heuristic approach can be used prospectively based on existing knowledge and retrospectively by gaining more knowledge for further product improvements [16].

4. Screening of the regulatory framework relevant for the RoadMap

Over the past 15 years, the patient's perspective has increasingly become the focus of regulatory science as one of the important factors in the treatment cascade. The guidelines and reflection paper cover a variety of aspects to achieve better PCDP e.g., by including patient involvement in drug development, addressing safety issues like medication errors, considerations for special populations (e.g. pediatric, geriatric, frail), considerations for dosage forms (e.g. beads, sprinkle, administration through feeding tube) and the use of digital tools like real world data and evidence (table 1, supplemental material).

For example, Patient Reported Outcomes (PRO) defined as a "report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else" were introduced in

Table 1
The theoretical development of a new drug product profile for Diabetes Type 1 & 2. Process to determine and analyze product requirements in the Target Product Profiling step*.

Step 1 Investigational attribute (Design input)	Step 2 Consequence of attribute	Step 3 Area of attribute impact	Step 4 Priority level** 1 (low) to 10 (high) scale	Step 5 Derived requirements and options for TPP (Design output)
Drug Characteristics				
Design consideration: Drug profile				
Bioavailability variability	Over-, under-dosing	Safety, efficacy		Biomarker, adherence monitoring
Drug lipophilicity/solubility	Food effect, Over-, under-dosing	Safety, efficacy		Solubility enhancement
Drug absorption	Pharmacogenomics	Safety, efficacy		Clinical data and guidance
Drug metabolism	Pharmacogenomics	Safety		Clinical data and guidance
Drug clearance	Organ functions	Safety, efficacy		Number of dose strengths options
Drug stability	Degradation products	Efficacy, safety		Stability targets
Polymorphs	Bioavailability	Efficacy		Stable or stabilized crystalline form
…	…	…		…
Design consideration: clinical efficacy & safety				
Dose requirement	Dosage form, volume size	Usability, Acceptability		Alternate forms (injectable) or multiple dosing units
Biologic half-life	Drug concentration within the therapeutic window	Efficacy, safety		Dosing regimen, Modified release formulations
Taste	Negative perception	Adherence		Taste masking
Adverse Drug Reactions	Patient harm	Safety, non-adherence		Prescribers information & education
pH dependent solubility	Bioavailability	Safety, efficacy		Drug delivery technology (e.g. amorphous, enteric form)
…	…	…		…
Patient Characteristics				
Design driver: Medical conditions/criteria				
Varying glucose level	Hyperglycemia	Efficacy, long term co-morbidities		Flexible dosing, drug half-life
Varying glucose level	Hypoglycemia	Safety, cardiovascular disease		Glucose control, adherence monitoring, biomarker
Disease cluster	Distinct co-morbidity profiles	Drug-drug & drug-disease interactions		Prescribers information & education
Nephropathy	PK changes	safety		Dose adaptation guidance, Range of dose strength
Retinopathy	Visual impairment	Usability, medication errors		non-filigree distinguishing feature
Neuropathy	Physical functioning	usability		Dosage form design, packaging design
Achlorhydria	Bioavailability	Safety, efficacy		Drug delivery technology (e.g. modified release)
…	…	…		…
Design driver: Patient conditions				
High age	vulnerability	Safety, Adverse Drug Reaction		Clinical data and guidance
Homeostasis	vulnerability	Safety, Adverse Drug Reaction		Clinical data and guidance
Kidney function	CKD	Safety		Clinical data and guidance
Multimorbid conditions	Cardiovascular disease	Drug-drug-interactions, safety		Clinical data and guidance
Multimorbid conditions	Chronic Kidney Disease	Drug-drug-interactions; safety		Clinical data and guidance
Dexterity impairments	Dosage form manipulation/ handling	Adherence, safety		Ready to use dose strength options
Grip strength limitations	Usability – product handling	Adherence safety		Dosage form design, Packaging design
Visual impairments	Product identification	Medication errors Safety		non-filigree distinguishing feature
Visual impairments	Dose adjustment/ selection (e.g. insulin)	Safety, efficacy		non-filigree distinguishing feature
Visual impairments	Product information	Medication errors Safety		Leaflet letter size, audio option
Stigmatization	Social participation	Adherence, efficacy		Discrete design
…	…	…		…
Design driver: Therapeutic conditions/criteria				
Polypharmacy	Therapeutic complexity	Adherence safety		Once daily, FDC
Polypharmacy	Drug-drug-interaction	Safety		Physician education/alert, label warning
Swallowing function	Oral dosage form size/shape	Adherence, safety		Formulation/product design
Swallowing function	Medication error – tablet crushing	Adherence, safety		Formulation/product design
PPI co-prescription	Bioavailability	Safety, efficacy		Drug delivery technology (e.g. modified release)

