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Review

Quality by Design: A Suitable Methodology in Industrial Pharmacy for Costa Rican Universities

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Abstract: The aim of this review is to present the Quality by Design (QbD) model as a suitable methodology to perform research in the academic Costa Rican institutions that teach Pharmacy. Pubmed, Science Direct, and Google Scholar databases were screened for original and review papers, as well as short communications published not more than 10 years ago. Publications were screened by title and abstract. Relevant references were used to develop three important themes: The University's Research Model in Costa Rica, QbD Model, and QbD as a Research Methodology for Industrial Pharmacy in the Academy. In this sense, the QbD model is a great methodology for carrying out research projects regarding Pharmaceutical Sciences but especially for Drug Development. Academic research based on this model enables training and developing practical, scientific, and leadership skills in pharmacy students. The generated knowledge can be shared in the classrooms, which represents an ideal environment to communicate their research results and to foster collaborative work between researchers, professors, and students. The participation of all these actors allows a high level of commitment to research work, which benefits the scientific advancement of the university and society. It is important to visualize the student body as potential key actors in the research process, encouraging in them the desire to become trained scientific researchers who want to pursue a career in the academy, giving continuity to it.

Keywords: academy; drug development; industrial pharmacy; pharmaceutical technology; research methodology

1. Introduction

Historically, public universities in Costa Rica have taken the lead in research activities, however, only one of them teaches Pharmacy, which is the University of Costa Rica (UCR). On the other hand, the private educational system has played a role in the knowledge economy (i.e., a university corporate system that focuses on instrumentalism and marketability). As a result, the private university model in Costa Rica is characterized by academic institutions with little research and personnel dedicated to it [1–4]. Specifically, these private institutions that offer the Pharmacy major lack of a research system properly focused on Pharmacy and Pharmaceutical Sciences.

Regarding the previous, every university, either public or private with the Pharmacy major as part of its academic offer has policies created by the International Federation of Pharmacy (FIP) that can be used as tools for the evaluation, review, and improvement of its educational and scientific standards [5]. Currently, the FIP has focused its efforts on supporting research for drug discovery, drug development, pharmaceutical technology, natural products, pharmacokinetics and pharmacodynamics, pharmacology,

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personalized medicine, biotechnology, analytical science and quality control, regulatory affairs, drug metabolism, pharmacoeconomics, pharmacovigilance, among others [6].

A methodology that allows research in some of the aforementioned areas, especially in the ones related to Industrial Pharmacy, is Quality by Design (QbD). The model is based on an adequate understanding of the sources of variability and the processes involved. In addition, it is of great importance all the knowledge about the impact caused by materials and process parameters on the quality profile of the finished product [7,8]. The concept of QbD was initially introduced by the quality expert, Joseph Juran, who in his book "Juran on Quality by Design" described it through a dynamic triad, consisting of Quality Planning, Quality Control, and Quality Improvement [9]. Since then, great advances in the model have been experienced, and its benefits in the academy have been demonstrated by high quality works performed by Yu, et al [10], Sangshetti, et al [11], and Grangeia, et al [12].

Costa Rican universities that teach the Pharmacy major must follow a strategy that systematically guides the development of scientific research in the industrial field. Therefore, this comprehensive review aims to present the QbD model as an opportunity and suitable methodology to perform research in Industrial Pharmacy in the academic Costa Rican institutions. Pubmed, Science Direct, and Google Scholar databases were screened for original and review papers, as well as short communications not older than 10 years. Publications were screened by title and abstract. In addition, institutional repositories from the different universities were reviewed, and valid guidelines from the International Conference on Harmonization (ICH) and the United States Food and Drug Administration (FDA) related to QbD were considered as suitable references due to their relevance on the topic.

To our knowledge, there are no other papers that describe the research system for Industrial Pharmacy in Costa Rican universities, nor present a suitable methodology for promoting feasible and high-quality research in the field.

2. University's Research Model in Costa Rica

Universities along with industry and government research entities are the main actors in national research, development, and innovation systems [13]. Nonetheless, the public academic environment possesses the greatest research freedom within society, and the generated knowledge has a social impact, which according to the philosopher Immanuel Kant, shows a bidirectional behavior, that is, from the world to science, and from science to the world [14].

Research projects from the academy can influence the theory of a certain phenomenon. The term "academy" is used to describe a community composed of students and academics, committed to higher education and research as a fundamental activity in the creation of knowledge [15]. A large majority of high-impact publications are the product of the thesis work of master students and doctoral candidates, affiliated with a specific research group from public universities in order to become trained scientists [16–18]. In this sense, the creation of knowledge must be ethically; always placing the quality of research over quantity, and avoiding any practice that encourages the opposite [19].

In contrast, Costa Rican private universities where Pharmacy majors are taught have not paid special attention to research activities for the discipline as such, thus, they cannot be considered an academy yet. This private system, however, is being replaced by a university model with more complex thinking, which seeks to participate in the national social agenda, as well as taking a leading role in the generation of knowledge as the central axis of the research process. This new model aims to organize research priorities around strategic areas that bring them closer to become an academy [20,21].

The new vision in the Costa Rican private educational system, besides focusing on the search and design of research methodologies, allows the dissemination of scientific knowledge. The participation of their personnel and students in national and international events (e.g., conferences, symposia) and the production of scientific manuscripts

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are of great relevance when evaluating the quality of a certain institution [22,23]. These activities give great support to the research program established by the majors, and at the same time provide prestige to it, to its researchers, and the universities [24].

Likewise, some Costa Rican universities have created open-access journals, which facilitate the publication of research without the financial issue that submitting the manuscripts in a large majority of international journals would represent. This open-access model is also a transparent and affordable means of knowledge. In addition, it allows the development of collaborative inter-institutional networks, expanding the ideals of the universities [25–27].

Nonetheless, despite the great progress of the new model in the private universities, and the consolidated system from the UCR, the establishment of scientific work in both cases is based on the institutional development plan. This can promote the figure of the "slow professor" (i.e., an individual with few research tasks), either due to little affinity with the research topics or due to poor suitability to participate in them [2,28]. Similarly, it is important to highlight that not every university is capable of conducting research, or at least, not at the same level, as well as not all teaching personnel can be included in the category of academic. In many cases, their research possibilities are reduced due to lack of resources, economic and political pressures, or lack of time due to overload in teaching [29,30].

In this sense, the adoption of methodological guidelines or research models in Costa Rican universities that teach Pharmacy may improve professor and student integration into research activities. This will not only provide great academic training tools for both, but represent an integral indicator of credibility, compliance, efficiency, and competitiveness of the major and the research system [31–33]. The relevance of such parameters also lies in their use as an internal mechanism of evaluation in the control and budgetary prioritization of research [34].

