Pharmaceutical quality by design in academic nanomedicine research: stifling innovation or creativity through constraint?

Lea Ann Dailey*

Institute of Pharmacy, Wolfgang-Langenbeck-Str. 4, 06120, Halle (Saale), Germany

Keywords
Control space, Design of experiment, Design space, Quality target product profile, Quality by design.

Abstract
Pharmaceutical quality by design (QbD) is a systematic approach to drug development that begins with predefined objectives and emphasises product and process understanding and control based on sound science and quality risk management. First and foremost, QbD is an experimental design philosophy, which emphasises the value of thorough intellectual planning prior to the commencement of laboratory studies. Academic researchers whose ambitions lie in translational science may benefit from the lessons learned by the pharmaceutical industry following implementation of QbD into their development philosophy. However, because of the very interdisciplinary nature of academic nanomedicine research, it is likely that very few investigators are aware of QbD and how aspects of it may be judiciously implemented in an academic research setting. This review provides an introduction to the main elements of QbD and gives examples of case studies where QbD has been applied to nanomedicine research.

What Defines Quality in Nanomedicine Research?
In *The Cambridge Handbook of Creativity*, psychologists James Kaufman and Robert Sternberg define creativity as “an original piece of work that is distinctive from other work with which it is compared.” In order for a piece of work to be considered “distinctive,” it must possess two characteristics: novelty and quality. Thus, a truly creative piece of work is “not merely novel, but also good, or perhaps even useful, according to some reference group” (Kaufman & Sternberg, 2010). The process of defining novelty and quality in scientific research has been in the headlines (Baker, 2016; Fanelli, 2018). In 2011, researchers from Bayer HealthCare reported that, despite significant time and effort, only a very small percentage, 20–25%, of published results from major studies on new drug targets could be reconfirmed in their labs (Prinz et al., 2011). A year later, scientists at Amgen reported that from 53 papers on new cancer targets, only six cases (11%) were deemed sufficiently validated for further preclinical development (Begley & Ellis, 2012). The ensuing
public discussion on the causes of this “reproducibility crisis in biomedical research” has not yet abated (Baker, 2016; Bhattacharjee, 2017; Fanelli, 2018). The salient question remains unanswered: does the current scientific culture promote novelty over quality in the evaluation of research through the peer-review/publication process? If so, what are the implications for translation of this research into something generally useful?

Most scientific journals today include quality assessment guidelines for reviewers in the peer-review process of submitted manuscripts. Typically, these comprise instructions on how to evaluate the work for replicability and repeatability (Wiley, 2018).

Replicability refers to the sufficient use of control experiments, repeated analyses, repeated experiments, and sampling numbers, all of which will influence whether the statistical analyses will be valid and conclusive (Wiley, 2018). The choice of statistical method is increasingly under scrutiny (Fraley & Vazire, 2014), as this will influence whether an observed trend is likely to be repeatable by independent researchers. Repeatability often refers to the provision of a sufficiently detailed methodology description, which allows other researchers to reconfirm the findings independently (Wiley, 2018). In their 2012 report, Amgen scientists stressed that the common factor between all six successful validation studies was the provision of a

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Outline of the main quality by design elements as applied in the pharmaceutical development process (modified from Bastogne, 2017).
particularly detailed methodology section (Begley & Ellis, 2012).

Quality in nanomedicine research can also be understood on a further level and relate to the concept of “fitness for purpose,” that is, whether a system or technology has the attributes to one day become a viable nanomedicine intended for a specific medicinal use. This definition lies at the heart of translational research and industrial product development. Many years of pharmaceutical development experience have demonstrated that this concept of quality cannot be tested into a product or technology but must be “built in by design,” thereby giving rise to the concept and practice known as quality by design (QbD) (Yu et al., 2014).

**Quality by Design: What Is It and What Does It Entail?**

Pharmaceutical QbD is a systematic approach to drug development that begins with predefined objectives and emphasises product and process understanding and control based on sound science and quality risk management (Pharmaceutical Development Q8(R2), 2009). First and foremost, QbD is an experimental design philosophy, which emphasises the value of thorough intellectual planning prior to the commencement of laboratory studies. The main elements of the QbD process as applied in pharmaceutical development (Bastogne, 2017) are depicted in Figure 1.

