mRNA drugs production from very small to very large-scale capacity: when to use batch versus continuous strategies

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WHO/MPP mRNA Technology Transfer Programme
Regional meeting in South-East Asia

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Vision for Biomanufacturing Technologies with Affordability, Scalability and Flexibility in mind

Engineering approach

Technology-driven innovation applying chemical engineering rules and bioprocessing expertise

Intensification
for high performance operations

Chaining
of unit operations for automated, integrated & continuous processing

Advantages that matters

Affordability	Intensified technologies reduce facility footprint, reducing the CAPEX barrier while achieving high capacity through enhanced performance
Scalability	Technology designed to scale seamlessly from lab/(pre)clinical to mass commercial production.
Flexibility	Technology capable of accommodating a) changeovers, b) different products, c) very different quantities Technology providing a) simplified process dev, b) easier optimization, c) easier characterization and validation

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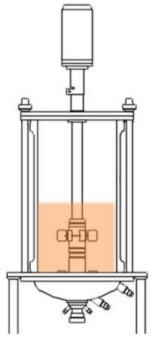
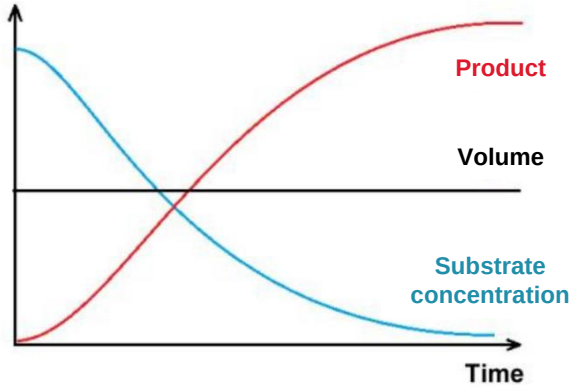
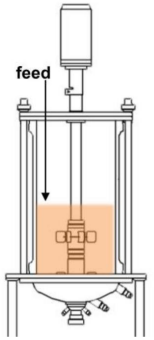
Industrial Biomanufacturing may be divided into three main principles: Batch, Fed-batch, And Continuous Processes

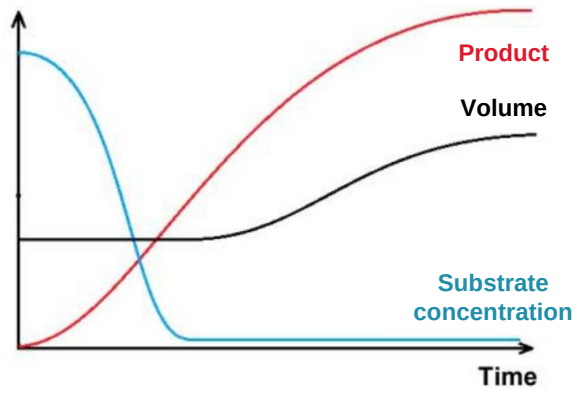
Batch



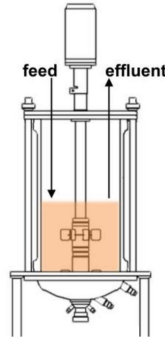


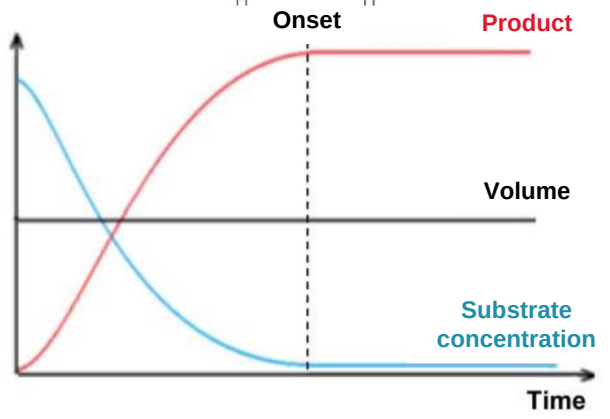
Fed-batch





Continuous





Source: Bolmanis E. et al. Model Predictive Control—A Stand Out among Competitors for Fed-Batch Fermentation Improvement. Fermentation. 2023,9,206.

While Continuous Manufacturing Processes are a standard for Chemical and Petrochemical Industries…

Total Energies' Refining and Petrochemicals Platform, Antwerp, Belgium

Affordability & Scalability Advantages

Higher Efficiency

- Smaller reactor volumes
- Greater throughput
- Time effective

Cost effective

- Lower CAPEX – depreciation
- Lower energy consumption
- Reduced labor costs

Source: Domokos A. et al. Integrated Continuous Pharmaceutical Technologies—A Review. Organic Process Research & Development 2021 25 (4), 721-739

…It has not been widely adopted by Biological and Pharmaceutical Industries, sticking to Batch Mode Manufacturing

Lonza's mRNA manufacturing facility, Portsmouth, New Hampshire.