3. Quality by Design Model

The ICH guideline Q8 (R2) defines the model as a systematic approach for pharmaceutical development, which begins with predefined objectives and places special emphasis on understanding the product, the process, and its controls [35]. Also, the U.S. FDA considers that quality in a Drug Quality System cannot be evaluated or determined in a product, but must be introduced and promoted from its design [36].

Historically, pharmaceutical companies have determined the quality of their products through "Quality by Test" (i.e., to evaluate the quality of the finished product without prior controls) [37]. Nevertheless, the demand of producing medicines of the highest quality and improve competitiveness within the pharmaceutical, industrial and health fields, forced many institutions to adopt new measures to guarantee the quality of their products. The adoption of the QbD is of great relevance as the predictions made by the model are useful in the design of experimental investigations, in time management, and the use of resources throughout the process [38].

The QbD model's lifecycle (Figure 1) is directly related to the different constituent elements such as the Target Product Profile (TPP), Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), Critical Process Parameters (CPP), and Design Space [39–41]. In addition, Quality Risk Management (QRM), Design of Experiments (DoE), and Process Analytical Technologies (PAT) are used as tools for guaranteeing the quality of the products being developed [42].

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Figure 1. QbD lifecycle. Reprinted with permission from Fornaguera. et al. *Journal of Personalized Medicine*, 7(4). Copyright (2017) MDPI [39].

3.1. Quality by Design Approach for Industrial Pharmacy in the Academy

QbD can be used in any section of the pharmaceutical development process; from the preformulation stages to manufacturing on an industrial scale (Figure 2).

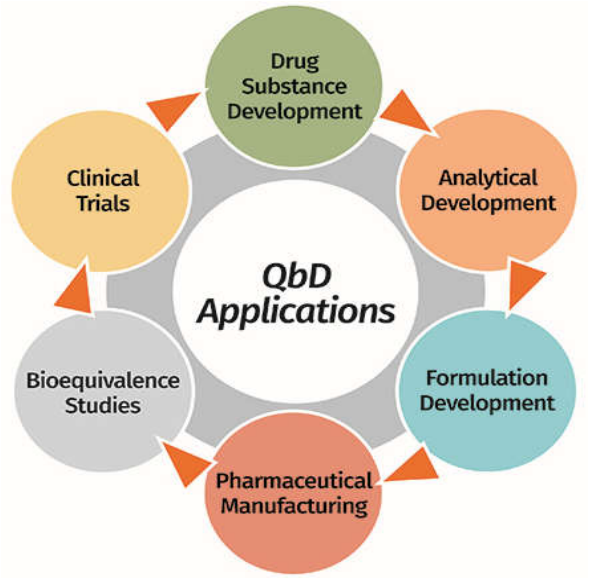

Figure 2. Potential applications of QbD approach in diverse stages of product development lifecycle. Reprinted with permission from Rahman, M. et al. *European Pharmaceutical Review*, 22(1). Copyright (2017) Rusell Publishing Limited [38].

Furthermore, QbD meets the current demand for research processes as it is considered cost-effective in project development. This is possible thanks to using the different tools such as DoE, QRM, and PAT, which allow better understanding regarding the materials and processes involved [43–45]. For instance, an adequate QRM can provide products of the highest quality and safety, thus becoming an excellent resource for the identification and control of possible quality problems during research [46]. Also, this tool allows better decision-making when a problem related to quality arises, making their justification easier, and allowing greater confidence in the research group [47].

According to the ICH Q9 guideline on Quality Risk Management; CQAs, CMAs, and CPPs can be identified thanks to adequate risk management as it detects those

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problems in the development of the product and their associated risks [48,49]. In general, nine tools are recommended for risk management. However, among the most widely used are the Ishikawa's Fishbone Diagram (Figure 3) and the Failure Mode and Effects Analysis (FMEA), which are thoroughly explained to the students in Drug Analysis courses [48,50,51].

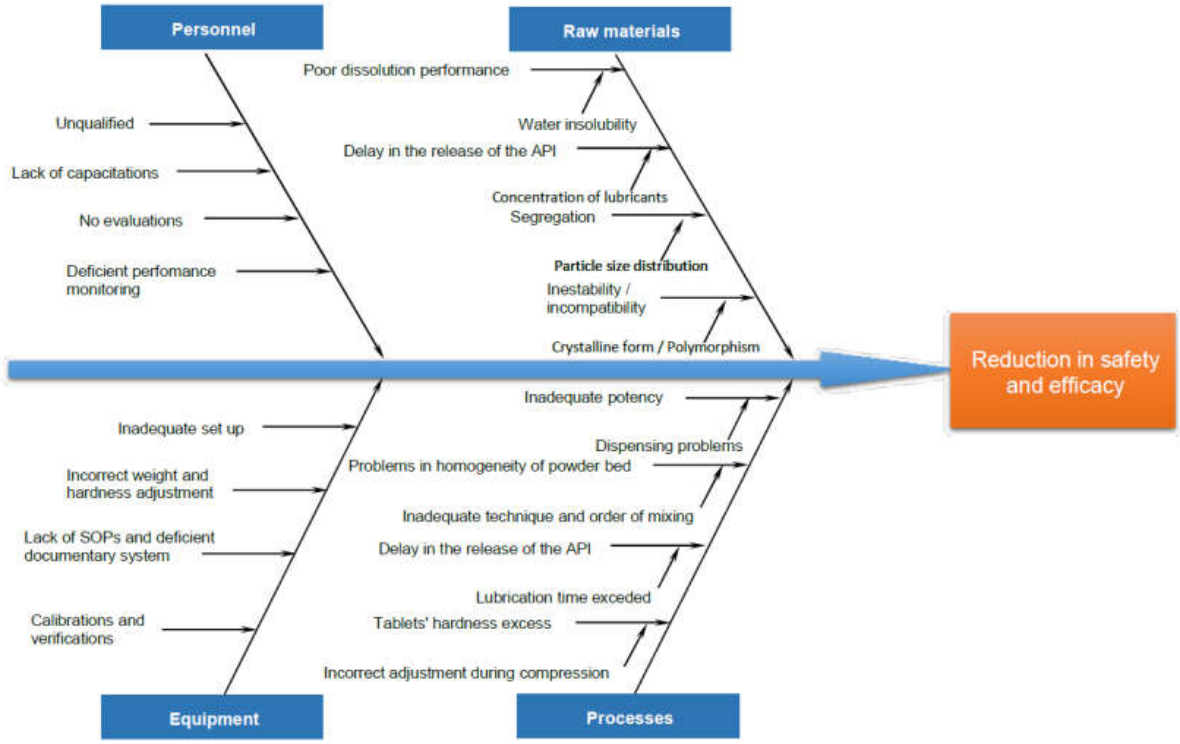

Figure 3. Example of an Ishikawa diagram for the risk management in drug development carried out in the academy. Reprinted with permission from Castillo, L. et al. *Drug Development and Industrial Pharmacy*, 45(10). Copyright (2019) Taylor & Francis [43].

