Quantoom Biosciences | mRNA Production Reinvented

White paper

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A New Paradigm in mRNA Bioprocessing

How Ntensify™ Reshapes Affordability and Reduces Time-to-Market

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Abstract

Recent development in mRNA bioprocessing represent a promising solution in therapeutic development, by offering rapid manufacturing, enhanced safety profiles, and flexibility. However, and partly due to the lack of dedicated manufacturing solutions, their full potential has yet to be realized. This paper introduces Ntensify™ as an innovative mRNA production system and demonstrates how it significantly enhances productivity and cost-effectiveness. Ntensify™ leverages an optimized mRNA production process executed by a fully automated equipment, resulting in industry-leading yields and recovery rates. Its adaptability is showcased across a wide range of constructs, underscoring its robustness and sequence-agnostic capabilities. Furthermore, its streamlined approach reduces costs, making mRNA-based therapeutics more accessible. Finally, in the context of pandemic preparedness, Ntensify™ emerges as a critical asset, enabling swift response with its production capabilities. All in all, Ntensify™ transformative potential reshapes the landscape of mRNA drug development and reinforces global healthcare preparedness.

Content

Introduction

mRNA-based vaccines and therapies represent a transformative leap in the field of drug development, gaining significant attention and recognition since the COVID-19 outbreak[1]. Unlike traditional treatments that often rely on attenuated or inactivated pathogens, mRNA-based vaccines are made of a synthetic piece of genetic material that instructs cells to produce a harmless antigenic protein found on the target pathogen's surface that triggers the immune response[2]. This approach not only eliminates the need for cultivating live pathogens but also expedites vaccine development, allowing rapid adaptation to emerging variants[3].

However, despite these remarkable benefits, the full potential of mRNA vaccines has yet to be realized due to several bottlenecks in their processing. One major challenge lies in the absence of dedicated manufacturing solutions specifically designed for mRNA production[4]. Existing mRNA-based vaccine manufacturing infrastructures are currently ill-suited, requiring significant reconfiguration to ensure consistency, effectiveness or safety of mRNA-based products. Consequently, this lack of tailored equipment and processes hampers production efficiency and can lead to increased costs and delays.

Furthermore, scalability emerges as another critical hurdle for mRNA-based vaccine manufacturing[5]. While initial production volumes were manageable, the demands of global vaccination efforts have highlighted the limitations of existing manufacturing capacities. Achieving large-scale production of mRNA vaccines remains a complex task, as the delicate nature of mRNA molecules demands precise conditions and stringent controls of critical quality attributes. Scaling up while maintaining consistency and efficacy becomes a complicated task.

To address these challenges, Quantoom Biosciences developed a suite of purpose-built production technologies for mRNA manufacturing which – alongside an optimized process - significantly enhances manufacturing efficiency and reduces production costs. Additionally, implementation of process intensification features and streamlined automation contributes to addressing the scalability bottleneck, enabling rapid response to pandemic threats and ensuring equitable access to vaccines on a global scale.

This white paper spotlights the groundbreaking innovation brought forth by Quantoom's Ntensify™ approach, demonstrated across the entire journey of mRNA-based vaccine development, spanning both routine endemic scenarios and times of pandemic.

How does Ntensify™ reinvent mRNA production?

Ntensify™ combines an automated solution with set of optimized reagents and consumables to produce naked mRNA. Featuring a small footprint, it efficiently synthesizes and purifies bulk RNA using Quantoom's reagent pre-mixes, optimizing yield and quality from a selected DNA template. During the process, mRNA is synthetized and capped, followed by DNA cleavage and reaction quenching. Then, the produced mRNAs are purified during a 1-step purification process, enabling outstanding recovery yields.

