The importance of Quality Control in pharmaceutical industry

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What does the 'quality' of a pharmaceutical product mean?

A high quality *pharmaceutical* product is one that is both safe and effective. It should therefore be of consistent composition and be free of unwanted by-products and contaminants. *Medical practitioners* and consumers will then have confidence in the product and will be more likely to choose it.

If the quality of a product drops:

- Patients' health may be compromised which could have long lasting effects.
- The manufacturer's reputation may be damaged, lowering confidence in other products and decreasing sales.
- In the case of a '*Flagship product*' reputational damage can endanger the whole company and put jobs at risk.

A high-quality pharmaceutical product is one that is produced from high quality ingredients, using consistent processes that prevent contamination and is in compliance with relevant legal requirements. It benefits both the producer and the consumer. In the long term, quality costs less and is more beneficial to both companies and patients.

Can you measure quality?

The quality of pharmaceutical products can be checked by regular testing of samples, to ensure they are up to the required standards. For example, a product such as *paracetamol* is typically produced in tablet or capsule form. The tablets are commonly sold in packs of 12 and each tablet is individually sealed. Random samples are taken from each batch of product and tested for composition, weight, packaging, labelling, etc.

Quality by Design — not just by testing

It is not enough to rely solely on testing to maintain the quality of a product, i.e. '**quality by testing'**. Quality should be 'built in' to the whole manufacturing process and be based on a fundamental understanding of what happens at every stage, i.e. '**quality by design**'.

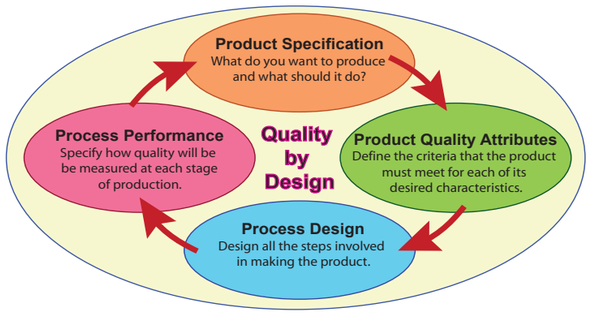
Implementing Quality by Design

Today 'Quality by Design' is a key feature of the pharmaceutical industry. The concept was developed over the past 30 years or so and is now implemented by all the leading businesses in the sector.

The main features of Quality by Design may be summarised in the following steps:

1. What do you want to produce? What should the product do or what characteristics should it have? (e.g., a tablet that relieves fever and mild headaches and is effective and safe to use.)
2. Define the criteria that the product must meet for each of its desired characteristics. These can be regarded as product quality attributes.
3. Design all the steps involved in making the product, e.g. selection and analysis of raw materials, the chemical and physical processes required to make the product and the order in which they must be carried out, sampling, testing, packaging, etc.
4. Specify how the quality of the product's characteristics and the manufacturing processes are measured and what action must be taken if standards are not met. Ideally, these actions should be built into the whole production process so that they are carried out automatically.

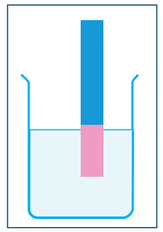
These features may be summarised in the following simplified diagram.



The role of analysis in Quality Control

You may have carried out simple tests to show the presence of starch, sugar, vitamin C, etc. in various foods. *Qualitative* tests indicating that various fruits and vegetables contain vitamin C, do not tell you how much vitamin they contain or which foods have the most or the highest concentration; for that, *quantitative* tests are required.

Modern pharmaceutical analysis involves a range of qualitative and quantitative methods. Qualitative methods determine precisely what substances are present in a product. Quantitative methods assess the concentration of the active ingredient.



Qualitative analysis

In school you may have carried out a test for acid using litmus paper or a test for carbon dioxide by bubbling it through *limewater*. Blue litmus paper changes to red in an acid. Carbon dioxide makes limewater go cloudy. These are qualitative tests; they indicate the presence of some substance but do not tell you how much is present. Other relatively simple qualitative tests include flame tests and precipitation tests for various *anions* and *cations*.

Qualitative tests provide a 'yes' or 'no' answer to a question such as: "Is this solution acidic or basic?" or "Is the product free of *E. coli* ?". Qualitative tests are usually easier to carry out than quantitative tests.

Quantitative analysis

Quantitative tests involve some measurement of quantities such as mass, volume, concentration, etc. Acid-base or *redox titrations* that are carried out in school chemistry classes are examples of quantitative analysis. Their purpose is to measure the concentration of particular solutions.

The classical quantitative methods of analysis include titration, *precipitation*, filtering and weighing. These methods are still important and are included in school and college courses.

Modern analysis includes methods and equipment such as *mass spectrometry*, *chromatography*, *electrophoresis* and several kinds of *spectroscopy*.

In contrast to the classical methods, instrumental methods typically require expensive equipment as well as expertise in its use. Instrumental methods can often be used for both qualitative and quantitative chemical analysis.