In addition, DoE allows researchers to use their knowledge regarding the product and/or process instead of merely applying the commonly known "trial and error" [52,53]. DoEs are used to organize, conduct and interpret results of experiments in an efficient way, guaranteeing the collection of the greatest possible amount of useful information through the execution of a small number of tests. The main objective of an experimental study (Figure 4) is to find the relationship between independent variables (i.e., factors) and dependent variables (i.e., responses) that affect a certain process and its final product. An adequate DoE can help identify optimal conditions, CMAs, CPPs, and their impact on CQAs [54].

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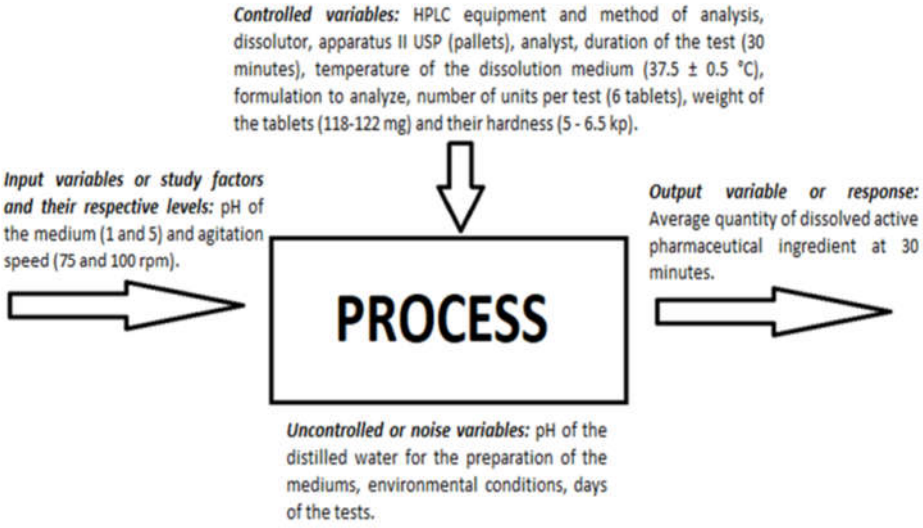

Figure 4. Example of a Design of Experiments carried out in the academy for assessing the performance of solid formulations in the dissolution test. Adapted with permission from Castillo, L. et al. *Journal of Drug Delivery and Therapeutics*, 9(1-s). Copyright (2019) JDDT [55].

In Pharmaceutical Technology, DoE represents an excellent tool that allows to systematically manipulate factors according to a design prior to the establishment of specifications [56,57].The independent variables are usually formulation factors or test conditions, while the dependent variables are product properties or parameters that indicate the performance of the process [58]. However, it is important to note that according to QbD, risk management has priority over the DoE [50,51,59]. Moreover QbD have gained importance in the natural products development not only for their high demand but also due to the intrinsic variability that represents working with natural raw materials [60].

For example, our group evaluated the impact of sample's mass and temperature on the moisture content in *Camelia sinensis*, *Cassia fistula*, *Chamaemelum nobile*, and *Lippia alba* with a gravimetric method developed through a 3^2 full factorial design. A response optimizer was performed to define the test conditions that allow obtaining a response according to a target value from a certified method (Figure 5). The designed model was able to explain the response variability for all samples based on the R^2 (adj) [61].

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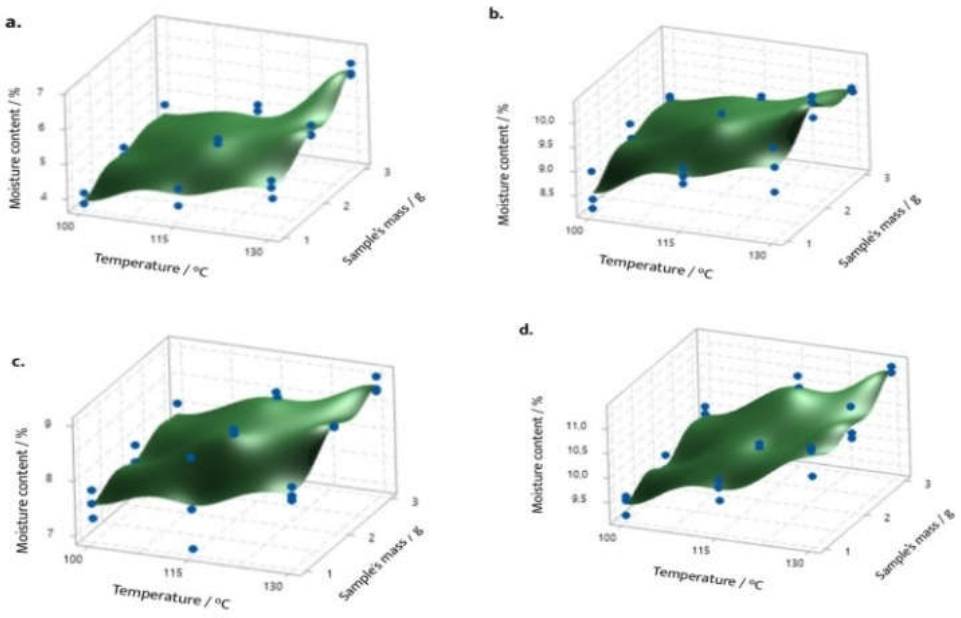

Figure 5. Example of a 3^2 full factorial design for evaluating the moisture content (%) in natural raw materials as a function of the balance's temperature (°C) and sample's mass (g), carried out in the academy. Reprinted with permission from Castillo, L. et al. *Borneo Journal of Pharmacy*, 3(1). Copyright (2020) Institute for Research and Community Services Universitas Muhammadiyah Palangkaraya [61].

Furthermore, in previous research from our group, we have employed QbD for the development of different pharmaceutical formulations. In 2017, as part of the main author's undergraduate thesis at UCR, and in collaboration with the National Laboratory of Nanotechnology (LANOTEC), we worked on the formulation of immediate release Rupatadine fumarate 10 mg tablets by direct compression. The research involved identifying the TPP in terms of the target population, administration route, posology, potency, composition, and desired performance regarding drug release and physicochemical stability compared to the commercialized reference product, Rupax®. Also, we employed QRM for identifying the CMAs and CPPs, which allowed us to define the CQAs, a safe process, and formulations with no physicochemical incompatibilities. Spectroscopic and thermal analysis techniques were employed to assess the physicochemical compatibility and the suitability of the manufacturing process [43]. In addition, DoE was used to evaluate the different formulation prototypes in the dissolution test [55]. Further on, knowledge and technological transference to a local pharmaceutical industry resulted in the commercialization of the drug product.