(*continued on next page*)

Table 1 (*continued*)

Step 1 Investigational attribute (Design input)	Step 2 Consequence of attribute	Step 3 Area of attribute impact	Step 4 Priority level** 1 (low) to 10 (high) scale	Step 5 Derived requirements and options for TPP (Design output)
…	…	…		…
Product characteristics				
Design driver: Product requirements				
Product differentiation to other products used in this indication	Acceptability, Identification	Safety, Medication errors		Product design (colors, imprints, shapes)
Packaging requirements	Acceptability, country specific requirements	Adherence safety		Packaging design
Acceptability & usability of self-diagnostic devices	Therapeutic monitoring	Efficacy, safety		Human Factors Design
Independent of food	Therapeutic complexity	Acceptance, Medication errors		Formulation design, drug delivery
No preparation steps required	Intuitive/learned use	Safety, Medication errors		Minimize specific use requirements
Stability in targeted regions	Drug degradation, impurities	Safety, accessibility		Formulation, stabilizer
Excipient characteristics	Toxicity, bioavailability modulation	Safety, drug-drug-interactions		Alternative excipient
…	…	…		…
Design drivers: Manufacturing requirements				
Physical state	Stability	Safety, efficacy		Formulation
Dosage form	Capabilities	Adherence		Alternative dosage form
Excipients	Stability	safety		Alternative excipient
Excipient variability	Out of specification	Accessibility, out of stock		Alternative excipient/formulation
…	…	…		…
Design drivers: Supply chain requisites				
Manufacturing site	On time supply issue	Out of stock		Higher safety stocks, flexible manufacturing (additive, continuous)
Manufacturing cycle time	Limited on demand reactivity	Out of stock		Higher safety stocks, flexible manufacturing (additive, continuous)
Number of qualified supplier	Dependency on supplier	Out of stock		Multiple sourcing strategy
…	…	…		…
Design drivers: Market Access criteria/regulatory				
Added value evidence	third line classification	Patient access		Comparative study to golden standard
Added value evidence	Re-imbursement	Patient access		HTA measure on drug product design impact
Manufacturing costs	affordability	Limited patient access		flexible manufacturing (additive, continuous)
Health Insurance	No reimbursement	Limited patient access		Early negotiation, patient value demonstration (HTA measure)
…	…	…		…

* Some companies use e.g., Multi-stakeholder or Active Listening Meetings which serve as a process to systematically collect information for the Target Product Profile, ** Classification criteria for the ten priority levels have to be defined and established in advance. Since the prioritization highly depends on the drug compound characteristics, no priority numbers were included in this case study example.

2009 [8]. These were included in the latest regulatory science initiative to develop a series of Patient Focused Drug Development guidance [17]. This initiative has been taken up by the ICH publishing a Reflection Paper on how to progress the inclusion of the patient experience and perspectives into patient focused drug development [18].

Real world data are emerging as an important source to understand the patient perspective and support regulatory decisions [19]. The EMA has recently set up the DARWIN EU coordination center to integrate real world data in the medicine evaluation process [20]. Furthermore, the *European Network to Advance Best practices & technoLogy on medication adherencE* (ENABLE) is a multi-disciplinary EU network aiming to raise awareness of adherence enhancing solutions, foster knowledge on medication adherence at patient, treatment and system levels, accelerate translation of this knowledge to useful clinical application and, work collaboratively towards economically viable implementation of adherence enhancing technology across European healthcare systems [21].