High Performance Liquid Chromatography. Source: Shutterstock

Sampling and statistical analysis

Throughout the whole process of pharmaceutical manufacture samples are taken out for inspection and analysis. All samples from a particular step will not yield exactly the same result; there will always be slight variation in the quantities and in the measurements. Statistical analysis is applied to see if the variations are within the expected range.

Since the mathematical formulae used in statistical analysis are valid only for random data, it is vital that the samples are taken randomly.

Product purity – an example

The active ingredient in Tylenol tablets is paracetamol (also known as acetoaminophen). Tylenol tablets are produced in a range of 'strengths', i.e. containing different amounts of paracetamol for different age groups: 80 *mg*, 160 mg, 325 mg, 500 mg. It is clearly important that the tablets or capsules contain the correct amount of the active and inactive ingredients and that they are labelled accordingly. Inactive ingredients – called *excipients* – are commonly added to tablets to give them bulk and to bind and stabilise them. They also facilitate detection of *counterfeit* products. All the ingredients, both active and inactive, must be of very high purity and be free of harmful contaminants and allergens.

Product potency

While the purity of a pharmaceutical product can be measured objectively, its potency is more difficult to measure. Potency of a product may be defined as the concentration or amount needed to produce the desired effect. (There are several other definitions.) If a pain relief tablet 'cures' a headache, would half a tablet be 50% effective? Potency can be measured by *ELISA* (Enzyme Linked Immunosorbent Assay) and other biological *assays*. The effectiveness is likely to vary from person to person.

The solution is to conduct *double blind trials* to determine statistically what amount of the product (as distinct from the *placebo*) has the desired effect on 50% of those who received it. In this way the potency can be estimated more objectively and the results allow comparisons to be made with other products or formulations.

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Syllabus References

The main syllabus references for the lesson are:

Leaving Certificate Chemistry

Instrumental methods of separation or analysis:

- Mass spectrometry. Gas chromatography
- High-performance liquid chromatography (HPLC). (p. 23)
- Additional industrial chemistry: Characteristics of effective and successful industrial chemical processes…, co-products (separation, disposal or sale) … , quality control (p. 27)
- Infra-red absorption spectrometry
- Ultraviolet absorption spectrometry (p. 60)

Leaving Certificate Technology

- A Process of Design (p. 11 - 13)
- Investigation and Research. Making and Testing. Evaluation
- Project and Quality Management (p. 14 - 17)
- Define quality and identify the quality attributes of products.

Leaving Certificate Biology

- Chemical or hormonal system, nerve and sense organ system, muscular, skeletal and an immune system. (p. 37)

Science and Technology in Action is also widely used by **Transition Year** classes.

Learning Outcomes

On completion of this lesson, students should be able to:

- Explain what is meant by the word 'quality' in relation to pharmaceutical products and discuss the benefits of quality products to both producers and consumers
- Outline the risks associated with low quality production
- Distinguish between 'quality by testing' and 'quality by design'
- Outline the main features of 'quality by design'
- Distinguish between qualitative and quantitative analysis
- List some important instrumental methods of chemical analysis and explain their importance
- Explain why statistical methods are necessary in evaluating the efficacy and potency of a pharmaceutical product
- Explain why pharmaceutical products are often produced in a range of 'strengths'
- Explain what is meant by the potency of a pharmaceutical product and outline why it might be difficult to measure
- Explain what is meant by a double blind trial and why such trials are necessary in establishing the potency of a pharmaceutical product.

Student Activities

1. Quality Assurance focusses on the quality of the manufacturing **process** while Quality Control focusses on quality of the **product**. Discuss the importance of these areas for the future of Irish biopharmachemical industry. (https://dbei.gov.ie/en/Publications/Publication-files/Future-Skills-Needs-of-the-Biopharma-Industry-in-Ireland.pdf)
2. How can the contribution of the biopharma sector, both nationally and globally, be developed into the future.
   (See pages 3 & 5 of the **report** of the BioPharma Ambition Conference 2020 here: https://www.biopharmaambition.com/)
3. Find the mass of 10 similar coins, one by one using an electronic balance. Assuming that the accuracy of the last digit is +/- 1, calculate the percentage range of the possible error in each case. Then weigh all ten coins together and calculate the possible percentage range of error. Discuss your results.

4. Prepare a set of slides for your class summarising what the work of a Quality Control analyst entails. Online videos such as the following should help: https://www.getreskilled.com/what-is-a-quality-control-associate/
5. The following online video introduces the Deming Cycle: https://www.youtube.com/watch?v=e4gOPeHSRo8
   Find out more about this cycle and summarise your findings in five slides.