Following that, two other investigations involving students at UCR applied a QbD approach for the development of pharmaceutical formulations. Firstly, Cantillo et al. designed the film coating process of tablets at a pilot-scale in a local pharmaceutical industry. In this case, the group employed a full factorial design to evaluate the impact of the CMAs and CPPs on the weigh increase and appearance of defects. As a conclusion, they reported that the main effects were caused by the drum's rotational speed, core bed temperature, and the feed rate of the coating solution [62].

Likewise, Hanley et al. developed an oral suspension with an anti-ulcer and gastroprotective effect. Remarkably, they reported the thickening agents' concentration as a CMA, and the pretreatment of the drug using a wetting agent as a CPP. Once they identified the previous, a DoE was designed and executed in order to determine the effect of these on the suspension's viscosity, which was defined as a CQA. The results revealed that only one of the prototype formulations was suitable for development. In this case, the technological transference was also done to another local pharmaceutical industry that is in process of registering the product and commercializing it in the country [63].

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At a private university, Universidad Internacional de Las Américas (UIA), Ramírez et al. developed a sustained release tablet formulation of a non-steroidal and anti-inflammatory drug (NSAID) for treating chronic pain. In this approach, the research group sought to fulfill the CQAs established by the United States Pharmacopoeia (USP) and the British Pharmacopoeia (BP) for the product. The QRM they performed was based on Ishikawa's diagram, FMEA, and the creation of an adequate strategy for risk control and mitigation [64]. Moreover, there are currently other research projects on the way to use this methodology at UIA, such as the development of a self-emulsifying drug delivery system (SEDDS) for improving itraconazole oral bioavailability.

More recently, collaborative work between the Faculty of Pharmacy of UCR, LANOTEC, Laboratory of Biopharmacy and Pharmacokinetics (LABIOFAR) of UCR, and the Laboratory of Polymers of the National University (POLIUNA) allowed the development of a topical chitosan-based thermo-responsive scaffold loaded with Dexketoprofen trometamol (DKT). In this case, the TPP was defined as a function of the intended application for chronic and non-healing wounds caused by different diseases (e.g., diabetes). The scaffold was required to provide controlled release of DKT for 24 h use; having a small release rate at or below the normothermia, and taking advantage of the local hyperthermia presented in wounds for inducing a sol-gel transition in the polymer's structure, and thus, increase the drug's release rate. This QbD approach contributed to avoiding an excessive DKT loading in the polymer matrix as most conventional drug systems do to achieve a concentration gradient for Fickian diffusion as the main release mechanism [65].

As can be seen in Table 1, in the rest of the world the QbD methodology has been extended to different areas of the pharmaceutical discipline, such as: Excipient development, analytical methods, dissolution tests, stability studies, bioequivalence studies, clinical trials, and others [66–69]. All the previously mentioned and described examples have allowed advances in the academy, pharmaceutical development, and the regulatory environment, moving from empirical processes to research based on science and risk control [70,71]. Therefore, the model application allows obtaining tangible results (e.g., pharmaceutical products) of the highest and reproducible quality, which can be easily predicted or anticipated [72].

Moreover, the implementation of this approach generates an increase in students' practical and scientific skills, as well as confidence in the research group, customers, the industrial sector, and health authorities about the quality of the research, products, and knowledge that are being developed and created in the academy [10,11,73].

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Table 1. Quality by Design applications in Pharmacy and Pharmaceutical Sciences developed by the Academy.

Application	Purpose	Ref.
Microcrystalline cellulose for direct compression	Excipient development	[74]
Cyclosporine ophthalmic emulsion	Bioequivalence studies	[75]
Validation of a bioanalytical method for quantification fluoxetine in human plasma		[76]
Telmisartan potassium tablets		[77]
Development of microsponges by double emulsion-solvent-diffusion technique	Drug delivery	[78]
Development of long-acting injectable PLGA/PLA-based microspheres		[79]
Determination of critical quality attributes for monoclonal antibodies	Biotechnological drug analysis	[80]
Development of a reversed-phase liquid chromatography method for protein quantification		[81]
Formulation of a bilayer combined tablet manufactured via high-shear wet granulation	Drug development	[82]
Ultraperformance liquid chromatrography method for quantification of teriflunomide	Dissolution and stability testing	[83]
Development of severe fever with thrombocytopenia syndrome vaccine	Biologic drug development	[84]
Development of resveratrol loaded ethosomal hydrogel	Dermal delivery system	[85]
Determination of partially pre-gelatinized starch effect on rapid orally disintegrating tablets	Identification of CQA	[86]
Development of green HPLC method for artesunate and amodiaquine impurities	Quality control	[87]
Liquid chromatography method to evaluate cannabinoids content in cannabis olive oil extracts	Quality control of natural products	[88]
Cell culture in bioreactor for the production of foot-and-mouth veterinary vaccine	Biopharmaceutical process development	[89]
Development of electrospinning coatings for metal microneedles	Process optimization	[90]

5. Conclusions

The change in the educational paradigm and the organizational structure of Costa Rican universities has allowed some Pharmacy Schools from these institutions to stand out in terms of scientific research and to seek the consolidation of groups of experts in the industrial field of the discipline. The implementation of research methodologies is the reason for the experienced progress in the last years. Therefore, the QbD model is a great methodology for carrying out research projects regarding Pharmaceutical Sciences. Academic research based on this model enables training and developing practical, scientific, and leadership skills in pharmacy students. In addition, the generated knowledge can be shared in the classrooms, which represents an ideal environment for the professors to communicate their research results and to foster collaborative work between researchers, professors, and students. The participation of all these actors allows a high level of commitment to research work, which benefits the scientific advancement of the university and society. It is important to visualize the student body as potential key actors in the research process, encouraging in them the desire to become trained scientific researchers who want to pursue a career in the academy, giving continuity to it.

