An Integrated Framework for Biopharmaceutical Drug Design, Development, and Implementation

A Multi-Stakeholder and Macro-Modeling Approach

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BACKGROUND: Quality by Design (QbD) for Biopharmaceuticals

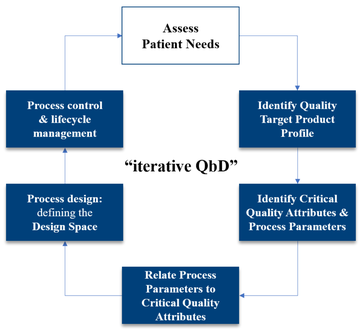

Figure 1:
Iterative QbD approach as stipulated by the ICH guidelines

Biopharmaceutical research and development (R&D) follows a standardized, phased procedure to prove the safety and efficacy of the drug candidate [1]. Overall, drug development goes through three stages before the medicine gets commercialized: the discovery phase, early development, and the late development phase.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) discusses the QbD approach in the Q8(R2) guideline on Pharmaceutical Development by means of several successive steps (*Figure 1*) [2-3].

QbD is a systematic and risk-based approach to drug development and has a strong emphasis on product and process understanding as well as on quality risk management to control the variability of quality attributes [4]. It is a proactive approach to the entire drug product lifecycle to help ensure that biopharmaceuticals are developed to "meet the needs of patients".

QbD has been strongly defined from the Chemistry, Manufacturing, and Control perspective to allow for scientific innovation without being a regulatory burden [5].

IMPLEMENTATION GAP: Systemic Issues

Disconnect between **drug developer** and **end-user:**

- Insufficient patient / end-user involvement in (early) drug development [6-7]
- Lack of communication and collaboration [6, 8-9]
- ICH guidelines don't provide guidance on assessing patient needs (not required for marketing authorization)
- Financially unsustainable system as return on investment not guaranteed [10-11].
- Lack of tools or frameworks for integrative product assessment in early development stages [12].

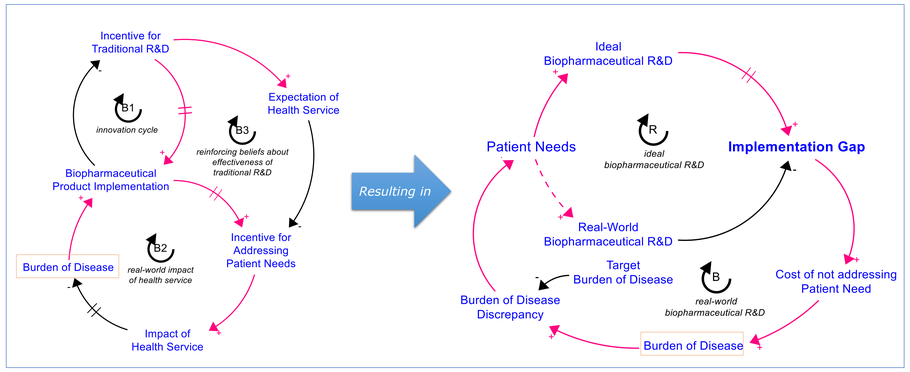

Figure 2:
The implementation gap (problem articulation)

Road to market is highly risky business:

1. Pre-Marketing Authorization:
Uncertainty of product innovation and the **translational gap** (the so-called "Valley of Death") [13].

2. Post-Marketing Authorization:
The ***implementation gap*** (the "second Valley of Death") is much more complex. It is the period or process between market licensure and public health impact, whereby access to the medicine has been delayed or canceled, particularly upon the recommendations of national health authorities, which is often based on traditional health technology assessments [14].

