# Define Q, make by QbT then warm to enjoy QbD? Making Sense of this Pharmaceutical Quality Alphabet Soup

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| Ajaz Hussain, PhD | Saeed Qureshi, Ph.D.  |
| Insight Advice & Solutions LLC | PharmacoMechanics |

# **QbD in current manufacturing environment: A debate**

A debate among two ex-regulators (AH & SQ) on fundamentals of pharmaceutical quality, testing, and design; or is it a yearning to see more clearly an *elephant in the dark*? One of us (SQ) spent the entire career at Health Canada and is an award-winning laboratory scientist; the other (AH) is recognized for his laboratory-based research and policy contributions at the US FDA and is a systems practitioner with experience across multiple sectors. The decision to write this blog originated in SQ’s recurring snippets of sniping on AH’s LinkedIn postings. Perhaps, in writing this blog, we will also shed new light on important challenges confronting the sector.

# **Quality of pharmaceutical products, an elephant in the dark**

Often patients and physicians cannot differentiate between a pharmaceutical product and its placebo (e.g., a sugar pill with no drug designed to look alike). Unlike consumer goods assessment of pharmaceutical quality is complicated and based on proxies of safety and efficacy.

The difficulty in assessing quality is, in part, a reason to regulate the quality of pharmaceutical products.

# **We agree**

As scientists, we believe regulatory policies and procedures should be based on science and that this is the best way to mitigate the risk posed by patients due to poor quality. We agree that the pharmaceutical community must do more today to ensure and to improve the scientific basis for defining pharmaceutical quality attributes (Q).

**And we disagree**

SQ wishes to see the pharmaceutical community establish Quality by Testing (QbT). AH is firm in his belief that the US FDA’s CGMP doctrine - *quality cannot be tested into products, it must be built-in by design* (the origin of Pharmaceutical Quality by Design or QbD) provides the (higher) level of assurance of quality demanded by patients. SQ is firm in his belief that QbD is not possible; because, at present, one cannot monitor quality.

# **Sorting out our differences**

Sorting out our differences and seeking a common understanding will certainly help us. Perhaps, this blog will also be useful for the entire community.

## Drug dissolution

Most pharmaceutical products contain a drug in solid form, as in a tablet or a capsule. The process of drug release and dissolution in fluids of stomach and intestine is necessary for absorption of drugs into the blood stream and for its distribution to various sites in the body where its actions are expected.

## Critical Quality Attribute

Differences in amount and rate of drug release in fluids of stomach and intestine can have a significant effect on the availability of drugs in blood and on the response patients and their physicians expect from a pharmaceutical product. Therefore, how much and how fast a drug releases in stomach and intestine is an important characteristic. It relates to the quality of pharmaceutical products because differences in amount and rate can change the therapeutic response. Drug release can, and often is, a Critical Quality Attribute (CQA).

## Dissolution Testing

It is difficult to measure drug release or dissolution in the stomach and intestine. To do currently requires putting in tubes down people's throat and position these in stomach and intestine to collect samples to measure how fast the drug is releasing. Not a convenient method. So, instead, research and QC testing of drug release are predominantly conducted *in vitro*, in a laboratory vessel with agitators containing fluids which represent, to differing levels, fluids in stomach and intestine. The history of science of dissolution testing in the USA and Canada dates to the early 1960’s – however, reproducibility, relevance, and validation of the compendial methods are still actively debated.

## In Vitro Release Testing a proxy of Release In Vivo (Quality Attribute)

The rate and extent of drug release in *vivo* (e.g., stomach and intestine) are the attributes that relate to pharmaceutical quality. Dissolution testing, an *in vitro* method, is a proxy for *in vivo* drug release. Human trials are occasionally conducted during drug development to measure rate and extent of drug absorption by measuring drug levels in the blood. There are mathematical techniques to calculate *in vivo* drug release and assess the relation or correlation between measured *in vitro* and calculated *in vivo* release.