**Intellectual planning**

The process begins with a brainstorming session about what the ideal product for the intended application would look like. What is the disease to be treated? Who are the patients? How should the drug be administered? What is the ideal length of therapy? What are the efficacy/safety targets compared with the current standard of care? What is the value proposition? These discussions culminate with the creation of the target product profile (TPP), which is then distributed to a team of experts whose task is to create a quality target product profile (QTPP). The QTPP defines the product specifications, which must be fulfilled to achieve efficacy, safety, and pharmaceutical quality requirements (Bastogne, 2017; Troiano et al., 2016). It establishes a link between the proposed performance targets in the TPP with the actual physicochemical properties of the product (Troiano et al., 2016). An informative example of a QTPP for the development of drug-loaded polymeric nanoparticles for intravenous administration was published by Troiano et al. (2016). This extremely well-written article is an excellent primer for understanding the QbD process as applied to a nanomedicine and will be used throughout as an example.

To devise a meaningful QTPP, a thorough knowledge of pharmacopoeial quality standards for the intended dosage form and administration route is required. This knowledge is reflected a list of quality attributes for the product. For parenteral products, quality attributes will include sterility, endotoxin content, isotonicity, pH value, and the presence of large particulates (Lambert, 2010; Troiano et al., 2016). The next step is a risk assessment (criticality ranking), whereby each quality attribute is scored for its ability to negatively impact the safety or efficacy of the product (Table 1). Attributes with the highest criticality scores therefore require the most stringent specifications throughout the manufacturing process (Yu et al., 2014; Pharmaceutical Development Q8(R2), 2009; Bastogne, 2017; Troiano et al., 2016). An excerpt from the Troiano et al. (2016) QTPP with the ranked quality attributes (Table 2) highlights that sterility, endotoxin content, and container integrity are high-risk critical quality attributes for parenteral products.

Many process parameters during production can influence both the quality attributes and the physicochemical properties of the final product. Therefore, identification and ranking of all critical process parameters and critical material attributes (CMAs) in terms of their impact on performance, safety, and quality is the next step (Yu et al., 2014; Pharmaceutical Development Q8(R2), 2009; Bastogne, 2017; Troiano et al., 2016). Nanoparticle size after production, lyophilisation, and reconstitution is an excellent example of a CMA. The size and size distribution profile are known to impact the therapeutic efficacy (e.g. blood circulation time, tumour accumulation, and drug release rate), safety profile (e.g. embolism and off-target accumulation), and quality parameters (e.g. loss on filtration and aseptic preparation, Table 1). Certain processing parameters (e.g. choice of solvent and mixing time and speed) will influence the particle size and size distribution; therefore, identification and ranking of important process conditions prior to lab work is vital. The use of cause-effect or Ishikawa fishbone diagrams (Fig. 2) is favoured to capture the many variables identified to influence the quality and material attributes and perform root cause analysis in the event of system failure (Pharmaceutical Development Q8(R2), 2009).
Knowledge, design, and control space

Once the QTPP has been prepared, the lab work commences. Here, the aim is to understand, through hypothesis-driven research, how the production processes will impact the material and quality attributes. Where appropriate, a so-called design of experiments approach (Pharmaceutical Development Q8(R2), 2009), that is, a factorial design or multivariate analysis, is used to study the simultaneous effect of two or more variables on the product properties concurrently (Yu et al., 2014; Pharmaceutical Development Q8(R2), 2009; Bastogne, 2017; Troiano et al., 2016). A simplified example depicting the influence of drug loading (% w/w) and total solids concentration in an organic feed solution (mg/mL) on the hydrodynamic diameter of self-assembling polyethylene glycol-poly(lactic-co-glycolic acid) nanoparticles is provided (Fig. 3). The use of two-dimensional and three-dimensional contour maps based on the generation of models through multivariate analysis is a favoured concept in QbD studies (Pharmaceutical Development Q8(R2), 2009), as this form of data presentation can demonstrate results across a wide range of study conditions (knowledge space) and can be used to highlight the range of conditions feasible for achieving target specifications (design space) as well as the range of conditions that consistently meet target specifications (control space) (Pharmaceutical Development Q8(R2), 2009). It is often emphasised that the quality of the model must be established before reliable interpretations can be made about the impact of investigated variables (Yu et al., 2014; Pharmaceutical Development Q8(R2), 2009; Bastogne, 2017). However, this type of study design and data presentation has the advantage of depicting all data sets tested and precluding cherry picking of exclusively “positive” results. It helps to gain a better understanding of what is occurring in the process or complex reaction mixture and where the limit conditions are to be found. It is also useful for preserving knowledge to inform related projects, thus reducing the costs of future development work.