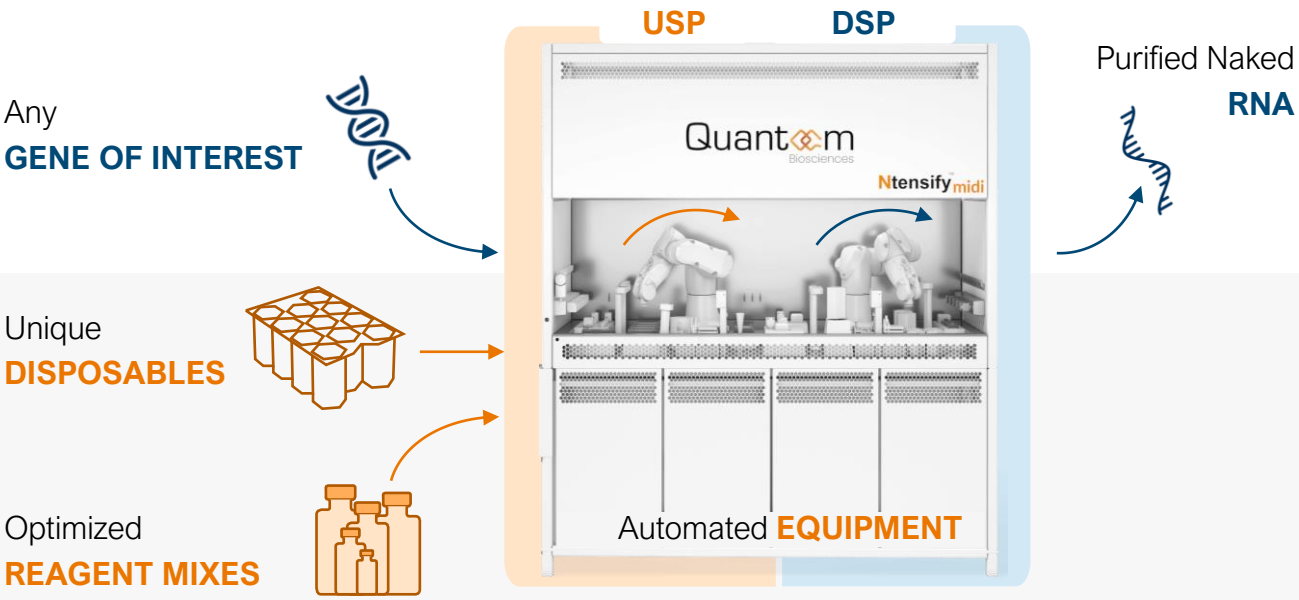


Figure 1: Ntensify™ for mRNA manufacturing, combining optimized reagent mixes with unique disposables and automated equipment

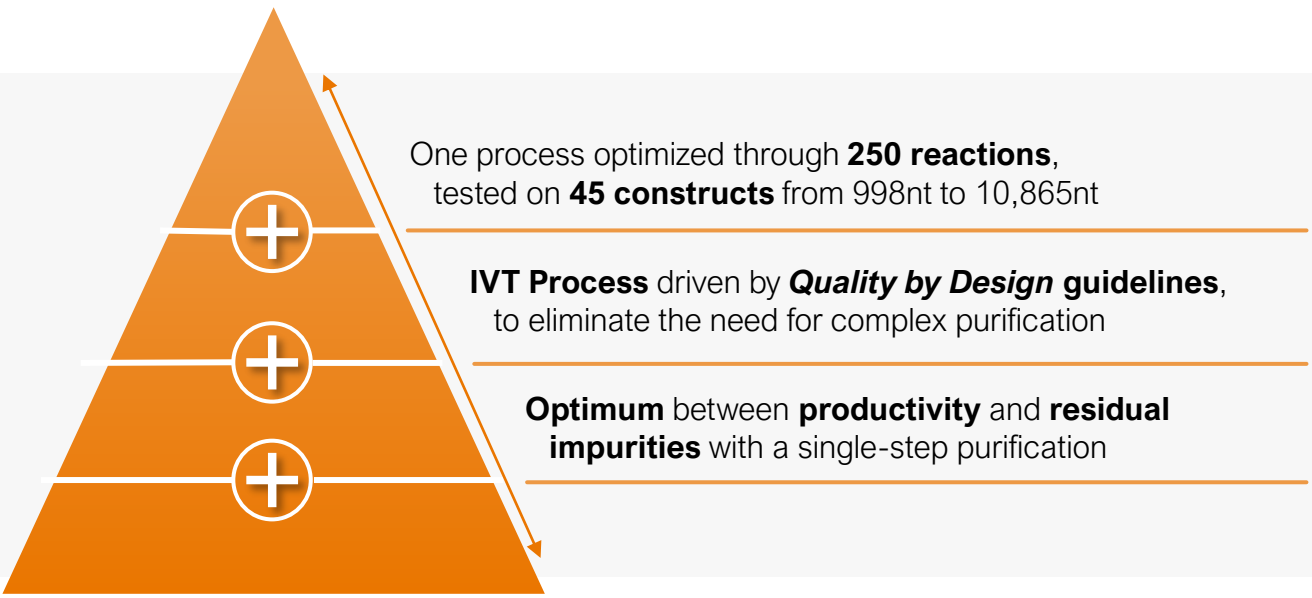


Figure 2 : Ntensify™'s proprietary mRNA synthesis process, optimized through a rigorous process development involving multiple experiments using various DNA constructs.