True/False Questions

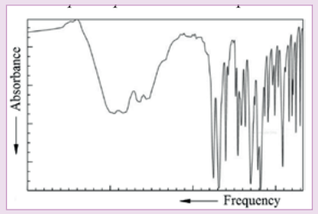
a) A high quality pharmaceutical product is one that is both safe and effective. **T F**
b) High quality products benefit the consumer but not the producer. **T F**
c) Quality is subjective and so cannot be measured. **T F**
d) 'Quality by Design' eliminates the need for testing. **T F**
e) Quantitative tests involve some measurement of quantities such as mass, volume, concentration, etc. **T F**
f) Mass spectrometry, chromatography and electrophoresis are instrumental methods of analysis. **T F**
g) In a 'double-blind trial' the patients don't know if they have received the real product or not, but their doctors do. **T F**
h) The potency of a pharmaceutical product is the minimum amount of it that is effective, for 50% of recipients. **T F**
i) School chemistry practicals involve both qualitative tests and quantitative measurements. **T F**
j) Litmus paper gives quantitative results. **T F**

Check your answers to these questions on www.sta.ie.

Examination Questions

Leaving Certificate Chemistry 2016 (HL) Q. 4 f

By referring to the diagram of the infrared spectrum of aspirin, or otherwise, give a simple explanation of the principle of infrared spectrometry.



Leaving Certificate Chemistry 2009 (HL) Q. 7

According to the EPA (Environmental Protection Agency) publication '*The Provision and Quality of Drinking Water in Ireland (2006-2007)*': Drinking water must be clean and wholesome. That means it must meet the relevant water quality standards and must not contain any other substance or microorganism in concentration or numbers that constitute a potential danger to human health.

(i) Describe how suspended solids are removed in water treatment.
(ii) What treatment is carried out to ensure low levels of micro-organisms in drinking water?
(iii) What problems would arise if the pH of a public water supply were outside the range 6 – 8?
(iv) EU standards specify that the concentration of lead (in the form of Pb^{2+}) in drinking water must be below 10 µg/l (micrograms per litre). Why must the Pb^{2+} concentration be kept so low? How are heavy metal ions like Pb^{2+} removed from large quantities of water?

Leaving Certificate Technology 2017 (HL, B) Q. 4 b iii

(iii) A Quality Control scheme is in operation for a process which produces ball bearings. Each hour 6 bearings are taken and their diameters measured. The process delivers a mean diameter of 20 mm with a standard deviation of 0.03 mm. The lower and upper specification limits are 19.97 mm and 20.01 mm respectively.

Calculate the process capability index and give the 'control state' of the process, where: $Cp = (Tolerance\ Range)/\ 6\sigma$

Leaving Certificate Technology 2014 (HL, A) Q. 8 b ii

Explain the purpose of a Quality Control (QC) system in product manufacture.

Leaving Certificate Technology 2019 (OL, B&C) Q. 2 c

Manufacturers of commercial sensor alarms use quality management techniques to ensure that their products are of the highest quality. The Deming Cycle focuses on continuous improvement and consists of four stages - Plan, Do, Study and Act.

(i) Briefly outline any two stages of the Deming Cycle.
(ii) Outline two consequences for a company that manufactures faulty goods.

Did You Know?

Biopharmaceutical manufacturing in Ireland

- "Ireland has a large biopharmaceutical manufacturing presence relative to other sectors and to other similar-sized countries.
- The industry is responsible for over 45,000 jobs and accounts for 62% of the country's exports. Its presence is regionally distributed.
- This cannot be taken for granted. The biopharmaceutical industry is not static and now is not a time for complacency...
- As sectors like technology, medical technology and biopharmaceuticals converge, similarly the gap between industry, policy, research and clinical leaders is narrowing. ..
- We must focus on driving innovation, connecting and aligning key players across sectors, and work on enhancing Ireland's reputation for life sciences and competitiveness proposition."

BioPharma Ambition 2020: Tomorrow's Cures, Conference Report: (https://www.biopharmaambition.com/Sectors/BPCI/Conference2020.nsf/vPages/Report~2020?OpenDocument) p.3

Biographical Notes

Diarmuid Buckley – QC Microbiology Analyst, MSD Brinny

Diarmuid joined MSD in July 2018, having previously worked as a Student Intern in the same role at MSD for 6 months in 2017. He then completed his final year college project in MSD at the start of 2018, titled 'The long-term storage of Bacterial Isolates, and the effects of this on their viability'.

Diarmuid graduated from Cork Institute of Technology in May 2018 with a bachelor's degree in Pharmaceutical Biotechnology. This course allowed him to develop broad expertise across Microbiology, Chemistry, and Biochemistry. These skills are invaluable for the pharmaceutical sector.

He works with a diverse team based in the QC Microbiology laboratory at MSD Brinny, Co. Cork. His role includes the sampling and testing of water systems across the site to ensure their quality – a crucial part of the manufacturing process.

Revise The Terms

Check the meaning of the following key terms:

anions, assay, cations, chromatography, counterfeit, criteria, double blind trials, electrophoresis, ELISA, excipients, flagship product, limewater, mass spectrometry, medical practitioner, mg, paracetamol, pharmaceutical, precipitation, qualitative, quantitative, redox, spectroscopy, titration.

Check the Glossary of terms for this lesson on www.sta.ie