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References

1. Aithal, P.S.; Kumar, P.M. *Opportunities and Challenges for Private Universities in India*; Social Science Research Network: Rochester, NY, 2016;
2. Berg, M.; Seeber, B.K. *The Slow Professor: Challenging the Culture of Speed in the Academy*; University of Toronto Press, 2016; ISBN 978-1-4426-6310-7.
3. Morales-López, Y. Costa Rica: The Preparation of Mathematics Teachers. In *Mathematics Teacher Preparation in Central America and the Caribbean: The Cases of Colombia, Costa Rica, the Dominican Republic and Venezuela*; Ruiz, A., Ed.; SpringerBriefs in Education; Springer International Publishing: Cham, 2017; pp. 39–56 ISBN 978-3-319-44177-1.
4. Morales, R.A. Recibido: enero/2016 Publicado: mayo/2016. **2016**, 12.
5. Law, M.; Bader, L.; Uzman, N.; Williams, A.; Bates, I. The FIP Nanjing Statements: Shaping Global Pharmacy and Pharmaceutical Sciences Education. *Research in Social and Administrative Pharmacy* **2019**, *15*, 1472–1475, doi:10.1016/j.sapharm.2019.03.013.
6. Tucker, G.; DeSilva, B.; Dressman, J.; Ito, M.; Kumamoto, T.; Mager, D.; Mahler, H.-C.; Maitland-van der Zee, A.H.; Pauletti, G.M.; Sasaki, H.; et al. Current Challenges and Potential Opportunities for the Pharmaceutical Sciences to Make Global Impact: An FIP Perspective. *Journal of Pharmaceutical Sciences* **2016**, *105*, 2489–2497, doi:10.1016/j.xphs.2015.12.001.
7. García Aponte, O.F.; Vallejo Díaz, B.M.; Mora Huertas, C.E. La calidad desde el diseño: principios y oportunidades para la industria farmacéutica. *Estudios Gerenciales* **2015**, *31*, 68–78, doi:10.1016/j.estger.2014.09.005.
8. Pramod, K.; Tahir, M.A.; Charoo, N.A.; Ansari, S.H.; Ali, J. Pharmaceutical Product Development: A Quality by Design Approach. *Int J Pharm Investig* **2016**, *6*, 129–138, doi:10.4103/2230-973X.187350.
9. Juran, J. (1992). *Juran on quality by design*. New York: The Free Press.
10. Yu, L.X.; Amidon, G.; Khan, M.A.; Hoag, S.W.; Polli, J.; Raju, G.K.; Woodcock, J. Understanding Pharmaceutical Quality by Design. *AAPS J* **2014**, *16*, 771–783, doi:10.1208/s12248-014-9598-3.
11. Sangshetti, J.N.; Deshpande, M.; Zaheer, Z.; Shinde, D.B.; Arote, R. Quality by Design Approach: Regulatory Need. *Arabian Journal of Chemistry* **2017**, *10*, S3412–S3425, doi:10.1016/j.arabjc.2014.01.025.
12. Grangeia, H.B.; Silva, C.; Simões, S.P.; Reis, M.S. Quality by Design in Pharmaceutical Manufacturing: A Systematic Review of Current Status, Challenges and Future Perspectives. *Eur J Pharm Biopharm* **2020**, *147*, 19–37, doi:10.1016/j.ejpb.2019.12.007.
13. Bentley, P.J.; Gulbrandsen, M.; Kyvik, S. The Relationship between Basic and Applied Research in Universities. *High Educ* **2015**, *70*, 689–709, doi:10.1007/s10734-015-9861-2.
14. Haleem, A.; Javaid, M.; Vaishya, R.; Deshmukh, S.G. Areas of Academic Research with the Impact of COVID-19. *The American Journal of Emergency Medicine* **2020**, *38*, 1524–1526, doi:10.1016/j.ajem.2020.04.022.
15. Naidu, P.; Derani, N.E.S. A Comparative Study on Quality of Education Received by Students of Private Universities versus Public Universities. *Procedia Economics and Finance* **2016**, *35*, 659–666, doi:10.1016/S2212-5671(16)00081-2.
16. Chang, M. *Principles of Scientific Methods*; Chapman and Hall/CRC, 2016; ISBN 978-0-429-17190-1.
17. Pagliaro, M. Enhancing the Use of E-Mail in Scientific Research and in the Academy. *Heliyon* **2020**, *6*, e03087, doi:10.1016/j.heliyon.2019.e03087.
18. Wilkins, S.; Neri, S.; Lean, J. The Role of Theory in the Business/Management PhD: How Students May Use Theory to Make an Original Contribution to Knowledge. *The International Journal of Management Education* **2019**, *17*, 100316, doi:10.1016/j.ijme.2019.100316.
19. Lubowitz, J.H.; Brand, J.C.; Rossi, M.J. Medical Device and Pharmaceutical Industry Employees as Medical Research Publication Authors. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* **2018**, *34*, 2745–2747, doi:10.1016/j.arthro.2018.05.008.

20. Egri, N.; Ortiz de Landazuri, I.; San Bartolomé, C.; Ortega, J.R.; Español-Rego, M.; Juan, M. CART Manufacturing Process and Reasons for Academy-Pharma Collaboration. *Immunology Letters* **2020**, *217*, 39–48, doi:10.1016/j.imlet.2019.10.014.
21. Salau, O.; Osibanjo, A.; Adeniji, A.; Oludayo, O.; Falola, H.; Igbinoba, E.; Ogueyungbo, O. Data Regarding Talent Management Practices and Innovation Performance of Academic Staff in a Technology-Driven Private University. *Data in Brief* **2018**, *19*, 1040–1045, doi:10.1016/j.dib.2018.05.081.
22. Stewart, D.; Klein, S. The Use of Theory in Research. *Int J Clin Pharm* **2016**, *38*, 615–619, doi:10.1007/s11096-015-0216-y.
23. Ware, M.; Mabe, M. The STM Report: An Overview of Scientific and Scholarly Journal Publishing. *Copyright, Fair Use, Scholarly Communication, etc.* **2015**.
24. Pineda, M.A. Cómo comunicar la investigación desde la academia. *Revista Ciencia y Tecnología* **2019**, 13–15, doi:10.5377/rct.v0i24.7873.
25. García-Peñalvo, F.J. Publishing in Open Access. **2017**.
26. Tapasco, O.A.; Giraldo, J.A. Estudio Comparativo Sobre Percepción y Uso de Las TIC Entre Profesores de Universidades Públicas y Privadas. *Formación universitaria* **2017**, *10*, 03–12, doi:10.4067/S0718-50062017000200002.
27. Vicente-Saez, R.; Gustafsson, R.; Van den Brande, L. The Dawn of an Open Exploration Era: Emergent Principles and Practices of Open Science and Innovation of University Research Teams in a Digital World. *Technological Forecasting and Social Change* **2020**, *156*, 120037, doi:10.1016/j.techfore.2020.120037.
28. Ahluwalia, A.K.; Preet, K. The Influence of Organizational Commitment on Work Motivation: A Comparative Study of State and Private University Teachers. *IUP Journal of Organizational Behavior* **2017**, *16*, 55–69.
29. Asaduzzaman, M.; Hossain, M.; Rahman, M. Service Quality and Student Satisfaction: A Case Study on Private Universities in Bangladesh. *International Journal of Economics, Finance and Management Sciences* **2014**, *1*, 128, doi:10.11648/j.ijefm.20130103.11.
30. Xiong, X.; Yang, G.; Guan, Z. Estimating the Multi-Period Efficiency of High-Tech Research Institutes of the Chinese Academy of Sciences: A Dynamic Slacks-Based Measure. *Socio-Economic Planning Sciences* **2020**, *71*, 100855, doi:10.1016/j.seps.2020.100855.
31. Gayá, P.; Brydon-Miller, M. Carpe the Academy: Dismantling Higher Education and Prefiguring Critical Utopias through Action Research. *Futures* **2017**, *94*, 34–44, doi:10.1016/j.futures.2016.10.005.
32. Gómez Vargas, M.; Galeano Higuita, C.; Jaramillo Muñoz, D.A. El estado del arte: una metodología de investigación. *rev.colomb.cienc.soc* **2015**, *6*, 423, doi:10.21501/22161201.1469.
33. Stein, K. Propelling the Profession with Outcomes and Evidence: Building a Robust Research Agenda at the Academy. *Journal of the Academy of Nutrition and Dietetics* **2016**, *116*, 1014–1030, doi:10.1016/j.jand.2016.02.018.
34. Koshkina, I.; Sharamko, M. Economic Security and Internal Control of the Academic Research Projects. *Procedia - Social and Behavioral Sciences* **2015**, *214*, 858–865, doi:10.1016/j.sbspro.2015.11.741.
35. International Conference on Harmonization. (2009). ICH Q8 (R2) Pharmaceutical development. *European Medicines Agency*. Retrieved from https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development.
36. Food and Drug Administration Guidance for Industry. (2006). Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations. U.S. Department of Health and Human Services. Text Retrieved from https://www.fda.gov/media/71023/download.
37. Pallagi, E.; Ambrus, R.; Szabó-Révész, P.; Csóka, I. Adaptation of the Quality by Design Concept in Early Pharmaceutical Development of an Intranasal Nanosized Formulation. *Int J Pharm* **2015**, *491*, 384–392, doi:10.1016/j.ijpharm.2015.06.018.
38. Rahman, M.; Beg, S.;Panda, S.S. Pharmaceutical QbD: Omnipresence in the Product Development Lifecycle. *European Pharmaceutical Review* **2017**, *22*, 58–64.