Ntensify™ for substantial saving for any construct at any scale

A construct-agnostic process

Our de-risked construct agnostic process ensures high yields and quality, while minimizing reagent consumption for equivalent output. Originally based on technology from partner eTheRNA™, this process has been jointly refined and optimized through extensive D.o.E on various mRNA constructs, eliminating the need for multiple optimization rounds and directly implementing a versatile, and streamlined approach. The high yield and quality allow single-step purification, reducing time, cost, and space requirements, all contributing to cost-effectiveness.

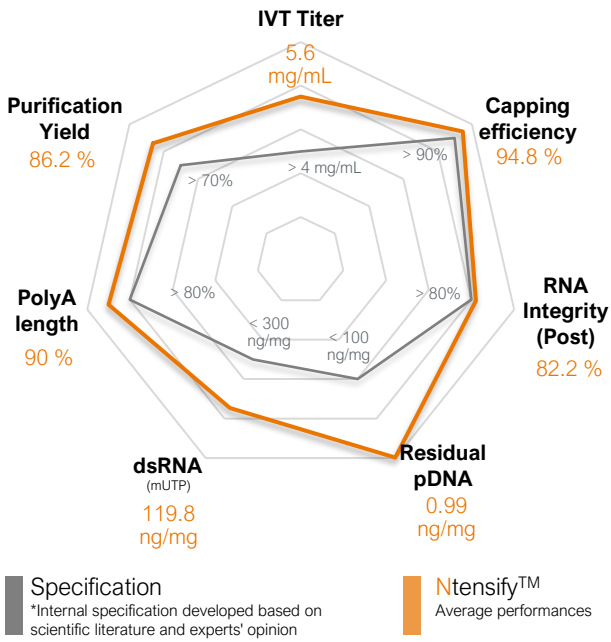


Figure 3 : Process chart of our Ntensify™'s , highlighting the high yield, recovery and quality profile while minimizing contaminants.

Reduced Scale-up needs

Ntensify™'s approach eliminates the conventional scale-up complexity. Unlike conventional approaches that require resource-intensive step-by-step scaling, Ntensify™'s continuous batch mode at a consistent scale accelerates production, enabling efficient large-scale production without the necessity of increasing reaction volumes.