From the regulatory guidance documents, the EMA Good practice guide on risk minimisation and prevention of medication errors [21,22] describe some important drug product design related factors including tools for the evaluation during development to mitigate the risk of medication errors. Similar guidance has been published by the FDA [23].

Regulatory guidance and reflection papers provide consideration on the pharmaceutical drug product development and design for the pediatric population as well as for older people (see supplemental materials). These considerations include aspects of the different dosage forms, formulations and physical attributes as well as aspects of their predicted practical use like stability in multi-dose compartment aids, subdivision and use in enteral feeding tubes. The EMA reflection paper on physical frailty provides regulatory consideration on the relevant assessment instruments to be used to ensure that truly frail patients are included in the clinical trials [24]. For a detailed compilation of regulatory guidance see supplemental material.

5. Summary of the working groups

The particular characteristics of the patient with a specific disease might differ across the span of age and disease stage. Patients with multimorbidity are increasingly present in specific disease classes whereby

disease clusters are common [25,26]. The number of index diseases correlate with the number of functional impairments, which both together determine the ability and/or willingness of a patient to administer a drug product of a specific product design [27,28]. The perceived and potentially real heterogeneity of the targeted patient populations, the concerns about patient involvement in drug product development as well as reimbursement issues are still considered as uncertainties and barriers.

Acceptability depends on the specific patient population and is achieved when the patient population is able and willing to use the drug product as intended [10]. The ability to (self-)administer a drug product as intended is the result of the ease of use and handling, route of administration, dosage form appearance, level of restrictive instructions and prior experience. The willingness to orally take a drug product is driven by sensory experience (e.g., taste, flavor, mouthfeel, texture, aftertaste and smell), swallowability (e.g., size, shape and surface) and psychological or perceptual interpretation (e.g., cultural, gender, social, economic, health or other beliefs on dosage form or route of administration) [29 –31]. The multitude of individual preferences for what is acceptable raise concerns about the variety of potential product variations required even within a single patient population. This in turn would limit commercial manufacturability and access to new products.

Acceptability is critical for adherence, avoiding medication errors and preventing inappropriate medication altering. Since the basic drug product design concept already determines critical factors for acceptability, an analysis of the particular characteristics of the targeted patient population has to be sufficiently reflected from the early product development phase onwards.

The drug product formulation and processing have to assure the product quality criteria (e.g., content uniformity, purity, excipient level and safety, stability, dissolution, etc.) and bio-performance (e.g., bioavailability, pharmacokinetics and pharmacodynamics) [32]. Compliance with existing regulatory guidance (e.g., child resistant packaging) as well as limited guidance on patient-centric drug product design (e.g., guidance on acceptability or usability) are still perceived as barriers. The drug product design has to assure that the product can be manufactured on a commercial scale at affordable costs and is suitable for the supply chain and distribution in the targeted countries.

The market access and reimbursement are national decisions based on data on the efficacy, safety, patient-reported outcomes, real-world effectiveness and additional phase 4 studies demonstrating the therapeutic and/or economic superiority of the new dug product [33]. Patient advocacy groups have started a worldwide initiative for patient involvement in Health Technology Assessment (HTA) in order to change the clinical and economic focus of HTA by better integration of the patient value and quality of life aspects [34]. Comparative effectiveness data which include the evaluation of benefit of a special product design in this context is still lacking and has to be considered as an important area for research, method development and regulatory guidance [35]. For detailed working group reports see supplemental material.