39. Fornaguera, C.; García-Celma, M.J. Personalized Nanomedicine: A Revolution at the Nanoscale. *Journal of Personalized Medicine* **2017**, *7*, 12, doi:10.3390/jpm7040012.
40. Faulhammer, E.; Fink, M.; Llusa, M.; Lawrence, S.M.; Biserni, S.; Calzolari, V.; Khinast, J.G. Low-Dose Capsule Filling of Inhalation Products: Critical Material Attributes and Process Parameters. *International Journal of Pharmaceutics* **2014**, *473*, 617–626, doi:10.1016/j.ijpharm.2014.07.050.
41. Manzon, D.; Claeys-Bruno, M.; Declomesnil, S.; Carité, C.; Sergent, M. Quality by Design: Comparison of Design Space Construction Methods in the Case of Design of Experiments. *Chemometrics and Intelligent Laboratory Systems* **2020**, *200*, 104002, doi:10.1016/j.chemolab.2020.104002.
42. Deepika, P.; Manisha, S.; Parijat, P.; Swagat, T.; Harish, D. Implementation of Quality by Design: A Review. *Applied Clinical Research, Clinical Trials and Regulatory Affairs (Discontinued)* **2019**, *6*, 99–111.
43. Castillo, L., et al. Development of Immediate Release Rupatadine Fumarate 10 Mg Tablets: A Quality by Design (QbD) Approach. *Drug Development and Industrial Pharmacy* **2019**, *45*, 1674–1681, doi:10.1080/03639045.2019.1652637.
44. Mishra, V.; Thakur, S.; Patil, A.; Shukla, A. Quality by Design (QbD) Approaches in Current Pharmaceutical Set-Up. *Expert Opin Drug Deliv* **2018**, *15*, 737–758, doi:10.1080/17425247.2018.1504768.
45. Singh, G. Chapter 5 - Target Product Profile and Clinical Development Plan. In *Pharmaceutical Medicine and Translational Clinical Research*; Vohora, D., Singh, G., Eds.; Academic Press: Boston, 2018; pp. 65–80 ISBN 978-0-12-802103-3.
46. Kumar, N.; Jha, A. Quality Risk Management during Pharmaceutical 'Good Distribution Practices' – A Plausible Solution. *Bulletin of Faculty of Pharmacy, Cairo University* **2018**, *56*, 18–25, doi:10.1016/j.bfopcu.2017.12.002.
47. Westgard, J.O.; Westgard, S.A. Six Sigma Quality Management System and Design of Risk-Based Statistical Quality Control. *Clinics in Laboratory Medicine* **2017**, *37*, 85–96, doi:10.1016/j.cll.2016.09.008.
48. Chen, J.; Nichols, B.L.B.; Norris, A.M.; Frazier, C.E.; Edgar, K.J. All-Polysaccharide, Self-Healing Injectable Hydrogels Based on Chitosan and Oxidized Hydroxypropyl Polysaccharides. *Biomacromolecules* **2020**, *21*, 4261–4272, doi:10.1021/acs.biomac.0c01046.
49. Stocker, E.; Becker, K.; Hate, S.; Hohl, R.; Schiemenz, W.; Sacher, S.; Zimmer, A.; Salar-Behzadi, S. Application of ICH Q9 Quality Risk Management Tools for Advanced Development of Hot Melt Coated Multiparticulate Systems. *Journal of Pharmaceutical Sciences* **2017**, *106*, 278–290, doi:10.1016/j.xphs.2016.09.025.
50. Coccia, M. *The Fishbone Diagram to Identify, Systematize and Analyze the Sources of General Purpose Technologies*; Social Science Research Network: Rochester, NY, 2018;
51. Paciarotti, C.; Mazzuto, G.; D'Ettorre, D. A Revised FMEA Application to the Quality Control Management. *International Journal of Quality & Reliability Management* **2014**, *31*, 788–810, doi:10.1108/IJQRM-02-2013-0028.
52. He, Z.; Zhou, P.; Zhang, M.; Goh, T.N. A Review of Analysis of Dynamic Response in Design of Experiments. *Quality and Reliability Engineering International* **2015**, *31*, 535–542, doi:https://doi.org/10.1002/qre.1627.
53. N Politis, S.; Colombo, P.; Colombo, G.; M Rekkas, D. Design of Experiments (DoE) in Pharmaceutical Development. *Drug Dev Ind Pharm* **2017**, *43*, 889–901, doi:10.1080/03639045.2017.1291672.
54. Paulo, F.; Santos, L. Design of Experiments for Microencapsulation Applications: A Review. *Materials Science and Engineering: C* **2017**, *77*, 1327–1340, doi:10.1016/j.msec.2017.03.219.
55. Castillo, et al. Design of Experiments for the Establishment of the Dissolution Test Conditions of Rupatadine Fumarate 10 Mg Tablets. *Journal of Drug Delivery and Therapeutics* **2019**, *9*, 331–336, doi:10.22270/jddt.v9i1-s.2359.
56. Fukuda, I.M.; Pinto, C.F.F.; Moreira, C. dos S.; Saviano, A.M.; Lourenço, F.R. Design of Experiments (DoE) Applied to Pharmaceutical and Analytical Quality by Design (QbD). *Braz. J. Pharm. Sci.* **2018**, *54*, doi:10.1590/s2175-97902018000001006.
57. Hasnain, M.S.; Ahmed, S.A.; Khatoon, A.; Afzal, M.; Ansari, M.T.; Khatoon, S.; Tabish, M.; Al-Marshad, F.M.; Nayak, A.K. Chapter 4 - Pharmaceutical Product Development: A Quality by Design (QbD) Approach. In *Advances and Challenges in*