➔ *A systemic issue that shows similarities with "eroding goals" and "shifting the burden" archetypes*

METHODS & OBJECTIVES

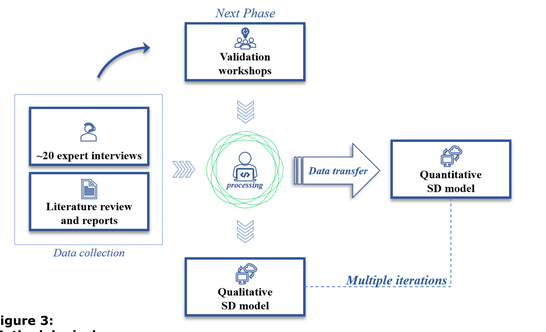

Figure 3:
Methodological process

Objectives:

Holistic approach

- Explore qualitative **stakeholder perspectives on vaccine implementation**, in the context of the neglected tropical disease "Rabies" as case study
- Develop a **qualitative integrated modeling framework** to address the implementation gap of biopharmaceuticals and increase understanding of its drivers
- Conduct **validation workshops** with stakeholders from private and public sector

- Translate these insights into a **quantitative SD model**
- Propose a new and **integrated model-based method** for **early health technology assessments** that can support decisions during drug design
- Conduct **scenario analyses** of multi-agent products and check for the added value of such investments. **Case study**: Rabies-Yellow fever combination vaccine

Future work

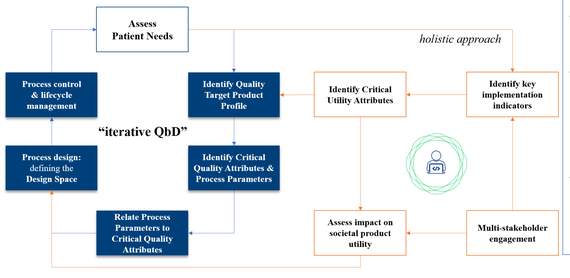

Figure 4:
Holistic approach to biopharmaceutical R&D

INTEGRATED FRAMEWORK: Macro-Model

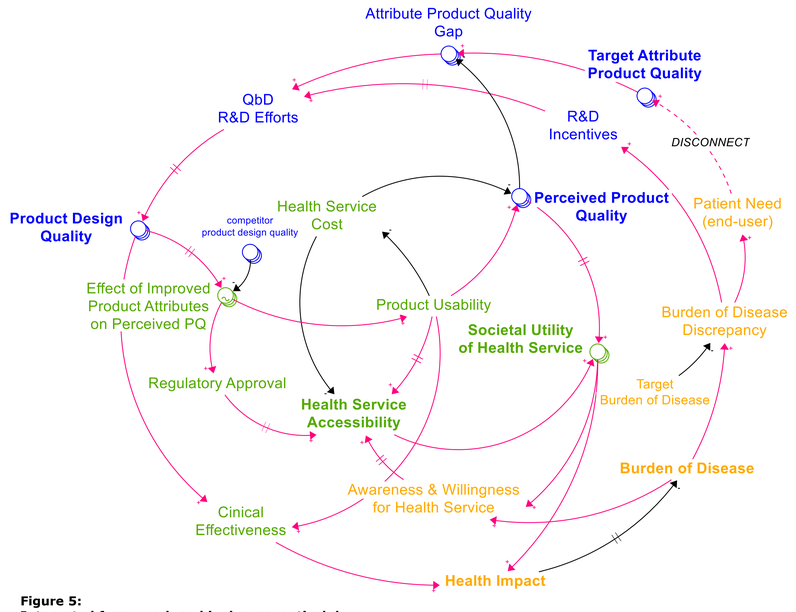

Figure 5:
Integrated framework on biopharmaceutical drug design, development, and implementation

PRIVATE SECTOR (R&D) FOCUS

General dynamics:
Incentives for R&D in biopharmaceutical companies arise from their intrinsic capabilities and the actual disease burden, prompting investment in a high-quality product defined by a target product profile (TPP). The TPP's quality is determined by exogenous technological factors. However, incorporating patient needs into the TPP is currently lacking. Product design quality is the outcome of an extensive R&D process, adjusting target attributes based on realistic feasibility. This impacts downstream systems, influencing perceived product quality and the flow back of information into the private sector through the attribute product quality gap. This dynamic fosters tension for continuous improvement and lifecycle management.

PUBLIC SECTOR (END-USER) FOCUS

General dynamics:
The public sector operates with limited resources, prioritizing the positive health impact and cost-effectiveness of healthcare services. Over time, a significant reduction in disease burden narrows the discrepancy between the actual burden and global targets, such as the elimination of dog-mediated rabies by 2030 (case study). Consequently, international policies incentivize innovation and patient engagement. A high disease burden raises awareness and encourages healthcare-seeking behavior, indirectly influencing the health impact of the healthcare service.