Table 1. Example of the criticality scoring process used by Troiano et al. (2016).

| Severity | Negligible | Minor | Moderate | Major | Catastrophic |
|----------|------------|-------|----------|-------|--------------|
| Safety score criteria | No patient impact | Minor, reversible patient impact not requiring medical intervention | Some patient impact requiring medical intervention, reversible | Major, possibly irreversible patient impact, not life threatening | Life-threatening illness or irreversible injury to patient |
| Safety score | 2 | 4 | 6 | 8 | 10 |
| Efficacy score criteria | No loss in efficacy | Minor loss in efficacy | Major loss in efficacy | Complete loss in efficacy | Negative efficacy, accelerates disease |
| Efficacy score | 2 | 4 | 6 | 8 | 10 |
| Uncertainty score criteria | Impact established with clinical or in vivo data | Impact established in vitro | Hypothetical impact based on the literature | Unknown |
| Uncertainty score | 0 | 2 | 4 | 6 |
| Criticality score = max score from safety or efficacy + uncertainty score | Less than 4 | 4-5 | 6-7 | 8-9 | 10+ |
| Criticality assessment | Not a critical attribute | Only a critical attribute if the safety/efficacy score = 4 | Attribute is critical (except when the safety/efficacy score ≤2) | Attribute is critical requiring tight acceptance criteria | Attribute is extremely critical requiring rigid acceptance criteria |
Table 2. Selected quality attributes and their criticality ranking scheme taken from the QTPP for intravenously administered drug-loaded polymeric nanoparticles Troiano et al. (2016).

| Quality attribute          | Test method | Specification range                                           | Safety score | Efficacy score | Max value | Uncertainty score | Criticality score |
|----------------------------|-------------|----------------------------------------------------------------|--------------|----------------|-----------|-------------------|------------------|
| Endotoxin content          | BET         | Dose-dependent (World Health Organization, 2017)                | 10           | 1              | 10        | 0                 | 10*              |
| Sterility                  | USP         | Negative                                                        | 10           | 1              | 10        | 0                 | 10*              |
| Container closure integrity| USP         | Negative                                                        | 10           | 1              | 10        | 0                 | 10*              |
| Content uniformity         | USP         | Per USP (905)                                                   | 8            | 6              | 8         | 1                 | 9*               |
| Large particulate matter   | SPOS        | >10 μm: <6000 per container >25 μm: <600 per container         | 8            | 2              | 8         | 0                 | 8*               |
| pH of reconstitute         | Potentiometric | 4.0-8.0                                                     | 6            | 2              | 6         | 0                 | 6*               |
| Particle size              | DLS         | 70-130 nm, PDI ≤ 0.3                                            | 4            | 4              | 4         | 2                 | 6*               |
| Residual solvents          | GC or UPLC  | ICH                                                             | 4            | 1              | 4         | 0                 | 4*               |

Please refer to the original publication for the entire list of quality attributes and critical processing parameters. QTPP, quality target product profile; BET, bacterial endotoxin test; USP, United States Pharmacopoeia; SPOS, single-particle optical sizing; DLS, dynamic light scattering; GC, gas chromatography; UPLC, ultra-pressure liquid chromatography; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; PDI, polydispersity index. The different colors represent the severity ranking, with red denoting the highest score. It would be good if the online version incorporated the colors, but they are not absolutely critical since the ranking scores are also listed in the table.

*The quality attribute is critical according to the criticality assessment criteria listed in Table 1.

Figure 2. Example of a cause-effect or Ishikawa fishbone diagram recommended by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Q8(R2) (Pharmaceutical Development Q8(R2), 2009) to capture all variables influencing critical quality attributes or critical material attributes. Cause-effect diagrams are useful for planning experimental work and can be effective in root cause analyses when specifications are not met.
Risk analysis and control strategy

Following analysis of experimental data, results are compiled in a database and used to perform a risk analysis of the identified critical process parameters to determine the probability and extent of impact on the critical quality attributes and CMAs. Typically, a scoring system is used to denote the probability of a negative impact, its likelihood of detection using existing analytical methods, and the certainty with which an impact on the product can be established (Pharmaceutical Development Q8(R2), 2009; Troiano et al., 2016). This scoring system helps to identify areas in the process that may require more stringent controls, for example, development of process analytical technology (Pharmaceutical Development Q8(R2), 2009; Bastogne, 2017). The summary of recommendations arising from the risk analysis is the control strategy (Yu et al., 2014; Pharmaceutical Development Q8(R2), 2009; Bastogne, 2017; Troiano et al., 2016). A well-defined control strategy is now a requirement for regulatory approval, as well as means to maintain consistent quality standards during manufacturing (Pharmaceutical Development Q8(R2), 2009).

Quality by Design in Academic Nanomedicine Research: Stifling Blue Skies Innovation or Creativity through Constraint?