6. RoadMap considerations

Three major aspects have been identified that must be compiled, analyzed and weighed in any development project at the same time (1) drug characteristics, (2) patient characteristics and (3) drug product characteristics. *Drug characteristics* review the physicochemical, biopharmaceutical, pharmacological etc. intrinsic properties of the active pharmaceutical ingredient (API), the *patient characteristics* review the typical patient capabilities, impairments, disease burden etc. and the *product characteristics* review the drug product in its final, packaged form and context of its use, manufacturing, supply chain etc. which together have to be considered, evaluated and addressed in the TPP to drive the pharmaceutical product design process. The outcomes of the working groups provide valuable guidance on these three different aspects to define the critical PCDP design elements within the industrial-technical product development matrix. Since the existing literature does not provide yet logical and rational process for identifying the needs of individual patient populations and their prioritization to increase product effectiveness and safety, this RoadMap intends to build on the existing development matrix by incorporating the most critical patient needs in a systematic and rational way early on into the drug product design process.

7. A proposed systematic and rational process for patient-centric product design

The proposed process is intended to serve as a roadmap to define the important patient needs in the targeted product profile (TPP) and how these could be addressed by product design. Fig. 1 graphically illustrates the 5 steps involved in the process. The process is further elaborated in Fig. 2, which shows the various characteristics (drug, patient, and, product), that need to be considered. The process is then used as a template for the development of a theoretical new drug compound and product for diabetes type 1 and 2 (Table 1).

The information in Table 1 represents some aspects in the development of this drug and serve only the purpose of providing an example for applying the roadmap to develop, prioritize, address, and document a PCDP development.

The process is based on a thorough analysis of the specific disease, patients/patient population, therapeutic context, drug properties and manufacturing requirements. It has to be developed with all disciplines involved in the development process, especially clinical, pharmaceutical, regulatory, manufacturing and supply chain functions.

As a starting point in the process a high-level overview of the therapeutic landscape and the market data on the product prescriptions are collected (e.g., through Pharma Circle, IQVIA) to understand the therapeutic burden of the patients, the available drug products and their share in the treatment. It is acknowledged that the products might differ in terms of brand names, composition etc. which can lead to some discrepancy. For the initial phase, this is acceptable but further analysis can be considered at a later stage understand a potential gap between efficacy and effectiveness.

Based on the thorough drug, drug product and patient profiling, the most critical risk factors that should be included and addressed in the TPP can be derived based on the level of priority. Even though the judgements might be subjective, they highlight the most important criteria for the development and design of the final drug product. The priority level assigned for each characteristic will depend on the individual drug product; for example, for drugs with a narrow therapeutic index, the pharmacokinetics (e.g., the absorption, metabolism and clearance) will have a higher priority level as well as for drugs with a pH dependent dissolution with a targeted patient population with high probability of achlorhydria or proton pump inhibitor (PPI) co-medication. The identification of such critical product attributes than leads to the product requirements including a set of options to address these accordingly in the drug product development and design. The RoadMap analysis will provides comprehensive evidence of the different attributes that will most likely be positively impacted by a certain product design element and how this can be achieved.

The RoadMap analysis is intended to be used within the overall context of the drug development program. The derived TTP will be a balance between the priorities defined by the patients and the different stakeholders from industry, healthcare professionals and providers. The RoadMap analysis is a process to achieve the best benefit-to-risk profile of a drug product by a systematic and rational definition of the priorities in a new drug development program. The RoadMap requires periodical reviews due to the generation of new data and information during the course of development. Continuing this process in the commercialization phase might support life cycle management and new drug development programs. It is expected that over the course of additional projects the TPP and the RoadMap items form a comprehensive

collection of items that are applicable on a generic basis and facilitate the process for PCDP design of other drugs, indications and/or patient populations.

Nevertheless, there are still major gaps that need to be closed. The most important area relates to validated methods of qualifying and quantifying the acceptability, usability, effectiveness, and safety of different pharmaceutical drug product designs in relevant patient populations and their implementation in the regulatory process.

8. Discussion

The analysis of the literature, the regulatory guidance and reflections and their own experiences have helped the authors in designing the proposed RoadMap. Since the individual stakeholder judgments might be biased by their own disciplinary point of view, it is still considered essential to involve all stakeholders to cover the entire spectrum of the industrial, clinical, provider, payer as well as patient perspectives in the future discussions.

