The Solution to Improve Profitability in Pharmaceutical Development; How to Increase Pre-clinical Productivity and Success Rates in Clinical Trials

The limited availability and usage of pre-clinical laboratory instruments which provide biologically relevant data has resulted in unnecessarily high failure rates of pharmaceutical drug candidates in clinical trials, the single most expensive component of the pharmaceutical development process. Attana's QCM technology and pre-clinical validation of drug candidates has been shown to improve the efficiency and reduce the costs associated with bringing new pharmaceuticals to market, by increasing success rates in clinical studies and detecting unqualified candidates in the pre-clinical stage. The clinical results from Attana's validated drug candidates have shown impressive progress in a short time and increased productivity in clinical trials by an estimated 80 per cent, demonstrating an unparalleled offering to clients seeking to maximise the returns of their R&D efforts.

PINPOINTING THE OPPORTUNITY FOR INCREASED PROFITABILITY

Costs Related to Pharmaceutical Development

Pharmaceutical development is associated with substantial costs and long lead times. The average cost to develop a pharmaceutical drug was $2 billion in 2019, an increase of 76 per cent over the last decade[1]. Clinical trials are the single most expensive component of the pharmaceutical development process, constituting roughly half of the total development cost of a drug[2]. The increased costs of clinical development are a consequence of performing more extensive, and thus more expensive, quality assurance (QA) assessments in clinical trials. The costs successively increase in each clinical phase as they become more comprehensive, emphasising the importance of identifying potential flaws in early stages and avoiding late-stage failures.

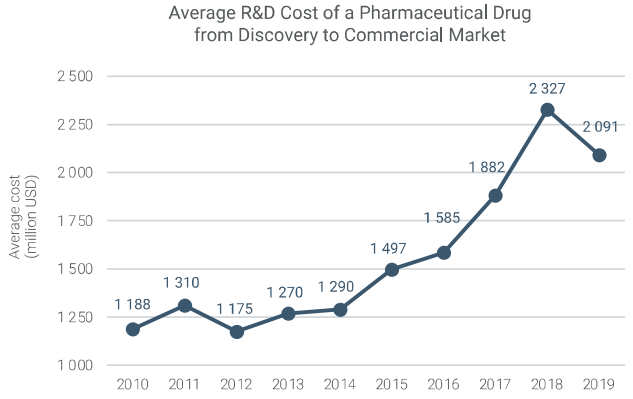

Figure 1. Average R&D cost of a pharmaceutical drug from discovery to commercial market (2010–2019)[1].

The Challenge Lies in Clinical Trial Preparation

Only one in ten pharmaceutical drug candidates that enter clinical trials successfully reach the commercial market. Although a majority of all candidates entering clinical trials move from Phase I to Phase II, only 22 per cent of candidates reach Phase III[2]. One explanation is that pharmaceutical development has traditionally relied on pre-clinical research in artificial *in vitro* laboratory systems. The artificial experimental conditions, in which the drug candidates are initially assessed, result in artificially positive test results. Accordingly, this often leads to an overestimation of the drug's efficacy and an underestimation of the side-effects that are only revealed later in subsequent human clinical trials.

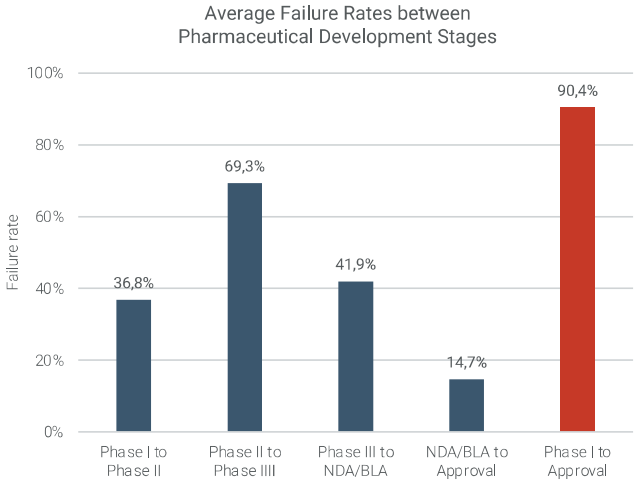

Figure 2. Average failure rates between pharmaceutical drug development stages (Phase I to approval)[3].

The limited availability and usage of pre-clinical laboratory instruments which provide biologically relevant data, has resulted in unnecessarily high failure rates of drug candidates in clinical trials. More thorough and insightful evaluations during pre-clinical testing will contribute to improved characterisation and optimisation of candidates before they enter billion-dollar clinical studies. This article will investigate a solution to the challenge that the pharmaceutical industry is facing:

How can productivity and profitability be increased in pharmaceutical development?

THE QCM TECHNOLOGY – A PROVEN SOLUTION TO IMPROVE THE DEVELOPMENT PROCESS

Valuable Pre-clinical Insights from QCM-based Biosensors

Historically, the QCM (quartz crystal microbalance) technology has been utilised to measure picogram-level changes in mass per unit area. It was discovered in 1959 by Prof. Günter Sauerbrey and has since then contributed to multiple industries. In the last two decades, Attana has leveraged the technology and pioneered the development of QCM systems for applications in pharmaceutical research & development. Attana's proprietary instruments have been proven as a reliable solution to several of the technical challenges facing the pharmaceutical industry in the drug development process.