The interdisciplinary nature of academic nanomedicine research is one of the most exciting, dynamic aspects of the field. The complexity of nanosystems also presents greater hurdles to translation into useful medicinal products. Academic researchers whose ambitions lie in translation may benefit from the lessons learned by the pharmaceutical industry following implementation of QbD into their development philosophy. However, because of the very interdisciplinary nature of academic nanomedicine research, it is likely that very few investigators are aware of QbD and how aspects of it may be judiciously implemented in an academic research setting.

Perhaps the most useful aspects of QbD for academic research are the initial elements of planning and design of experiments. Although currently many new ideas for a nanomedicine platform come from the material or clinical sciences, rather than from a pharmaceutical company, this does not preclude academic researchers from envisioning potential therapeutic areas or routes of administration for their platforms. From this starting point, TPPs and fairly realistic, if not fully comprehensive, QTPPs for the new platforms may be developed.

Figure 3. A simplified example depicting a design of experiments analysis of the influence of two variables (drug loading (DL) and total solid (TS) content) on self-assembling polyethylene glycol-poly(lactic-co-glycolic acid) nanoparticle size (unpublished data). (A) Experimental and model-derived predicted values of nanoparticle hydrodynamic diameters produced with different DL values and TS contents. (B) Contour plot of the predicted nanoparticle sizes based on the modelled relationship: $[\text{Size}] = 1.8[\text{DL}] + 21.5[\text{TS}] + 83.8$. Examples of how the knowledge, design, and control space might be defined are depicted as outlined regions in the graph. (C) Correlation of predicted size values to measured data showing a coefficient of variation value ($R^2$) of 0.9069, that is, a high predictability of the model.
within the group. The advantages of designing academic studies around putative QTPPs are manifold. The QTPP provides a realistic structural framework of quality parameters that must be satisfied before an idea can become a medicine. Rather than stifling creativity though restrictive rules, such a framework can act as a stimulus for creative thinking and “distinctive” solutions (Kaufman & Sternberg, 2010). Furthermore, if an academic lab were to structure their nanomedicine research efforts around putative QTPPs, the data package generated is likely to increase the value proposition of the research for in-house start-ups or venture capital investors (Osherovich, 2011). Secondly, with its emphasis on intellectual planning and carefully conceived experimental design, the QbD philosophy is an excellent educational tool for training young researchers. Lastly, the incorporation of rigorous pharmaceutical quality standards in early phases of academic research is important for producing high-quality samples for preclinical in vivo studies. The number of reported in vivo studies of novel nanomedicine platforms is increasing dramatically, yet many of the published studies on parenteral formulations do not report whether critical parameters such as sterility or endotoxin content (Mayala & Singh, 2008) were assessed. This should be addressed by investigators and manuscript reviewers for ethical reasons, as well as for appropriate data interpretation and reproducibility.

How do researchers unfamiliar with QbD find the relevant information to create a nanomedicine QTPP? What are the critical quality attributes for a particular route of administration? How are different factors ranked for criticality? How are target specifications decided upon? Fortunately, there is a small but growing body of literature reporting QTPPs for different nanoformulations and different administration routes (Table 3). Those published by companies developing nanomedicines are particularly informative. Further, organisations such as the Nanotechnology Characterization Laboratory (US and European Union branch; https://ncl.cancer.gov) have embedded pharmaceutical QbD at the heart of their core mission to help translate academic research towards clinical applications. Publications from these institutes are a vital resource for standardised assay guidelines to test nanomaterials for pharmaceutical quality parameters (Nanotechnology Characterization Laboratory, 2018). Other projects, such as the European Technology Platform Nanomedicine (https://www.etp-nanomedicine.eu/public/about-nanomedicine/nanomedicine-community/nanomedicine-related-national-platforms-initiatives), also provide QbD-inspired guidance for translating ideas from the early research phase towards the clinic.

**Concluding Remarks**

In light of the recent “reproducibility crisis in biomedical research,” it has become a routine practice for venture capital companies to commission independent reproduction of key findings from academic groups prior to investment in biomedical start-ups (Osherovich, 2011). Researchers may therefore find it

| Administration route | Nanomedicine platform | Reference |
|----------------------|-----------------------|-----------|
| Parenteral           | Drug-loaded PEG-PLA polymeric nanoparticles for intravenous administration | Troiano et al. (2016) |
|                      | Gefitinib-loaded polymeric nanoparticles for intravenous administration | Srinivas et al. (2017) |
| Oral                 | Self-nanoemulsifying drug delivery system containing lovastatin | Beg et al. (2015) |
|                      | Drug nanocrystals for oral dosage forms | Peltonen (2018) |
|                      | Self-assembled phospholipid nanomixed micelle system for oral dosage forms | Singh et al. (2018) |
| Intranasal           | Galantamine-loaded albumin nanoparticles for intranasal administration | Poddar and Sawant (2017) |
| Transdermal          | Lidocain-loaded nanostructured lipid carriers | Bakonyi et al. (2017) |
| Non-disclosed        | Tacrolimus-loaded PLGA nanoparticles | Shirshat and Chitlange (2015) |