The development of a new medicine follows a number of well-established processes to mitigate the risk, unnecessary delays and assure regulatory compliance and approval. Following these workflow processes and focusing mainly on the clinical efficacy bears the risk of underestimating the capacity of specific patient population to manage the therapeutic burden of the new medicine.

Changing or progressing the existing workflow processes to include PCDP design requires a higher degree of planning and propriety setting in early phases of a specific project while at the same time managing additional uncertainties regarding the corporate and regulatory proceedings [36–38].

The proposed roadmap is meant to overcomes some of these issues by allowing for the systematic recording of all drug substance-, dosage form-, manufacturing- and patient-specific properties. This provides a complete overview of the drug to be developed, allowing for prioritization of the product design and an analysis of possible solutions. Decisions to be made in the course of development can thus be evaluated with regard to their consequence for a patient-centric drug design of the intended patient population and can be made accordingly in an open or flexible manner.

The roadmap integrates into the Quality by Design process and follows the principles of the TPP and addresses the regulatory issues arising from the EMA's reflection paper on the pharmaceutical development of medicines for use in the older population [10]. Prioritization defines the critical product attributes and presents the various solution options that can be weighed against each other to best align product development and design with the targeted patient population in terms of usability and acceptance. The roadmap fits into the established development matrix but evolves the TPP around patient characteristics. These highlight and weight important product attributes and the possible courses of action at critical decision points. By considering prioritized patient-centric product design features during development, relevant decisions are made accordingly without negatively impacting development time or regulatory approval. The purpose of the proposed roadmap is to outline a possible path to patient-centric drug design and open it up for discussion. The roadmap is based on input from the various disciplines involved and recognizes that prioritization between disciplines will also need to be negotiated. However, these discussions are part of the roadmap as solutions can and should be developed from them. The roadmap is further intended to address the regulatory expectations e.g., set forward in the recent Reflection Paper on the pharmaceutical development of medicines for use in the older population [10] and to facilitate the regulatory discussion and approval process. Finally, with the proposed framework towards PCDP development we would like to call for a broader discussion and continue to advance the development of evidence-based methods to demonstrate improved treatment outcomes in concerned patient populations through improved pharmaceutical drug product design.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to thank Dr. Martin Bornhöft and the APV for hosting and supporting the PaCeMe consortium. A special thanks to Dr. David Clapham (Independent Pharmaceutical Consultant), Dr. Carsten Timpe (Roche) and Marcel Arndt (Evonik) for their valuable contributions to the discussion and the publication.