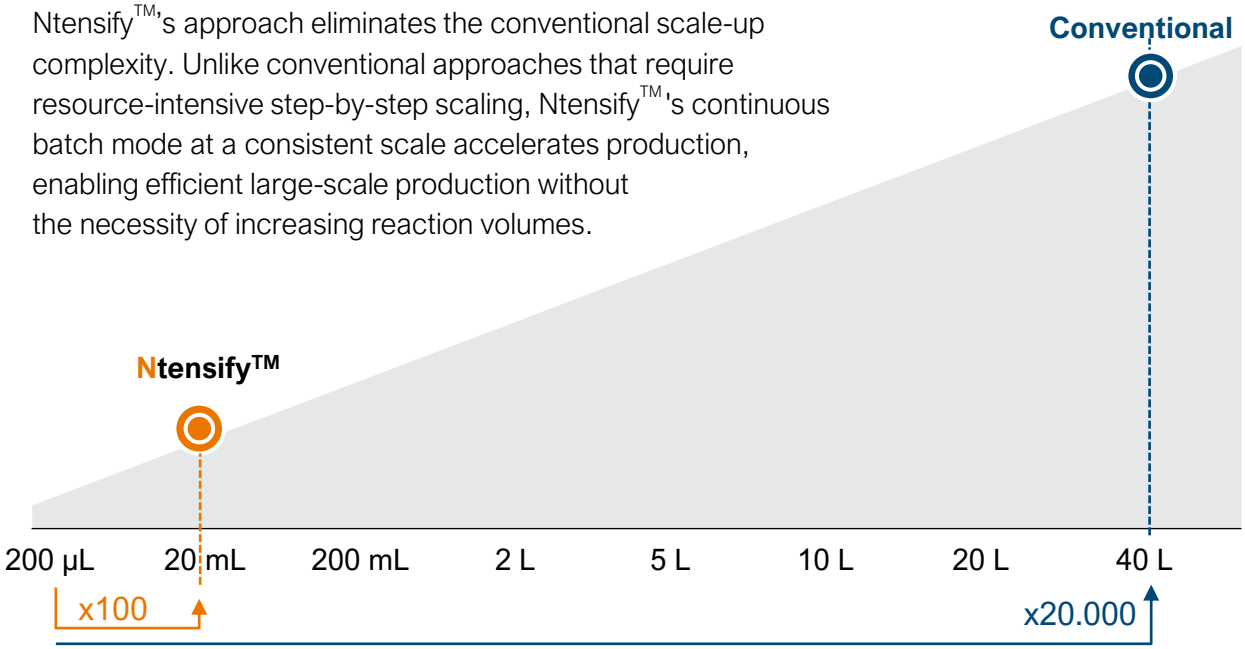


Figure 4: Equivalent production volume for 50 million doses (50 µg) of an mRNA vaccine. While conventional production methods will require you to scale from 20ml to 40L, our Ntensify™ with unique disposables enables production in continuous batch-mode

A simplified and automated workflow

Moreover, supplying ready-to-use reagents and disposables minimizes the space needed for buffer and material preparation and storage, further lowering costs and production time. Ntensify™'s simplified, intensified, and chained workflow enables mRNA production from DNA template to formulation in a space as compact as a shipping container , greatly impacting the Cost of Goods (CoGs).

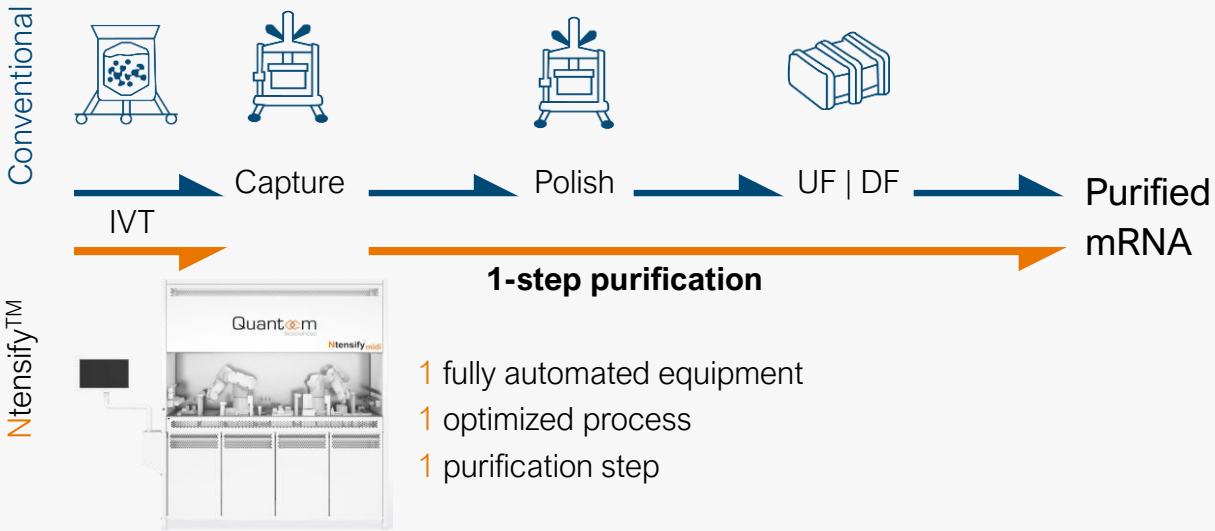


Figure 5: Comparative representation of an mRNA manufacturing workflow, from IVT to purification. The Ntensify™ process drastically reduces the number of required steps by using a single step purification.

A small facility footprint

Ntensify™'s equipment emphasis on minimizing facility footprint leads to a simplified workflow with compact equipment. This design streamlines operations by automating critical steps and reducing operators' intervention and space requirements. The small equipment footprint contributes significantly to cost savings and capital expenditure reduction while enhancing reproducibility.

