aptamer GROUP

Optimer®:
Accelerating your journey to the clinic

White Paper

Executive summary

For any affinity binder-based therapeutic or diagnostic, the cost and time-to-clinic can make the difference between the success and failure of the product.
When benchmarked against current antibody development processes, the use of Optimer binders can reduce timelines by as much as 75% through fewer and faster development steps.

This advantage could cut valuable months from development timelines, allowing scientists to reach critical milestones faster and offer a competitive advantage in entering clinical trials earlier. Reducing the time-to-clinic with Optimer binders could offer key savings, whilst simultaneously reducing risk in the development of new drugs and diagnostics.

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Introduction

Affinity binders are used across the life science industry to develop new therapeutics, diagnostics, and biomanufacturing processes. The cost and timelines for affinity binder development and subsequent manufacture can be critical to any commercial asset involving these molecules.

High material or service costs at any point in the development process may hinder commercialisation, potentially leading to project cessation and the loss of previous research. To prevent this, researchers and developers need to be aware of affinity binder costs and timescales from project initiation.

Effective new therapeutics and diagnostics are essential to improving patient outcomes. One study showed that for every year between discovery and approval of new therapeutics, over a million patient life years were lost.[1]

Developing a new drug from initial concept to commercialisation typically takes 10-15 years and is associated with an average cost of $1.3 billion.[2] Diagnostic developments are significantly faster but still take 18-24 months to develop, with costs in the region of $12-55 million.[3]

Considering the cost and risk associated with such development and the importance of new treatments and tests for patients, any opportunity to increase efficiencies or reduce the time-to-clinic, even by a few months, offers clear value.

Compared to antibodies, which currently account for the major component of the life science affinity binder market, employing Optimer binders as an alternative offers several time and cost benefits, which could be significant during this critical development period.

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Monoclonal antibodies: establishing a benchmark

Monoclonal antibodies (mAbs) represent the most commonly used affinity binder in the market, and account for the majority of binders in clinical development.[4] MAbs have been adapted for various research applications, incorporated into diagnostics, and become the predominant class of new drugs developed in recent years.[5]

However, mAb discovery is still primarily performed using immunized animals, with over 90% of the FDA-approved antibodies being animal-derived.[6] Reliance upon the immune system of an animal can limit the available target range, with small molecule, toxins and non-immunogenic targets often failing to generate sufficient immune responses to allow antibody generation.[7] Indeed, antibody discovery has been identified as the biggest challenge in antibody therapeutics by professionals across the field.[8]

If successful in discovery, further antibody engineering steps are often required before the antibody is ready for clinical application. These include humanisation, to improve safety, and modulation of affinity and half-life, to ensure biological function. Each of these steps requires additional time and cost, and present a potential risk of failure, before a suitable candidate molecule can be progressed.

Commercial production of mAbs is currently achieved by stable gene expression of recombinant DNA, with more than 70% of commercial mAbs industrially produced in Chinese Hamster Ovary (CHO) cell lines.[9,10] This is often preceded in initial discovery phases and early-stage pre-clinical studies by using transient expression at smaller scales.

To support the increased demand for mAbs, their development processes have been intensively refined. Current CHO engineering processes are able to generate high production yields of 5-10 g/L,[11] recovery rates of up to 70-80% and reduce development timelines, requiring 12-15 months from the generation of a stable mAb-producing cell line to full manufacturing and quality processes that can support IND filing for drug development processes.

Although CHO cell-based processes are successfully used for mAb production, they involve time-consuming cell line development and cloning steps for each new product

Binder generation via the Optimer platform was compared with current industry-standard mAb processes, timelines, and costs, for mammalian-cell culture-derived molecules. This research was carried out by surveying over 20 industry-leading sources, including industry consultants, therapeutic developers, diagnostic developers, and antibody and oligonucleotide developers and manufacturers, in addition to the available current literature.

Over 90% of FDA-approved antibodies are animal-derived.[6]

The capabilities of the Optimer platform

The Optimer platform generates oligonucleotide-based affinity binders that can be used to enable novel and improved solutions across the life science industry. The platform consists of three parallel processes that are specifically optimised to accommodate different target types:

1. small molecules
2. proteins and peptides
3. cells and tissues

The Optimer discovery and development processes offer complete control over affinity binder design, including specificity and cross-reactivity, with the opportunity to tune binding kinetics according to the desired application. Moreover, the wholly *in vitro* process ensures compliance with the latest directives concerning animal-derived binders for diagnostic use.[12]

Optimer binders are employed to pursue new targets and biomarkers and to develop new treatment methods, analysis, and biomanufacturing in the generation of therapeutics, diagnostics, and novel research solutions.