Reasons… Flexibility

Production Flexibility

- Frequent changeovers
- Different products
- Adaptable quantities

Research & Development

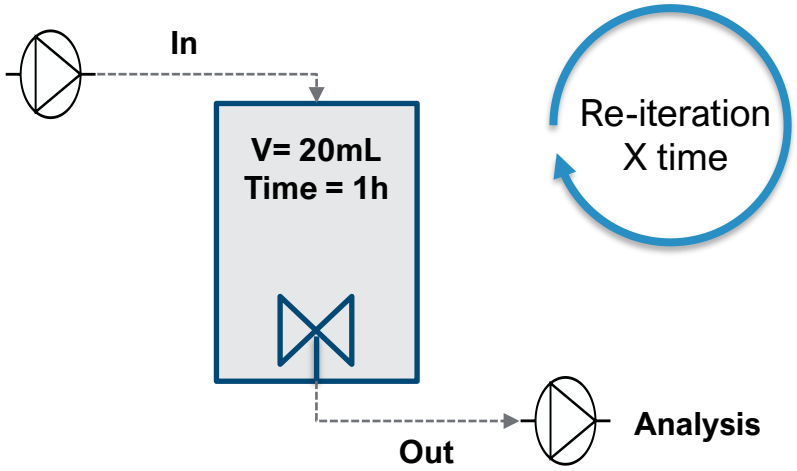
- Simplified process dev.
- Easier optimization
- Easier characterization and validation

Source: Domokos A. et al. Integrated Continuous Pharmaceutical Technologies—A Review. Organic Process Research & Development 2021 25 (4), 721-739

At early stages of Product Development, Batch Manufacturing allows for an easier and more flexible Process Development compared to Continuous Manufacturing

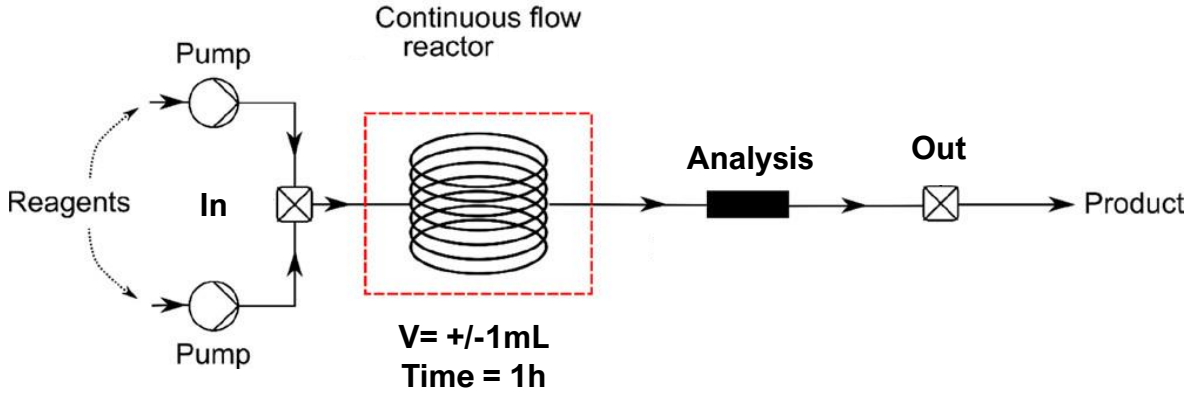
Batch – independent process parameters

- Fixed volume
- Fixed timing (to optimize)
- Fixed parameters per batch
- Re-iteration for optimization (following a DoE)



Continuous (residence time / volume / flowrate are linked process parameters)