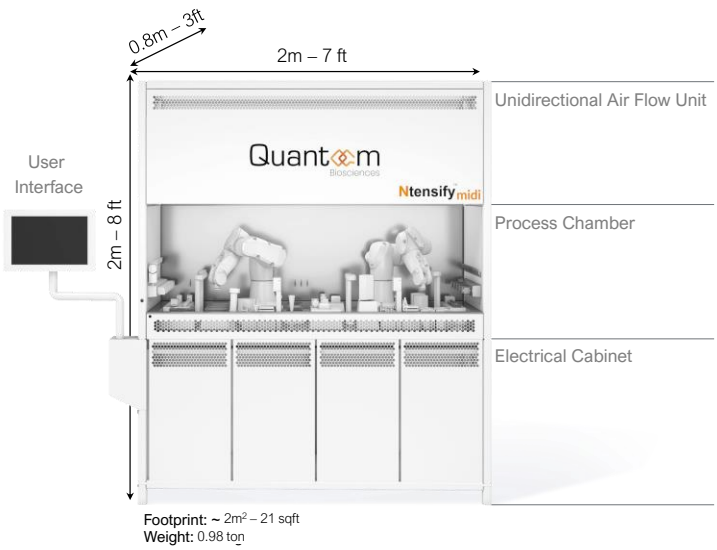


Figure 6: The Ntensify™ the combines both IVT and downstream purification in one small footprint equipment, reducing the required manufacturing space.

These advantages position Ntensify™ as a transformative solution, not only optimizing production processes but also driving substantial cost and time effectiveness.

Ntensify™ enables savings from drug development to commercial production

Drug development

The Ntensify™ benefits introduce a game-changer shift from conventional methods, driving substantial annual cost-of-goods (CoGs) savings. This significant impact spans the entire drug development journey. These savings start right at the beginning of drug development with the Ntensify™ Mini, tailored for drug discovery and preclinical phases, and followed by the Ntensify™ Midi, a key asset during clinical trials. Conventional drug development entails CoGs of around $2.3 million, while adopting Ntensify™ reduces this cost to only $0.7 million, translating to a remarkable $1.6 million savings. And that's not all – instant access to Ntensify™'s construct-agnostic and optimized process adds an extra $2.3 million savings, as well as enabling a sharper focus on candidates' development.

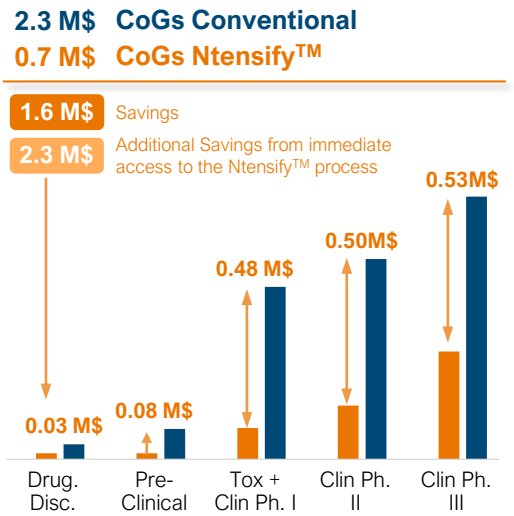


Figure 7 : cost comparison during drug development between our Ntensify™ and a conventionnal workflow.

Commercial production

As your candidate vaccine progresses to commercial production, your capacities are already at scale for a launch, fulfilled with Ntensify™ Midi, while a seamless upgrade to Ntensify™ Maxi accommodates ramp-up and final scale production needs for post-launch production. Starting the candidate's commercial launch, Ntensify™'s impact expands exponentially with over $50 million total annual savings, resulting over the course of a 3 years plan in $178 million total savings.

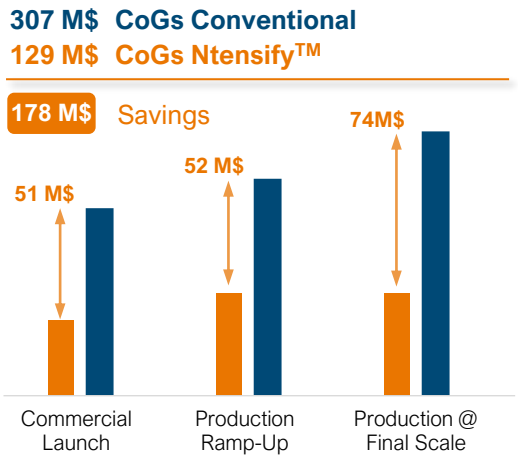


Figure 8 : cost comparison during commercial production between our Ntensify™ and a conventionnal workflow.

CoGs Savings through Ntensify™

In mRNA-based vaccines, reagents represent ~80% of the total manufacturing CoGs at each development step.