Comparing time and cost for binder discovery and development

The opportunity to speed the development process increases the potential to be first-to-market with a new product,[13] increases the period of potential patent protection for any developed product, and offers faster patient access to valuable treatments and tests to improve patient outcomes.[1]

Reducing timelines associated with affinity binder discovery and development can be achieved by making individual processes within the development pathway faster, or in some cases, the processes may be removed entirely. Optimer development speeds the time-to-clinic using both of these strategies to reduce the discovery and development timeline.

MAb discovery and development was found to take 98-198 weeks. The potential variance in the timeline is due to the requirement for additional antibody engineering steps and the timelines of various developers and suppliers. In comparison, to reach this stage with Optimer binders takes just 50-62 weeks.

Optimer binders can cut 2.8 years from discovery and development timelines, compared to antibodies.

The overall cost of mAb and Optimer development are comparable. MAb costs cover a broader range than Optimer, partially due to the increased number of steps required for mAb development. Limiting development steps with Optimer potentially offers less risk of failure. Increased costs for RNA Optimer binders are present early in development due to the higher cost of raw materials for RNA compared to DNA, though later development costs are comparable across both DNA and RNA.

Development stage	Optimer development time (weeks)	Optimer development cost ($1000s)		Antibody development time (weeks)	Antibody development cost ($1000s)
		DNA	RNA		
Discovery	10-12	70-150	70-150	16-40	40-120
Manufacture (100mg)	4	4-11	40-65	4-9	4-10
Humanisation	Not required	Not required	Not required	14*	48-60*
Manufacture (1g)	4	15-40	250-350	4-9	15-70
Affinity maturation	Not required	Not required	Not required	20-26*	150-280*
Stable cell line generation and cell banking	Not required	Not required	Not required	26-30	400-950 (250-1,000 for license)
Manufacture scale up and verification	20-22†	280-700	280-700	20-26†	140-600
Formulation	12-26†	250-400	250-400	12-30†	250-400
GMP clinical supply(100g)	12-16	300-1,000	300-1,000	16-40	85-150
TOTAL	**50-62**	**$919-2,301**	**$1,190-2,665**	**98-198**	**$1,184-3,640**

*Timelines and costs for Optimer and mAb discovery and development processes * denotes process steps that may not be required depending upon the outcomes of the discovery phase so have been removed from lower time estimates. † denotes processes that run in parallel, so timelines include the limits across the two stages.*

Discovery to lead candidate

1. Accelerating candidate discovery with Optimer

As a wholly *in vitro* synthetic process, Optimer discovery removes the reliance upon cell or animalbased systems, allowing highly automated, parallel, and rapid discovery processes. Standard Optimer development projects take between 10 and 12 weeks to progress from concept to developed candidate binders. If processes are aligned for speed rather than capacity, discovery can be completed in as little as four weeks.

1. half-life optimisation of therapeutic candidates
2. identification of binders with the required binding characteristics and specificity
3. NGS-screening for lineage mapping
4. candidate binding assessment

The Optimer discovery project timeline is up to ~30 weeks shorter than standard mAb discovery. The time for mAb discovery remains high as it relies on animal-derived systems, including immunisation and the generation of an immune response, which can take up to 12 weeks. Following the generation of an immune response to the target antigen, binder selection, involving B-cell enrichment and single-cell isolation and characterisation, account for a further ~16 weeks before the characterisation and purification of candidate clones.

Optimer discovery processes can fast-track this stage by as much as 75% while maintaining high success rates of up to 77%. Costs for Optimer and mAb discovery fall within the same range. Though Optimer discovery is at the high end of the range compared to mAb discovery, some of the mAb process costings were within this range. Often suppliers stated project complexity as the reason for the higher discovery costs.