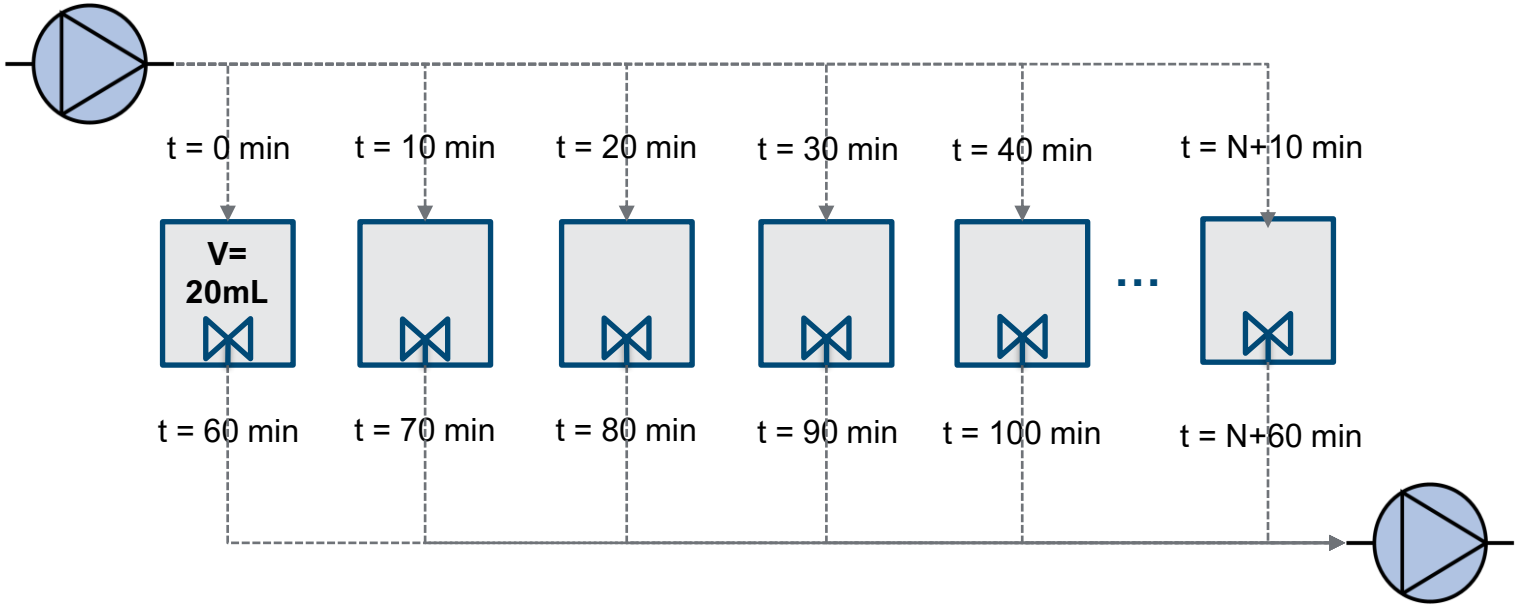
- Flow rate & volume impact reaction time
- Fixed process conditions per run
- Can do « real-time » optimization (following a DoE)
- Several reactor sizes will be needed to accomodate different quantities



Source: Domokos A. et al. Integrated Continuous Pharmaceutical Technologies—A Review. Organic Process Research & Development 2021 25 (4), 721-739

Developing a **Sequential-staggered Process** Combines the advantage of Batch Mode for Process Development while unlocking same benefits for Production as Continuous Mode

Sequential-Staggered: sequenced production of individual batches of small working volume



Affordability, Scalability & Flexibility combined

- High throughput via **scale-out approach**
- Incremental **capacity adaptation**
- Easier experimentation and process optimization
- Smoother transitions from small to large-scale production without a complete process redesign
- Smaller operating units with less downtime for more cost-effective manufacturing

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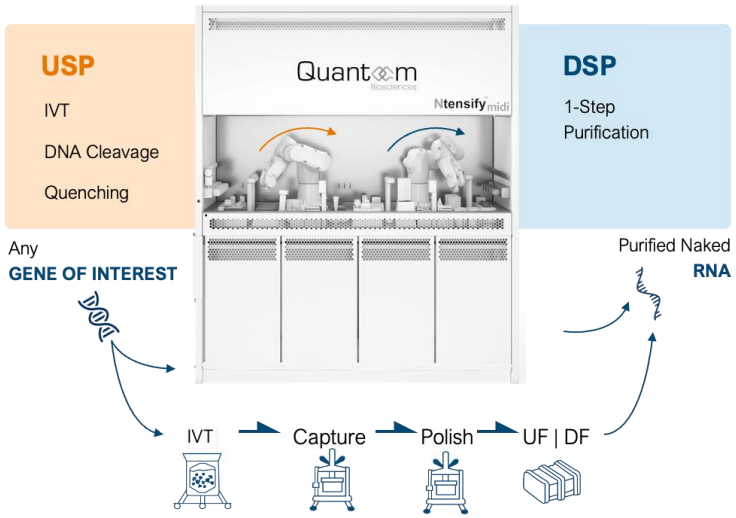
The 2-step journey of Quantoom Biosciences as an example