Pharmaceutical Technology; Nayak, A.K., Pal, K., Banerjee, I., Maji, S., Nanda, U., Eds.; Academic Press, 2021; pp. 131–146 ISBN 978-0-12-820043-8.

58. Dhoot, A.S.; Fernandes, G.J.; Naha, A.; Rathnanand, M.; Kumar, L. Design of Experiments in Pharmaceutical Development. *Pharm Chem J* **2019**, *53*, 730–735, doi:10.1007/s11094-019-02070-4.
59. Prajapati, P., Patel, H., & Shah, S. (2020). Quality risk assessment and DoE-based analytical quality by design approach to stability-indicating assay method for acidic degradation kinetic study of apremilast. *Journal of Planar Chromatography*, 33, 231-244.
60. Rodino, S.; Butu, M. 3 - Herbal Extracts—New Trends in Functional and Medicinal Beverages. In *Functional and Medicinal Beverages*; Grumezescu, A.M., Holban, A.M., Eds.; Academic Press, 2019; pp. 73–108 ISBN 978-0-12-816397-9.
61. Castillo, L.; Baltodano, E.; Ramírez, N.; Vargas, R.; Hanley, G. Design of Experiments Assessment for the Determination of Moisture Content in Five Herbal Raw Materials Contained in Tea Products. *Borneo Journal of Pharmacy* **2020**, *3*, 22–35, doi:10.33084/bjop.v3i1.1236.
62. Cantillo, G. Diseño del proceso de recubrimiento pelicular de tabletas a escala piloto mediante la aplicación del modelo de Calidad por Diseño en el departamento de Investigación y Desarrollo en Laboratorios Infarma LTDA. Informe Final de Práctica Dirigida. Facultad de Farmacia. Universidad de Costa Rica. Julio, 2018.
63. Hanley, G. Desarrollo de una suspensión oral con efecto anti-ulceroso y protector gástrico mediante el modelo de Calidad por Diseño en Laboratorios Raven S.A. Informe Final de Práctica Dirigida. Facultad de Farmacia. Universidad de Costa Rica. Julio, 2021.
64. Ramírez, J. Preformulación de un medicamento de liberación prolongada mediante el enfoque de Calidad por Diseño en Laboratorios Medigray durante el segundo y tercer cuatrimestre 2021. Tesis Final de Graduación. Facultad de Farmacia. Universidad Internacional de Las Américas. Agosto, 2021.
65. Castillo-Henríquez, L., et al. Topical Chitosan-Based Thermo-Responsive Scaffold Provides Dexketoprofen Trometamol Controlled Release for 24 h Use. *Pharmaceutics* **2021**, *13*, 2100, doi:10.3390/pharmaceutics13122100.
66. Butreddy, A.; Bandari, S.; Repka, M.A. Quality-by-Design in Hot Melt Extrusion Based Amorphous Solid Dispersions: An Industrial Perspective on Product Development. *European Journal of Pharmaceutical Sciences* **2021**, *158*, 105655, doi:10.1016/j.ejps.2020.105655.
67. Gurumukhi, V.C.; Bari, S.B. Fabrication of Efavirenz Loaded Nano-Formulation Using Quality by Design (QbD) Based Approach: Exploring Characterizations and in Vivo Safety. *Journal of Drug Delivery Science and Technology* **2020**, *56*, 101545, doi:10.1016/j.jddst.2020.101545.
68. Simões, M.F.; Silva, G.; Pinto, A.C.; Fonseca, M.; Silva, N.E.; Pinto, R.M.A.; Simões, S. Artificial Neural Networks Applied to Quality-by-Design: From Formulation Development to Clinical Outcome. *European Journal of Pharmaceutics and Biopharmaceutics* **2020**, *152*, 282–295, doi:10.1016/j.ejpb.2020.05.012.
69. Yekpe, K.; Abatzoglou, N.; Bataille, B.; Gosselin, R.; Sharkawi, T.; Simard, J.-S.; Cournoyer, A. Developing a Quality by Design Approach to Model Tablet Dissolution Testing: An Industrial Case Study. *Pharmaceutical Development and Technology* **2018**, *23*, 646–654, doi:10.1080/10837450.2017.1392566.
70. Patwardhan, D., Amrutkar, S., Kotwal, T., & Wagh, P. (2017). Application of Quality by Design to Different Aspects of Pharmaceutical Technologies. *International Journal of Pharmaceutical Sciences and Research*, 5, 3649-3662.
71. Peraman, R.; Bhadraya, K.; Padmanabha Reddy, Y. Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analytics. *International Journal of Analytical Chemistry* **2015**, *2015*, e868727, doi:10.1155/2015/868727.
72. Bai, G.; Chen, Z.; Raines, K.; Chen, H.; Dave, K.; Lin, H.-P.; Zolnik, B.S. Assessment of Applications of Design of Experiments in Pharmaceutical Development for Oral Solid Dosage Forms. *J Pharm Innov* **2020**, *15*, 547–555, doi:10.1007/s12247-019-09400-9.