2. No requirement for additional binder engineering with Optimer

Two substantial steps in the mAb development processes are not required in the development of Optimer binders:

1. humanisation
2. affinity maturation

Humanisation and affinity maturation of candidate mAbs typically takes ~14 and 20-26 weeks, respectively, from the suppliers surveyed as part of this report. These processes may not always be necessary if a human library or a humanised animal is used for mAb discovery (although the use of humanised animals is associated with higher cost) or should the performance of the candidate molecule be sufficient from the outset.

Currently, the majority of developed mAbs rely on standard animal-derived binders.[6] For therapeutic applications, humanisation of the mAb candidate is thus essential to prevent immunogenic side effects. Many diagnostic developers have effectively utilised animal-derived mAbs in their tests, negating the need for humanisation. However, reports of false positive or false negative results from human anti-animal antibody responses, e.g., human anti-mouse antibodies (HAMA-responses),[14] make humanisation of mAbs a potentially important step for developers of future diagnostics.

If the discovery processes identify mAbs with the required binding characteristics, affinity maturation would not be required. Nonetheless, affinity maturation is a renowned bottleneck for antibody development.[15] Engineered improvements in affinity often result in deficits in alternative characteristics, such as stability, specificity, solubility, and effector function,[16] and can cause candidates to fail to progress further in development.

Together, these mAb candidate engineering stages account for 34-40 weeks to achieve a fully optimised mAb, costing between $198,000-340,000 from the suppliers surveyed here. Neither of these processes is required in the Optimer development pathway. Optimer binders are not based on animal-derived molecules, and identification of the necessary affinity, specificity and functional activity is engineered into the Optimer discovery process.

3. Speeding small scale manufacture

Following candidate discovery, supply of small quantities (100mg-1g) for initial validation and pre-clinical studies is typically performed through small-scale manufacture. For mAbs, this can be achieved rapidly and at lower costs through the use of transient expression systems, while for Optimer binders, this is achieved through small-scale solid-phase synthesis.

Manufacture of DNA Optimer binders at smaller scales is rapid, typically taking just 3-4 weeks. The slight increase in timeframes for mAbs at this stage of manufacture is associated with ensuring sufficient mAb product quantities from potentially poorly expressing antibodies or cell systems, often with suboptimal titre at small-scale.[17]

MAb expression systems have been heavily engineered, yet some mAbs are innately poor expressors, and platform systems are not fully optimised for each molecule at smaller scales. These factors can add to manufacturing timelines, as an increased number of transient expressing cells are required to produce the necessary antibody mass.

Manufacture of DNA Optimer binders at smaller scales is rapid, typically taking just 3-4 weeks.

Scaling for the clinic

1. Establishing long-term supply

Progressing a binder from lead candidate to a commercial product requires a consistent long-term supply to generate sufficient quantities of the binder to support further pre-clinical evaluations and process development.

For mAbs, the most common method of achieving this is to generate a stably expressing recombinant cell line. The majority of mAb programmes use CHO cells adapted for serum-free culture conditions and with established integration sites. These cell lines offer a platform process for production, with the requirement to optimise upstream and downstream processes to support mAb production and purification. Generation of such a cell line takes 26-30 weeks and entails costs of $400,000-950,000, with potential further costs of $250,000-1,000,000 to secure

a license fee for the established cell line. It is worth noting that not all developers require a license fee for the generation of a stable cell line, particularly if ongoing manufacturing is to be retained with the cell line developer. Yet, the risk of safeguarding supply and enabling cheaper long-term manufacture must be balanced with the costs of licensing.

As Optimer binders are manufactured by solid-phase synthesis, this step is not required in their development. They can be synthesised according to the known binder sequence with processes that can be scaled in a linear fashion from gram to multi-kilogram ranges, and processes that can be transferred across multiple manufacturers.

2. Efficiency in development

Increasingly platform processes are leveraged to shorten process development timelines and save resources. Lessons learned from previously successful formulations to support structurally similar molecules of oligonucleotides and mAbs are invaluable in developing safe and effective formulations.[18-20] Timelines and costs for mAbs and Optimer binders were highly consistent across the suppliers surveyed, with development times of 12-30 weeks for mAbs and 12-26 for Optimer binders and costs ranging from $250-400,000, dependent upon the supplier.