IMPACT OF ATTRIBUTES (common interests)

General dynamics:
This multidimensional sector evaluates how enhanced attributes affect various subsystems within the public sector, including the in-country supply chain, health service delivery, and costs. Improvements have a positive impact on regulatory approval, expediting the process for timely implementation and access. The greatest impact of enhanced attributes lies in improved product usability, which, along with cost, determines the perceived product quality assuming similar high-quality – in terms of safety and efficacy – among alternative treatments. Hence, increased utilization (through reduced costs and working hours) elevates perceived product quality, assessed for individual attribute impact. Combined with accessibility, the societal utility of the health service serves as a proxy for implementation effectiveness, ultimately yielding more accurate health impact assessments.

CONCLUSIONS

- Existing tools for early-stage biopharmaceutical development lack an integrated view of biotech products' functional system.
- **Implementation science** should be incorporated into biopharmaceutical companies' innovation and development processes.
- Introducing the new concept of **societal product utility** aligns product development with real-world health impact challenges beyond safety and efficacy.
- Societal product utility **accounts for implementation effectiveness** and is supported by a methodological approach and practical modeling framework.
- The integrated framework enables **prospective assessment** of health technology in various implementation scenarios and **shows the broader value** of biopharmaceutical products.
- It captures the complexity of the entire implementation system, **considering common interests** of both the private and public sectors.
- It can be **systematically built into** the current good practices of the **QbD drug development process**.

REFERENCES

1. Deen, J. L. & Clemens, J. D. (2006). Issues in the design and implementation of vaccine trials in less developed countries. *Nat Rev Drug Discov* **5**, 932–940.
2. ICH Official web site : ICH. https://www.ich.org/.
3. ICH. *Q8(R2) guideline on Pharmaceutical Development*. (2009).
4. Yu, L. X. *et al*. (2014). Understanding pharmaceutical quality by design. *AAPS Journal* **16**, 771–783.
5. Rathore, A. S. & Winkle, H. (2009). Quality by Design for biopharmaceuticals. *Nature Biotechnology* **27**, 26–34.
6. Poduri, R. (2021). Pharmaceutical Industry, Academia, Regulatory Authorities and End User Collaboration in Successful Drug Discovery and Development. *Drug Discovery and Development*.
7. Lowe, M. M., Blaser, D. A., Cone, L., Arcona, S., Ko, J., Sasane, R., & Wicks, P. (2016). Increasing Patient Involvement in Drug Development. *Value in Health* **19**, (6).
8. Thorlund, K., Dron, L., Park, J., Hsu, G., Forrest, J. I., & Mills, E. J. (2020). A real-time dashboard of clinical trials for COVID-19. *The Lancet Digital Health* **2**, (6).
9. Parrish, M. C., Tan, Y. J., Grimes, K. v., & Mochly-Rosen, D. (2019). Surviving in the valley of death: Opportunities and challenges in translating academic drug discoveries. *Annual Review of Pharmacology and Toxicology* **59**.
10. Kiriiri, G. K., Njogu, P. M., & Mwangi, A. N. (2020). Exploring different approaches to improve the success of drug discovery and development projects: a review. *Future Journal of Pharmaceutical Sciences*, **6** (1).
11. Yildirim, O., Gottwald, M., Schüler, P., & Michel, M. C. (2016). Opportunities and challenges for drug development: Public-private partnerships, adaptive designs and big data. *Frontiers in Pharmacology* **7**, (Issue DEC).
12. Rodriguez Llorian, E., Waliji, L. A., Dragojlovic, N., Michaux, K. D., Nagase, F., & Lynd, L. D. (2023). Frameworks for Health Technology Assessment at an Early Stage of Product Development: A Review and Roadmap to Guide Applications. *Value in Health*.
13. Butler, D. (2008). Translational research: Crossing the valley of death. *Nature* **453**, 840–842.
14. Excler, J.-L., Privor-Dumm, L. & Kim, J. H. (2021). Supply and delivery of vaccines for global health. *Curr Opin Immunol* **71**, 13–20.

For more information on the different sectors of the **integrated framework** and a **key** for the legends used in the figures, please, see the appendix poster and **scan this QR code**

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