Process Development Maturity stages

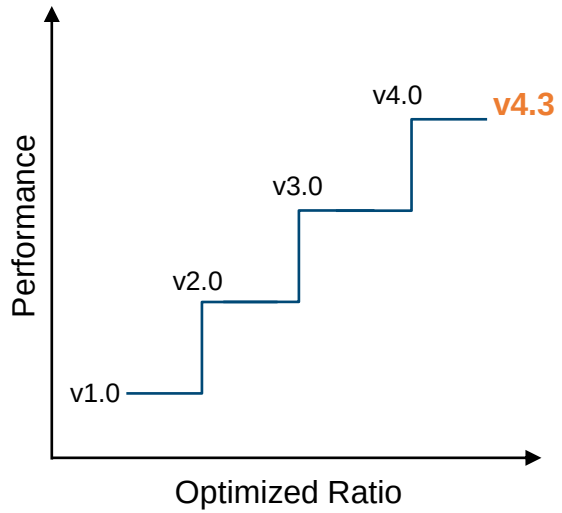
mRNA USP+DSP Redesigned into a simple 2-step Process



mRNA Process Characterized, optimized & construct-agnostic*

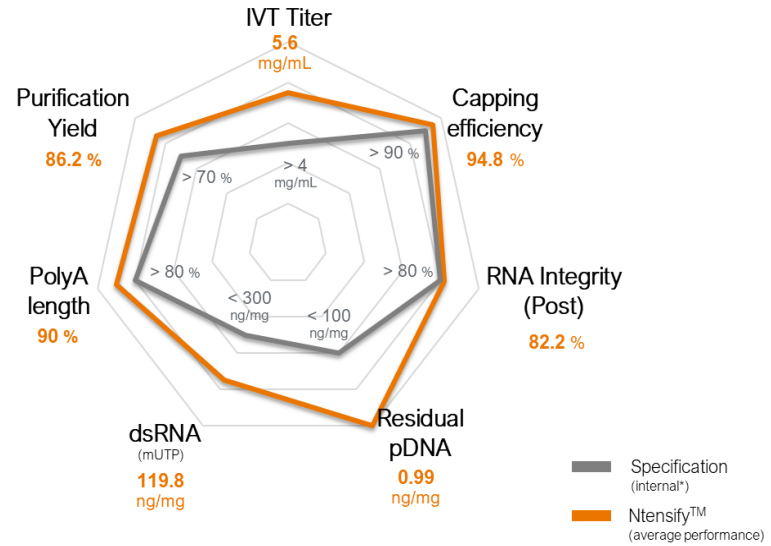
2-year development efforts

Number of reactions: 226
Number of constructs: 43



* co-developed with our partner Etherna

Robust Process Validated, all Process Parameters Locked



* Internal specification developed based on literature and expert options

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The 2-step journey of Quantoom Biosciences as an example

Process Development Maturity stages

mRNA USP+DSP Redesigned into a simple 2-step Process

mRNA Process Characterized, optimized & construct-agnostic*

Robust Process Validated, all Process Parameters Locked

1

Re-designed 2-step process easily
Automated via
Sequential-staggered process

Afrigen

- co-developed with our partner Etherna

eTheRNA engineering RNA

2

BILL & MELINDA GATES foundation

Automated via
Continuous process
Under development

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This approach was translated into Equipment, enabling us to achieve Today and Tomorrow a broad range of production capacities

Tomorrow

Very Small-scale Production

Today

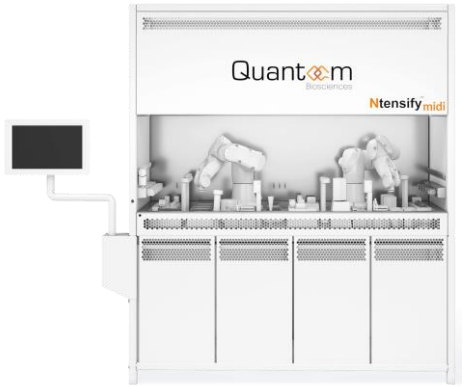
Small-scale Production → Mid-scale Production → Large-scale Production

Tomorrow

Very Large-scale Production

mini **midi** **maxi**

Integrated system
Under development



Continuous system
Under development

10mg E2E
“ready-to-inject"

5mg (screening)
100mg

1g
5g

6kg

From 120kg
To “unlimited"