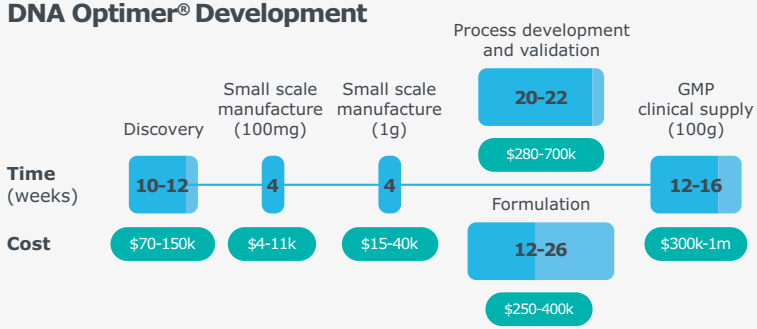
Timeframes for this scale-up and validation are comparable between antibody and Optimer development, at 20-22 weeks for Optimer development and 20-26 weeks for antibody development. The timeframes for establishing processes for Optimer development would fall at the larger end of this range when using longer binder sequences of over 40 nucleotides. As part of the standard Optimer development process, all binder sequences are trimmed from the parent clone to identify the minimal functional fragment. This increases compatibility with manufacturing.

3. Manufacturing for the clinic

Manufacturing larger batches (100g) of binders is faster for Optimer binders, taking 12-16 weeks, compared to typical timelines in the range of 16-40 weeks for antibodies. For Optimer binders, this rapidity in synthesis may remove as much as 28 weeks from development timelines. Reducing this time could offer significant advantages in speeding development to the clinic and new therapeutics and diagnostics that may be critical for patients.

Cost of Optimer synthesis at larger scales is higher than antibody manufacture, with costs in the region of $300,00-1,000,000 for 100g, compared to just $85,000-150,000 for antibodies. However, as chemistry, manufacturing and controls costs account for approximately 10% of total clinical trial costs across all phases,[17] these prices are within the expected range for many researchers and developers. Furthermore, the range of targets and therapeutic indications that can be approached using Optimer compared to antibody technology offers new solutions for patients and clinicians alike. As the oligonucleotide industry continues to expand to support the increase in therapeutics reaching the clinic and coming to market, these costs are predicted to decrease in a similar way as seen previously for markets such as mAbs and next-generation sequencing.[21]