## Different Perspectives

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| **Topic** | **SQ** | **AH** |
| **Quality attribute** | 1. The *in vivo* release (rate and extent)
 | 1. The *in vivo* dissolution (rate and extent)
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| 1. In vitro release a proxy
 | 1. In Vitro Dissolution a proxy
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| **Test method** | 1. The currently suggested methods are non-relevant to physiological aspects, QC and research methods must be same, and product independent, as both are assessing the same attribute.
 | 1. Test methods for QC and Research can (and must be) distinct. There is a need to improve reproducibility and repeatability of QC test methods.
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| **Acceptance criteria** | 1. It is not possible to set appropriate acceptance criteria using currently recommended apparatuses and methods as these are not relevant for the intended purpose.
 | 1. The process for setting acceptance criteria (e.g., as in ICH Q6a) can and should be improved utilizing QbD development reports per ICH Q8 guideline.
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| **QbT** | 1. Compendial apparatuses and tests pose serious limitation for effective monitoring of quality.
 | 1. Compendial tests are intended to be “market” standards. Use of these as QC test for batch release poses challenges that need to be considered.
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| **QbD** | 1. Not possible; because at present one cannot monitor quality thus QbD must wait for its application
 | 1. It is what we do (or are supposed to do). The doctrine - quality cannot be tested into the products, it should be built-in by design, has been the foundation of the [US] regulatory system. The ICH Q8 guidelines described a format, a QbD methodology, to describe the understanding gained via development program in a regulatory submission. The *by design* in QbD is essentially Plan-Do-Check-Act which is applicable broadly – throughout the product life-cycle.
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SQ’s Recipe: Define Q, make by QbT then warm to enjoy QbD

1. Establish a scientifically valid definition of quality of pharmaceutical products along with its measurable attribute. Suggested definition is – products’ capability to release the drug in the GI tract in an expected manner.
2. Recognize that currently recommended dissolution apparatuses are not qualified and validated for the intended purposes (QC or research). New apparatuses and methods are urgently needed to address this issue. Suggested way forward (a) Improve dissolution tester/method (see <http://www.drug-dissolution-testing.com/?p=2364b> ); (b) Predicting plasma drug levels from dissolution test (see <http://www.drug-dissolution-testing.com/blog/files/TODDJ-4-38.pdf>).
3. QbD depends on a clear, and agreed upon, the regulatory definition of Q (“quality” of pharmaceutical products) and its appropriate measurement. Thus, for the application and success of QbD definition of quality and its measurement are needed.

AH’s Recipe: Practice and enjoy QbD

1. Establishing clinical relevance of Q is critical, and it requires a Plan-Do-Check-Act mindset, which is the “by Design” of QbD. The definition of Q (should) evolves step-wise via scientific studies conducted over a life-cycle of drug and its products (New Drug: Target Product Profile (TPP) to QTTP via pre-formulation, formulation, Phase I-III, …. Generic Drugs: RLD characterization, QTPP….).
2. QbT, in and of itself, is not sufficient to provide the assurance of pharmaceutical quality in the 21st century. A systematic effort to more uniformly practice QbD requires the establishment of consensus standards.

Efforts to establish consensus standards, in the context of drug dissolution and other critical attributes, continue. Discussion at the US FDA Advisory Committee for Pharmaceutical Science relevant to this discussion may be useful to review (you can access the meeting transcripts and other materials via the US FDA website)

* Quality-by-Design Approach for Regulatory Decisions: Seeking Applications for Establishing Drug Dissolution/Release Specifications, Creating Flexibility for Continuous Improvement and Assessment of Therapeutic Equivalence. [Advisory Committee for Pharmaceutical Science, CDER, FDA May 2005](https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4137B1_03_Overview.htm).
* Achieving and demonstrating “Quality by Design” on drug release/dissolution performance for conventional or immediate release solid oral dosage forms. [FDA’s ACPS Meeting October 2005](https://www.fda.gov/ohrms/dockets/AC/05/briefing/2005-4187B1_01_03-Achieve-Demo-QbD.pdf)
* [Use and Limitations of In Vitro Dissolution Testing](file:///C%3A%5CUsers%5CSaeed%5CAppData%5CLocal%5CTemp%5CUse%20and%20Limitations%20of%20In%20Vitro%20Dissolution%20Testing). Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, August 8, 2012, and other more recent updates from US FDA.
1. As a professional community, we must be transitioning to, as FDA\CDER\OPQ calls it, “One Quality Voice.” For me, this opportunity to debate SQ is a step in this direction. What will be your [Pharmaceutical Quality by Design Travel Option](https://www.slideshare.net/a2zpharmsci/pharmaceutical-quality-by-design-travel-options-keynote-patheon-qbd-2016)?