References

[1] M.C. Beach, J. Sugarman, Realizing shared decision making in practice, JAMA 322 (9) (2019) 811–812.
[2] K. Notenboom, E. Beers, D.A. Riet-Nales, T.C.G. Egberts, H.G.M. Leufkens, P.A. F. Jansen, M.L. Bouvy, Practical problems with medication use that older people experience: a qualitative study, J. Am. Geriat. Soc. 62 (12) (2014) 2339–2344.
[3] A. Schenk, R. Eckardt-Felmberg, E. Steinhagen-Thiessen, S. Stegemann, Patient behavior in medication management – Findings from a patient usability study that may impact clinical outcome. Br. J. Clin. Pharmacol. (2020) 86, 1958–1968 (10.1111/bcp.13946).
[4] T. Vallet, H. Michelon, M. Orlu, Y. Jani, P. Leglise, S. Laribe-Caget, M. Piccoli, A. Le Fur, F. Liu, F. Ruiz, V. Boudy, Acceptability in the older population: the importance of an appropriate tablet size, Pharmaceutics. 12 (8) (2020) 746, https://doi.org/10.3390/pharmaceutics12080746.
[5] S. Stegemann, R.L. Ternik, G. Onder, M.A. Khan, D.A. Van Riet-Nales, Defining patient centric pharmaceutical drug product design, AAPS J. 18 (5) (2016) 1047–1055.
[6] R. Messina, R. Becker, D.A. van Riet-Nales, S. Stegemann, Results from a preliminary review of scientific evidence for appropriateness of preparations, dosage forms and other product design elements for older adult patients, Int. J. Pharm. 478 (2) (2015) 822–828.
[7] N. Drumond, D.A. van Riet-Nales, F. Karapinar-Çarkit, S. Stegemann, Patients' appropriateness, acceptability, usability and preferences for pharmaceutical preparations: results from a literature review on clinical evidence, Int. J. Pharmaceut. 521 (1-2) (2017) 294–305.
[8] C. Timpe, S. Stegemann, A. Barrett, S. Mujumdar, Challenges and opportunities to include patient centric product design in industrial medicine development to improve therapeutic goals. Br. J. Clin. Pharmacol. (2020) 86, 2020-2027 (10.1111/bcp.14388).
[9] FDA (2009) Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. (https://www.fda.gov/media/77832/download).
[10] EMA (2020) Reflection paper on the pharmaceutical development of medicines for use in the older population (https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-pharmaceutical-development-medicines-use-older-population-first-version_en.pdf).
[11] T.A. Simon, M.S. Khouri, T.D. Kou, A. Gomez-Caminero, Realizing the potential of the patient perspective, Patient. Pref. Adher. 14 (2020) 2001–2007.
[12] T. Severin, S. Corriol-Rohou, C. Christina Bucci-Rechtweg, K. An Haack, How is the pharmaceutical industry structured to optimize pediatric drug development? existing pediatric structure models and propose recommendations for structural enhancement. Therapeut. Innovat. Regulat. Sci. 54 (2020) 1076–1084.
[13] T. Sam, T.B. Ernest, J. Walsh, J.L. Williams, A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – an application for paediatric dosage form selection, Int. J. Pharm. 435 (2) (2012) 115–123.
[14] WHO (2018) Toolkit for research and development of pediatric antiretroviral drugs and formulations. Geneva: World Health Organization. (https://www.who.int/publications/i/item/9789241514361).
[15] FDA (2016) Applying Human Factors and Usability Engineering to Medical Devices. Guidance for Industry and Food and Drug Administration. (https://www.fda.gov/media/80481/download).
[16] M.A. Feufel, G. Rauwolf, F.C. Meier, F. Fatma Karapinar-Çarkit, M. Heibges, Heuristics for designing user-centric drug products: lessons learned from Human Factors and Ergonomics, Brit. J. Clin. Pharmacol. 86 (10) (2020) 1989–1999.
[17] FDA (2017) Plan for Issuance of Patient-Focused Drug Development Guidance. (https://www.fda.gov/media/105979/download).
[18] ICH Reflection paper Proposed ICH Guideline Work to Advance Patient Focused Drug Development. 2021 (https://admin.ich.org/sites/default/files/2021-06/ICH_ReflectionPaper_PFDD_FinalRevisedPostConsultation_2021_0602.pdf.
[19] FDA (2021) FDA Draft Guideline Considerations for the Use of Real-World Data and RealWorld Evidence to Support Regulatory Decision-Making for Drug and Biological Products. https://www.fda.gov/media/154714/download.
[20] EMA Initiation of DARWIN EU® Coordination Centre advances integration of real-world evidence into assessment of medicines in the EU. 2022 (https://www.ema.europa.eu/en/news/initiation-darwin-eur-coordination-centre-advances-integration-real-world-evidence-assessment) accessed March 18, 2022.