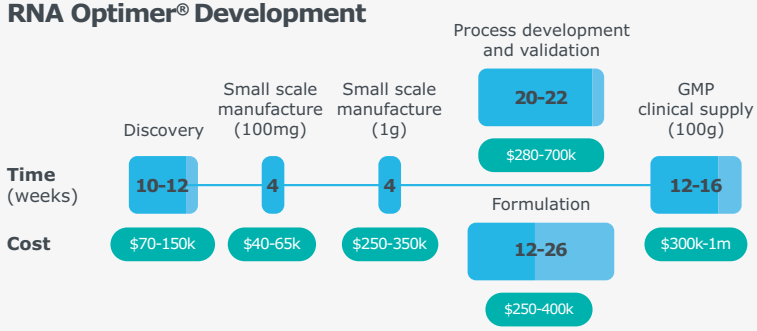
DNA Optimer® Development



50-62 weeks Optimer discovery and development work

$919,000-2,301,000 DNA Optimer discovery and development costs

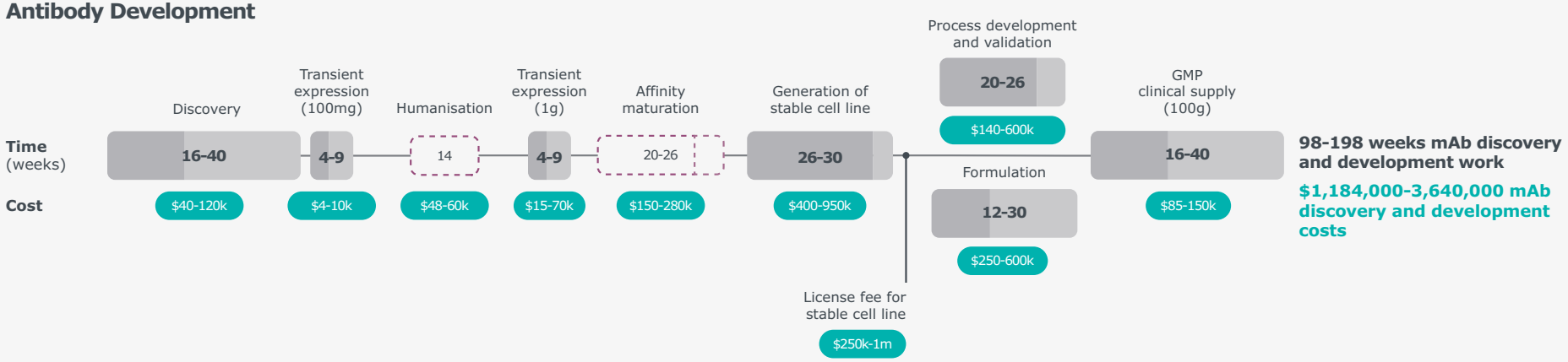
RNA Optimer® Development



50-62 weeks Optimer discovery and development work

$1,190,000-2,665,000 RNA Optimer discovery and development costs

Antibody Development



98-198 weeks mAb discovery and development work

$1,184,000-3,640,000 mAb discovery and development costs

Cost of supply

Following discovery and development, it is expected that large-scale manufacturing processes will be established to support later stage clinical trials and long-term supply. For smaller scale manufacturing and non-GMP production of DNA aptamers used in diagnostics and research applications, costs can be broadly similar to that of antibody-based manufacturing, $50,000-100,000. However, it must be noted that due to the significantly reduced size of Optimer at 1/10th the size of antibodies comparing mole for mole Optimer reagents offer cost benefits.

For GMP manufacturing, antibody supply can be achieved at lower cost than Optimer binders, with costs of $50,000-100,000 per kilogram (kg) for mAbs, compared to $500,000-700,000 per kg for Optimer binders.

The high cost of Optimer binder manufacture at this stage is due to the smaller size of the oligonucleotide market to date. Fewer oligonucleotide-based therapeutics or diagnostics have reached the market, as these technologies are newer and not as established as antibody technology. Consequently, there are currently fewer manufacturers capable of handling large-scale oligonucleotide synthesis and the manufacturing processes are still being engineered for increased efficiency and productivity, as well as reduced cost.[22]

With the increased numbers of oligonucleotide treatments, such as antisense oligonucleotides, siRNA and aptamers, that are progressing through the clinic, there is an increased drive to reduce these costs and increase competition in the marketplace.

Improvements in the pipeline

As the use of oligonucleotides, such as Optimer binders, increases across the life sciences many improvements are being made to the manufacturing processes to increase production capacity and improve efficiencies, including cost.

All of the current large-scale manufacturers that we investigated as part of this study stated their intention or current operations to expand production facilities.[23] Similarly, alternative manufacturers are now developing services within this area,[24] reflecting the rise in demand for commercial-scale manufacture of oligonucleotides and the reduction in perceived risk associated with the development of oligonucleotidebased products. Such expansions will be expected to increase capacity and competition across the industry.

At the start of 2021, a UK-based collaboration between key industrial partners (Medicines Manufacturing Innovation Centre, AstraZeneca, Exactmer, Novartis and UK Research & Innovation), was launched to develop scalable, sustainable, and more cost-effective oligonucleotide manufacturing processes.

The project is expected to be complete within three years and deliver methods to enhance the production capacity and viability of large-scale oligonucleotide synthesis, with the aim to transform the oligonucleotide supply chain.[21]

Critical elements that will be addressed include improvements to the yield and efficiency of the oligonucleotide manufacturing process and reductions in the consumption of critical raw materials (acetonitrile) to remove global supply challenges in the feasibility of large-scale manufacturing of oligonucleotides, such as Optimer binders.

Conclusion

The Optimer platform can be used to unlock novel targets and therapeutic strategies for the rapid development of new treatments. With accelerated discovery stages that incorporate binder optimisation to reduce further engineering of any selected candidates, the Optimer platform can speed time to clinic and help to overcome the challenges developers are facing in antibody discovery processes.[8]

Despite extensive optimisation of antibody discovery and development, this research has shown that the rapid discovery processes and reduced number of steps involved in Optimer discovery and development could offer important benefits to:

- expedite critical medicines and diagnostic tests into the clinic
- simplify project execution through fewer development steps
- achieve competitive advantage by entering clinical trials earlier than competing products

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