QTPP, quality target product profile; PEG-PLA, polyethylene glycol-co-poly lactic acid; PLGA, poly(lactic-co-glycolic acid).
QbD for nanomedicines

useful to incorporate QbD principles into their academic studies from the onset, as this will ultimately facilitate technology transfer in the long run. In cases where translation is not the immediate priority, the QbD philosophy, with its emphasis on intellectual rigour and sound science, has useful elements for all nanomedicine researchers in pursuit of novelty and quality.

Funding Information
No funding information provided.

Conflict of Interest
None declared.

REFERENCES

Wiley (2018). Step by step guide to reviewing a manuscript. https://authorservices.wiley.com/Reviewers/journal-reviewers/how-to-perform-a-peer-review/step-by-step-guide-to-reviewing-a-manuscript.html, accessed on 27 July 2018.

Beg, S., Sandhu, P. S., Batra, R. S., Khurana, R. K., and Singh, B. 2015. QbD-based systematic development of novel optimized solid self-emulsifying drug delivery systems (SNEDDS) of lovastatin with enhanced biopharmaceutical performance. Drug Deliv 22:765-784.

Begley, C. G., and Ellis, L. M. 2012. Raise standards for preclinical cancer research. Nature 483:531-533.

Bhattacharjee, S. 2017. Nanomedicine literature: the vicious cycle of reproducing the irreproducible. Int J Pharm 2:15-19.

Fanelli, D. 2018. Opinion: is science really facing a reproducibility crisis, and do we need it to? PNAS, March 12:2628, 201708272-2631. https://doi.org/10.1073/pnas.1708272114.

Fraley, R. C., and Vazire, S. 2014. The N-pact factor: evaluating the quality of empirical journals with respect to sample size and statistical power. PLoS One 9:e109019.

Kaufman, J., and Sternberg, R. J. 2010. p. 467. in J. Kaufman and R. J. Sternberg, eds. Constraints on creativity: obvious and not so obvious in the Cambridge Handbook of Creativity. Cambridge University Press, Cambridge.

Lambert, W. J. 2010. Considerations in developing a target product profile for parenteral pharmaceutical products. AAPS Pharm Sci Tech 11:1476-1481.

Mayala, P., and Singh, M. 2008. Endotoxin limits in formulations for preclinical research. J Pharm Sci 97:2041-2044.

Osheroivich, L. 2011. Hedging against academic risk. SciBX 4(15). https://doi.org/10.1038/scibx.2011.416.

Peltonen, L. 2018. Design space and QbD approach for production of drug nanocrystals by wet media milling techniques. Pharmaceutics 10:104.

Pharmaceutical Development Q8(R2) (2009) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf, accessed 27 July, 2018.

Poddar, A., and Sawant, K. K. 2017. Optimization of galantamine loaded bovine serum albumin nanoparticles by quality by design and its preliminary characterizations. J Nanomed Nanotechnol 8:459.

Prinz, F., Schlange, T., and Asadullah, K. 2011. Believe it or not: how much can we rely on published data on potential drug targets. Nature Rev Drug Disc 10:712.

Shirshat, A. E., and Chitilange, S. S. 2015. Quality by design approach to optimization of tacrolimus loaded PLGA nanoparticles. Int J Pharm Sci Res 6:4342.

Singh, K., Khurana, R. K., Gaspar, B. L., Welsby, G., and Katare, O. P. 2018. Improving the biopharmaceutical attributes of mangiferin using vitamin ETPGS coloaded self-assembled phospholipidic nanomixed micellar systems. Drug Deliv Transl Res 8:617632.

Srinivas, N. S. K., Verma, R., Kulyadi, G. P., and Kumar, L. 2017. A quality by design approach on polymeric nanocarrier delivery of gefitinib: formulation, in vitro and in vivo characterization. Int J Nanomedicine 12:15.

Troiano, G., Nolan, J., Parsons, D., Van Geen Hoven, C., and Zale, S. 2016. A quality by design approach to developing and manufacturing nanoparticle drug products. AAPS J 18:1354-1365.

Yu, L. X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G. K., and Woodcock, J. 2014. Understanding pharmaceutical quality by design. AAPS J 16:771-783.