[21] J.FM. van Boven, I. Tsiligianni, I. Potočnjak, J. Mihajlović, A.L. Dima, U. Nabergoj Makovec, T. Ágh, P. Kardas, C.M. Ghiciuc, G. Petrova, N. Bitterman, F. Kamberi, J. Culig, B. Wettermark, European network to advance best practices and technology on medication adherence: mission statement, Front. Pharmacol. 12 (2021), 748702.
[22] EMA (2015) Good practice guide on risk minimization and prevention of medication errors. (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guide-risk-minimisation-prevention-medication-errors_en.pdf).
[23] FDA (2016) Safety considerations for product design to minimize medication errors https://www.fda.gov/media/84903/download.
[24] EMA (2018) Reflection paper on physical frailty: instruments for baseline characterization of older populations in clinical trials.
[25] I. Schäfer, E.-C. von Leitner, G. Schön, D. Koller, H. Hansen, T. Kolonko, H. Kaduszkiewicz, K. Wegscheider, G. Glaeske, H. van den Bussche, J.S. Ross, Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions, PLoS ONE 5 (12) (2010), https://doi.org/10.1371/journal.pone.0015941.
[26] A. Nobili, A. Marengoni, M. Tettamanti, F. Salerno, L. Pasina, C. Franchi, A. Iorio, M. Marcucci, S. Corrao, G. Licata, P.M. Mannucci, Association between clusters of diseases and polypharmacy in hospitalized elderly patients: results from the REPOSI study, Eur. J. Int. Med. 22 (6) (2011) 597–602.
[27] S. Stenholm, H. Westerlund, J. Head, M. Hyde, I. Kawachi, J. Pentti, M. Kivimaki, J. Vahtera, Comorbidity and functional trajectories from midlife to old age: the health and retirement study, J. Gerontol. Series A, Biol. Sci. Med. Sci. 70 (3) (2015) 330–336.
[28] D.L. Vetrano, A. Roso-Llorach, S. Fernández, M. Guisado-Clavero, V.C. Violán, G. Onder, L. Fratiglioni, A. Calderón-Larrañaga, A. Marengoni, Twelve-year clinical trajectories of multimorbidity in a population of older adults, Nat. Commun. 11 (2020) 3223.
[29] E. Belissa, T. Vallet, S. Laribe-Caget, et al., Acceptability of oral liquid pharmaceutical products in older adults: palatability and swallowability issues. BMC Geriatr 19 (2019) 344 10.1186/s12877-019-1337-2.
[30] F. Ruiz, A. Keeley, P. Léglise, C. Tuleu, C. Lachuer, J.P. Rwabihama, N. Bachalat, I. Boulaich, F. Abdallah, M. Rabus, A.-C. Ribemont, H. Michelon, A.D. Wojcicki, M. Orlu, T. Vallet, V. Boudy, Sex differences in medicine acceptability: a new factor to be considered in medicine formulation, Pharmaceutics. 11 (8) (2019) 368, https://doi.org/10.3390/pharmaceutics11080368.
[31] D. Baguley, E. Lim, A. Bevan, A. Pallet, S.N. Faust, Prescribing for children – taste and palatability affect adherence to antibiotics: a review, Arch. Disease Childhood 97 (3) (2012) 293–297.
[32] ICH (2009) Pharmaceutical Development ICH Q8 R2.
[33] S. Sendyona, I. Odeyemi, K. Maman, Maman Perceptions and factors affecting pharmaceutical market access: results from a literature review and survey of stakeholders in different settings, J. Market Access Health Pol. 4 (1) (2016) 31660.
[34] J.-L. Wale, S. Thomas, D. Hamerlijnck, R. Hollander, Patients and public are important stakeholders in health technology assessment but the level of involvement is low – a call to action, Res. Involv. Engage. 7 (2021) 1.
[35] M.L. Berger, H. Sox, R.J. Willke, et al., Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making Pharmacoepidemiol Drug Saf. (2017) 26:1033–1039.
[36] M.M. Lowe, D.A. Blaser, L. Cone, S. Arcona, J. Ko, R. Sasane, P. Wicks, Increasing patient involvement in drug development, Value Health. 19 (6) (2016) 869–878.
[37] S. Parsons, B. Starling, C. Mullan-Jensen, S.-G. Tham, K. Warner, K. Wever, What do pharmaceutical industry professionals in Europe believe about involving patients and the public in research and development of medicines? A qualitative interview study, BMJ Open. 6 (1) (2016), https://doi.org/10.1136/bmjopen-2015-008928.
[38] M. Rosbach, J.s., Andersen Patient-experienced burden of treatment in patients with multimorbidity – a systematic review of qualitative data, PLoS ONE 12 (6) (2017), e0179916, https://doi.org/10.1371/journal.pone.0179916.