73. Jagan, B.G.V.S.; Mahapatra, A.K.; Murthy, N.P.; Patra, R.K. Quality by Design (QbD): Principles, Underlying Concepts and Regulatory Prospects. *Thai Journal of Pharmaceutical Sciences (TJPS)* **2021**, *45*.
74. Thoorens, G.; Krier, F.; Leclercq, B.; Carlin, B.; Evrard, B. Microcrystalline Cellulose, a Direct Compression Binder in a Quality by Design Environment—A Review. *International Journal of Pharmaceutics* **2014**, *473*, 64–72, doi:10.1016/j.ijpharm.2014.06.055.
75. Rahman, Z.; Xu, X.; Katragadda, U.; Krishnaiah, Y.S.R.; Yu, L.; Khan, M.A. Quality by Design Approach for Understanding the Critical Quality Attributes of Cyclosporine Ophthalmic Emulsion. *Mol Pharm* **2014**, *11*, 787–799, doi:10.1021/mp400484g.
76. Hasnain, M.S.; Siddiqui, S.; Rao, S.; Mohanty, P.; Ara, T.J.; Beg, S. QbD-Driven Development and Validation of a Bioanalytical LC-MS Method for Quantification of Fluoxetine in Human Plasma. *J Chromatogr Sci* **2016**, *54*, 736–743, doi:10.1093/chromsci/bmv248.
77. Oh, G.-H.; Park, J.-H.; Shin, H.-W.; Kim, J.-E.; Park, Y.-J. Quality-by-Design Approach for the Development of Telmisartan Potassium Tablets. *Drug Dev Ind Pharm* **2018**, *44*, 837–848, doi:10.1080/03639045.2017.1414233.
78. Simonoska Crcarevska, M.; Dimitrovska, A.; Sibinovska, N.; Mladenovska, K.; Slavevska Raicki, R.; Glavas Dodov, M. Implementation of Quality by Design Principles in the Development of Microsponges as Drug Delivery Carriers: Identification and Optimization of Critical Factors Using Multivariate Statistical Analyses and Design of Experiments Studies. *International Journal of Pharmaceutics* **2015**, *489*, 58–72, doi:10.1016/j.ijpharm.2015.04.038.
79. Zhang, C.; Yang, L.; Wan, F.; Bera, H.; Cun, D.; Rantanen, J.; Yang, M. Quality by Design Thinking in the Development of Long-Acting Injectable PLGA/PLA-Based Microspheres for Peptide and Protein Drug Delivery. *International Journal of Pharmaceutics* **2020**, *585*, 119441, doi:10.1016/j.ijpharm.2020.119441.
80. Alt, N.; Zhang, T.Y.; Motchnik, P.; Taticek, R.; Quarmby, V.; Schlothauer, T.; Beck, H.; Emrich, T.; Harris, R.J. Determination of Critical Quality Attributes for Monoclonal Antibodies Using Quality by Design Principles. *Biologicals* **2016**, *44*, 291–305, doi:10.1016/j.biologicals.2016.06.005.
81. Kopp, J.; Zauner, F.B.; Pell, A.; Hausjell, J.; Humer, D.; Ebner, J.; Herwig, C.; Spadiut, O.; Slouka, C.; Pell, R. Development of a Generic Reversed-Phase Liquid Chromatography Method for Protein Quantification Using Analytical Quality-by-Design Principles. *Journal of Pharmaceutical and Biomedical Analysis* **2020**, *188*, 113412, doi:10.1016/j.jpba.2020.113412.
82. Lee, A.R.; Kwon, S.Y.; Choi, D.H.; Park, E.S. Quality by Design (QbD) Approach to Optimize the Formulation of a Bilayer Combination Tablet (Telmiduo®) Manufactured via High Shear Wet Granulation. *International Journal of Pharmaceutics* **2017**, *534*, 144–158, doi:10.1016/j.ijpharm.2017.10.004.
83. Nadella, N.P.; Ratnakaram, V.N.; Srinivasu, N. Quality-by-Design-Based Development and Validation of a Stability-Indicating UPLC Method for Quantification of Teriflunomide in the Presence of Degradation Products and Its Application to in-Vitro Dissolution. *Journal of Liquid Chromatography & Related Technologies* **2017**, *40*, 517–527, doi:10.1080/10826076.2017.1330211.
84. Li, X.; Yang, Y.; Wang, R.; Liu, G.; Liu, X.; Liu, C.; Deng, Y.; Bai, Z. Quality by Design-Driven Process Development of Severe Fever With Thrombocytopenia Syndrome Vaccine. *Journal of Pharmaceutical Sciences* **2019**, *108*, 3785–3791, doi:10.1016/j.xphs.2019.09.008.
85. Arora, D.; Nanda, S. Quality by Design Driven Development of Resveratrol Loaded Ethosomal Hydrogel for Improved Dermatological Benefits via Enhanced Skin Permeation and Retention. *International Journal of Pharmaceutics* **2019**, *567*, 118448, doi:10.1016/j.ijpharm.2019.118448.
86. Alalaiwe, A.; Fayed, M.H.; Alshahrani, S.M.; Alsulays, B.B.; Alshetaili, A.S.; Tawfeek, H.M.; Khafagy, E.-S. Application of Design of Experiment Approach for Investigating the Effect of Partially Pre-Gelatinized Starch on Critical Quality Attributes of Rapid Orally Disintegrating Tablets. *Journal of Drug Delivery Science and Technology* **2019**, *49*, 227–234, doi:10.1016/j.jddst.2018.11.018.

87. Yabré, M.; Ferey, L.; Somé, T.I.; Sivadier, G.; Gaudin, K. Development of a Green HPLC Method for the Analysis of Artesunate and Amodiaquine Impurities Using Quality by Design. *Journal of Pharmaceutical and Biomedical Analysis* **2020**, *190*, 113507, doi:10.1016/j.jpba.2020.113507.
88. Deidda, R.; Avohou, H.T.; Baronti, R.; Davolio, P.L.; Pasquini, B.; Del Bubba, M.; Hubert, C.; Hubert, P.; Orlandini, S.; Furlanetto, S. Analytical Quality by Design: Development and Control Strategy for a LC Method to Evaluate the Cannabinoids Content in Cannabis Olive Oil Extracts. *Journal of Pharmaceutical and Biomedical Analysis* **2019**, *166*, 326–335, doi:10.1016/j.jpba.2019.01.032.
89. Li, X.; Liu, X.; Wang, R.; An, F.; Nie, J.; Zhang, Y.; Ahamada, H.; Liu, X.; Liu, C.; Deng, Y.; et al. Quality by Design-Driven Process Development of Cell Culture in Bioreactor for the Production of Foot-And-Mouth Veterinary Vaccine. *Journal of Pharmaceutical Sciences* **2019**, *108*, 2288–2295, doi:10.1016/j.xphs.2019.02.004.
90. Ali, R.; Mehta, P.; Kyriaki Monou, P.; Arshad, M.S.; Panteris, E.; Rasekh, M.; Singh, N.; Qutachi, O.; Wilson, P.; Tzetzis, D.; et al. Electrospinning/Electrospraying Coatings for Metal Microneedles: A Design of Experiments (DOE) and Quality by Design (QbD) Approach. *European Journal of Pharmaceutics and Biopharmaceutics* **2020**, *156*, 20–39, doi:10.1016/j.ejpb.2020.08.023.