BILL & MELINDA GATES foundation

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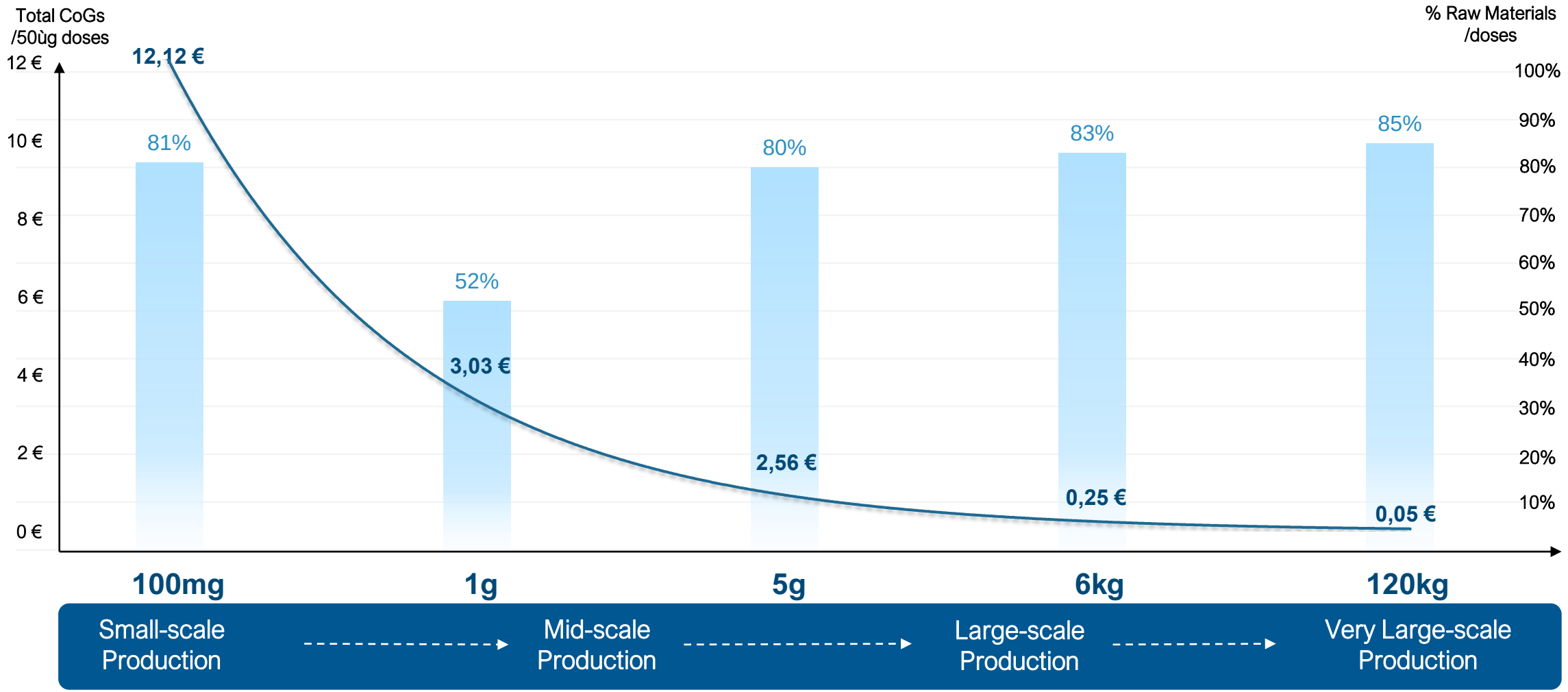
Ultimately allowing substantial savings for the drug developers



Note: CoGs per doses for Large and Very Large-scale production based on projected estimates from internal Total Cost of Ownership model. Full annual production capacity considered.

Key Takeways

- From early R&D to very large-scale production, **no single technology can fit all needs – we aim at providing the best technology/application fit**

- We **make the technology choice easier** for desired application(s):
  - **Redesigned & optimized 2-step mRNA process** know-how translated into **Ready-to-Use Mixes**
  - **Scalable and automated equipment** technologies to ensure repeatability, consistency, reproducibility with maximum flexibility

- Our **Ready-to-Use Mixes** are **assembled** in **two EU sites**, using **Raw Materials** sourced from **international established suppliers**, meeting all required quality attributes & can be used **with or without our equipment**

- **Critical Raw Materials** (8 enzymes, 10 r&d-NTP, 4 capping reagents) will be internalized and manufactured in cooperation with at least 2 members of the WHO/MPP RNA Hub
- Process/Ready-to-Use Mixes will eventually be produced in at least in one LMIC
- Looking for additional partnerships for formulation reagents

THANK YOU FOR YOUR ATTENTION

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