The **Ntensify™** has a **significant impact on the CoGs**. Indeed, our solution compared to the conventional solution allows to reduce the cost per mg of DS by **2 to 3x.**

It means that with the reduced CoGs, you can offer **more preferential prices** to your customers and hence **be more competitive in the market.**

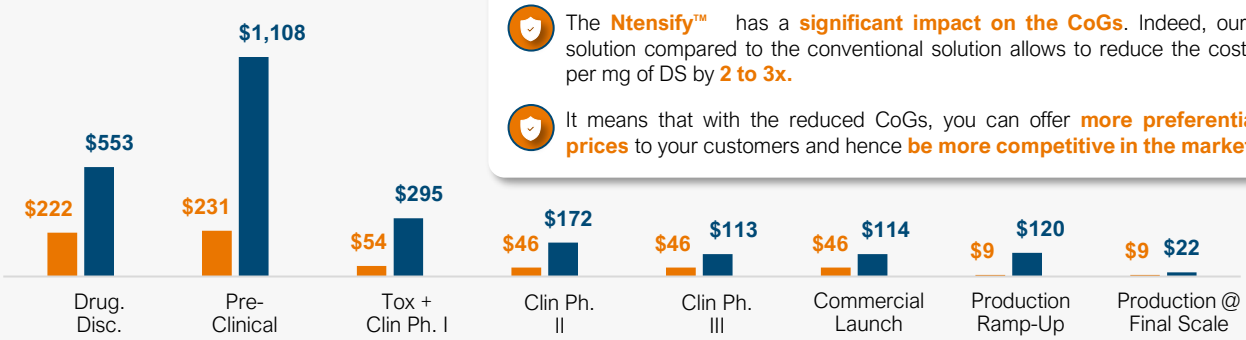


Figure 9 : cost comparison per mg of purified naked mRNA, between Ntensify™ and a conventional mRNA production workflow; alongside the drug development journey.

How Ntensify™ Empowers Pandemic Preparedness

Considering a scenario where production of an mRNA-based vaccine is crucial for pandemic management. By leveraging the cutting-edge capabilities of Ntensify™, the timeline for mRNA-based vaccine production is condensed to just three months, transforming pandemic preparedness by setting a new standard for emergency vaccine production.

Using below-mentioned equipment, three months of production are sufficient to cover the mRNA needs for each given country.

10 Ntensify™ Maxi

250M population

Indonesia
Brazil
Pakistan
USA

5 Ntensify™ Maxi

125M population

Mexico
Japan
Ethiopia
Bengladesh

1 Ntensify™ Maxi

25M population

Cameroon
BeNeLux
Autralia
Venezuela

Figure 10 : Projected amount of Ntensify™ Maxi equipment required to produce – in under 3 months - sufficient mRNA vaccines for given population, reported in country.

Ntensify™'s ability to swiftly produce vaccines at large scale paves the way for rapid and effective pandemic response. It transforms the landscape of vaccine availability, positioning us to be better prepared to safeguard communities on a global scale.

Ntensify™ for expedited vaccine development

In addition, Ntensify™ presents a revolutionary solution to expedite pandemic preparedness, transitioning from the traditional timeline that spans approximately 10 years[6]. Even with accelerated efforts during the COVID-19 pandemic[6], which reduced the timeline to around 20 months by parallelizing clinical trials and initiating risk-associated commercial production, there's still a pressing need to further shorten this duration in alignment with the CEPI 100 days program[7].

The primary goal of the CEPI 100 days program is to achieve a remarkable reduction in vaccine development time to just 100 days. In this pursuit, Ntensify™'s technology emerges as an ideal ally by offering a range of unparalleled benefits. First and foremost, it ensures a seamless scale-up, obviating the challenges of transitioning from research to large-scale production. Moreover, the technology boasts an optimized mRNA process, fine-tuned to maximize efficiency and output quality. One of the most impactful aspects is that Ntensify™ enables production without assuming any risk, a critical facet in the face of emerging pandemics. With Ntensify™'s capabilities, vaccine development can align more closely with the ambitious CEPI 100 days objective, ushering in a new era of pandemic responsiveness.

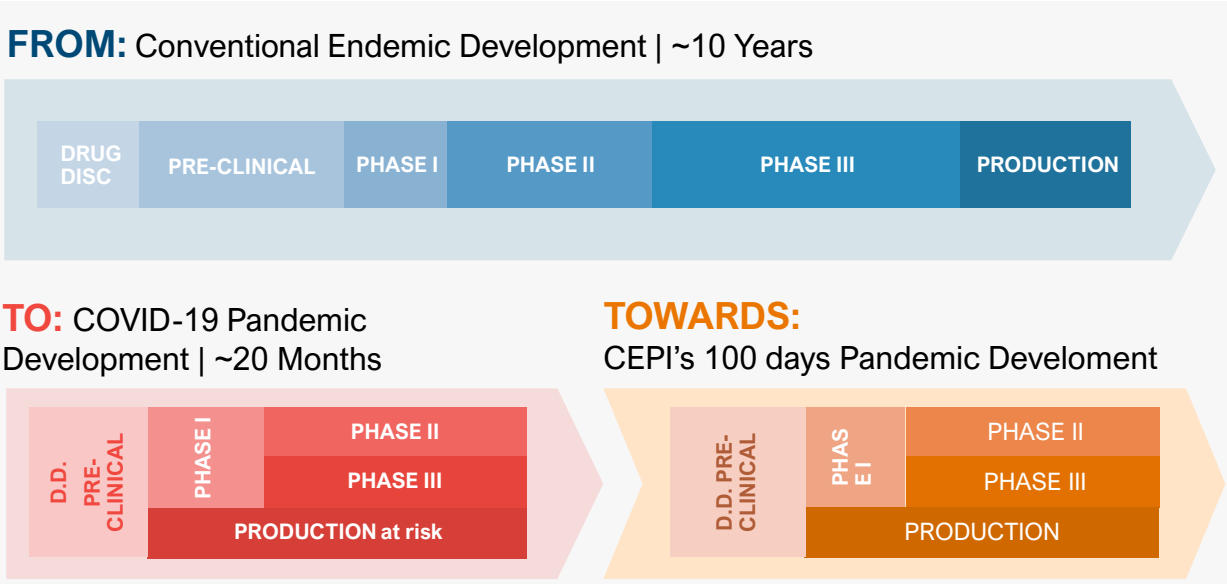


Figure 11 : Comparison of drug development timelines in an endemic context, in the context of a worldwide pandemic context and simulating CEPI's 100 days pandemic development timelines.

Ntensify™ solution

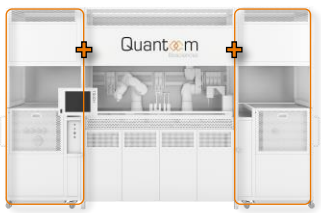
- Seamless scale-up
- Optimized mRNA process
- Production at **NO** risk

Assumptions on a drug development journey with Ntensify™

Our analysis model is based on a Total Cost of Ownership model. It is constructed based on the required amount of drug substance at each stage of a candidate development. For drug discovery, we assume 2 mg per construct; pre-clinical studies necessitate 100 mg of a single construct, both aligned with Ntensify™ mini's production capacity. To cover a full clinical trial, we assume that 1 g for toxicity, 1 g for phase 1, 5 g for phase II, and 10 g for phase III were needed, consistent with Ntensify™ Midi's batch output capacity. For commercialization of 15 million doses (50 µg/dose), accounting for our process IVT titer and purification yields, it requires a 0.8L reactor volume per batch with the Ntensify™ Midi. At final production, catering to a market need of 100 million doses, it necessitates a 28L reaction volume per batch achieved with the Ntensify™ Maxi.

Comparatively, we evaluate our Ntensify systems against an mRNA process model involving a one-step enzymatic in-vitro transcription (IVT) with 2-step chromatography purification and a UF/DF step. Step yields and recoveries have been assumed from literature to anticipate process volumes for each drug development steps.

This comprehensive approach enables us to strategically assess the cost implications at various production stages while considering realistic production capacities, market demands, and process complexities.

	Drug Discovery	Pre-Clinical	Clinical Trials Tox → PhI → PhII → PhIII	Commercial Launch	Commercial Ramp Up
Mass of DS	**2mg**	**100 mg**	**1g → 1g → 5g → 10g**	**750g** 15M Doses	**5.5kg** 100M Doses
# of Constructs	48	1	1	1	1
# Batches	1	1	1 → 1 → 1 → 2	150 (annual)	42 (annual)
	R&D  **Ntensify™ mini**	**cGMP**  **Ntensify™ midi**	**Upgrade**  **Ntensify™ maxi**		
Reactor Volume	**0,4mL**	**0,4mL**	**20mL**	**20mL**	**20mL**
Equiv. Batch Volume	0,4mL	19,2mL	200mL → 800mL	800mL	28L

Conventional mRNA vaccines manufacturing

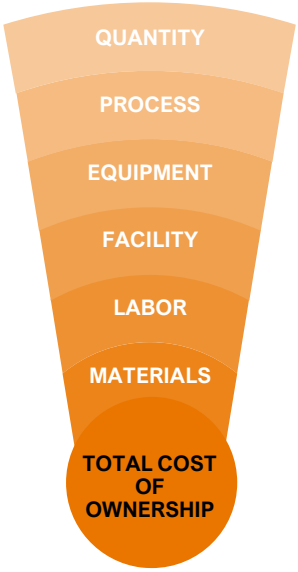
Batch Volume	**1mL**	**50mL**	**0,5L → 0,5L → 2L → 2L**	**2L**	**2*35L**

Note: 1 dose assumed to be 50µg. Full annual capacity of systems considered in our model.

The values displayed in this document reflect the current status of our knowledge in respect of the performance of the device and the production process. They are based on average values in production data observed with various inputs. The actual performance in a particular case can deviate from the values shown, in function of the type of material and other aspects affecting the output. As a result, these outputs cannot be warranted as absolute or typical values.

In essence, a cost model is a valuable tool for estimating costs, resource planning, and scenario comparison. Yet, it's important to acknowledge its limitations in terms of precision, market dynamics, and unforeseen technological advancements. It offers guidance for decision-making rather than exact predictions of the future.

How to build a *total cost of ownership* model



Our calculation model starts by establishing an envisioned production quantity expressed in doses per year, tied to the Drug Substance quantity per dose. Using this projected quantity, the model computes anticipated process volumes, driven by essential mRNA process parameters: IVT titer and recovery yield.

These calculated process volumes serve as a basis for estimating the entirety of required equipment and the manufacturing facility footprint. The costs associated with acquiring, enhancing, and maintaining these physical assets constitute the Capital Expenditure (CAPEX). Moreover, these anticipated process volumes enable the determination of the Full-Time Equivalents (FTEs) necessary for the entire manufacturing process.

Additionally, they facilitate the estimation of the Bill of Materials encompassing consumables (such as reagents and disposables) needed for the targeted production.

Consequently, the expenses related to these materials constitute the Operational Expenditure (OPEX). Ultimately, the outcome is a comprehensive cost modeling tool capable of assessing the cumulative direct expenses resulting from the mRNA-based vaccine production, thus allowing for a comparative analysis of the cost of goods sold (CoGs) arising from different methodologies.

Key Takeways

1. Ntensify™ is an automated technology that synthesizes and purifies bulk mRNA, enhancing yield and quality while minimizing reagent consumption. It offers a tailored solution for mRNA vaccine developers, supporting the entire drug development journey from candidate discovery to commercial production.
2. Ntensify™'s distinctive advantages include a de-risked construct-agnostic mRNA process that ensures high yields, reduced reagent use, and a unique design that eliminates the need for resource-intensive scale-up. Combined, these 3 elements result in efficient production and minimized costs.
3. Ntensify™'s adaptable significantly reduces reagent costs by an order of magnitude of 2 to 3 times. Our analysis shows that – for a 50µg mRNA vaccine candidate - our solution can drive 3.9M$ cost savings during de drug development cycle up to an impressive $178M savings at commercial production.
4. Ntensify™'s rapid vaccine production capability can achieve a remarkable time advantage for entering the market, revolutionizes pandemic preparedness and offering a transformative solution to safeguard global communities. Ntensify™'s streamlined approach for vaccine production establishes a new standard in pandemic response, while aligning with the ambitious CEPI 100 days program objective for expedited vaccine development.

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ABOUT QUANTOOM BIOSCIENCES

Quantoom Biosciences, part of Univercells Group affiliates, was founded in 2021 in the wake of the COVID-19 pandemic to pursue Univercells' mission in the sector of nucleic acid-based medicines. Quantoom's Nfinity™ platform encompasses a comprehensive suite of technologies to enable affordable end-to-end production of mRNA-based products, from DNA to bulk drug products. Ntensify™ production systems are fully automated compact manufacturing systems that integrate the complete mRNA manufacturing process in a unique sequential-staggered process train, delivering mg up to multi-g of purified drug substance per batch.

Univercells was founded in 2013 with the mission of making biologics available for all by pursuing radical innovation in production technologies to achieve a dramatic reduction in the cost of goods and capital investment.

CONTACT US

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