Figure 3. Attana's most recent instrument, the Cell™ 250, which was launched H1 2020.

The Attana Cell™ 250, launched earlier this year, has the ability to analyse how a given pharmaceutical drug candidate interacts with the human body by mirroring *in vivo* conditions (for more details on Attana's analyses, see section *Attana's validation process explained* below). By enabling the study of molecular interactions between, e.g., proteins, DNA, nanoparticles and viruses, as well as interactions with living cells cultured on the Attana sensor surface, the biosensors can, with exceptional accuracy, analyse a drug candidate's efficacy and potential side-effects – prior to the commencement of clinical trials.

Validating and Optimising Drug Candidates Prior to Clinical Trials

To improve the success rates of clinical trials, Attana can validate and optimise drug candidates in the pre-clinical phase. Typically, these analyses are initially performed through contract research projects where Attana's team of application specialists engage with R&D personnel at the institution or pharmaceutical company developing the drug candidate. Upon completing the Attana-enabled studies, data is generated and evaluated, allowing the drug candidates to be categorised:

a. **Promising candidates are identified and optimised for clinical trials.**
An initial assessment determines the candidate's potential for success. Some candidates show sufficient performance and are recommended for clinical studies without modification. Others are modified based on Attana's recommendations and if follow-up analyses prove successful, may be recommended for clinical trials.

b. **Unqualified candidates are identified prior to clinical trials.**
The high clinical trial failure rates are partly a consequence of too many de facto unqualified candidates (poor efficacy, poor safety, or both) being recommended for clinical trials, and partly due to factors beyond the laboratory's control (such as a competitor reaching the market with a similar drug). Attana has a strong track record in identifying unqualified drug candidates with high accuracy.

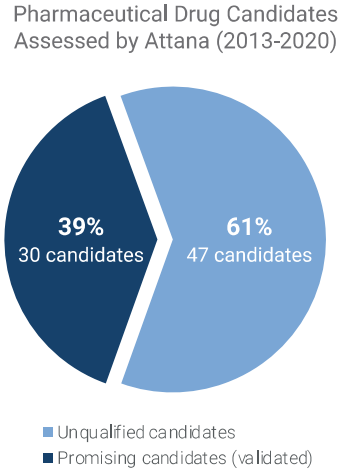

Figure 4. Pharmaceutical drug candidates assessed by Attana (2013–2020) categorised as either promising or unqualified.

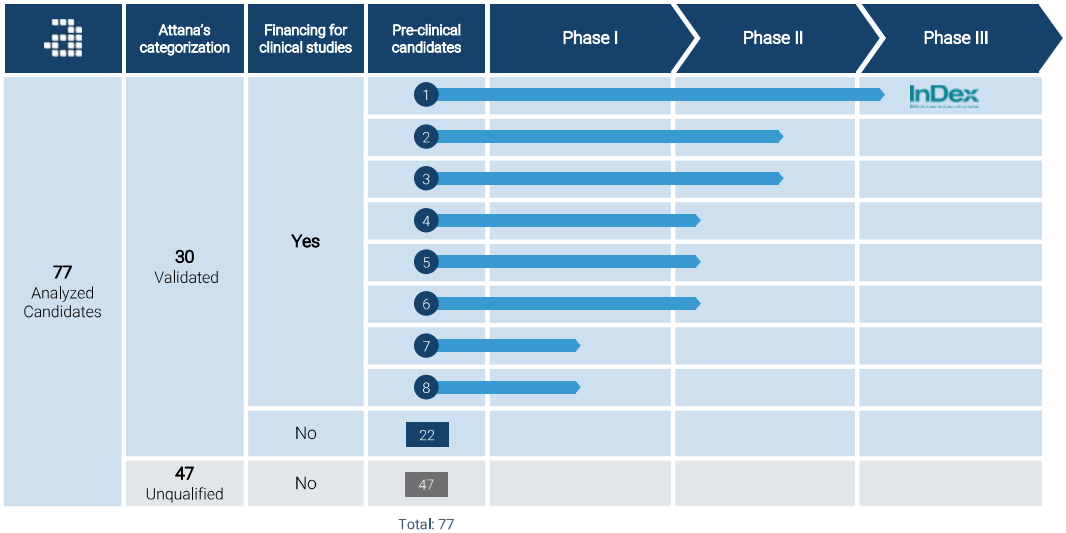

Figure 5. The clinical results from 77 pharmaceutical drug candidates analysed by Attana. Eight of the 30 validated candidates have received financing for clinical trials to date, and several of the other 22 validated candidates have financing pending. None of the unqualified candidates have entered clinical trials to Attana's knowledge.

Attana's Track Record in Pharmaceutical Drug Development
Attana has analysed 77 pre-clinical drug candidates between 2013 and 2020 in 26 contract research projects with over 20 international clients. Of the 77 candidates, Attana studies have rejected 47 (61%) for either showing poor safety or poor efficacy. The other 30 candidates (39%) have been validated and determined to have good chances for clinical trial success. Several of these validated candidates have also been modified based on Attana's recommendations (for details on modification recommendations, see subsection *Optimising the characteristics of validated candidates*).

Clinical Results from Drug Candidates Validated by Attana
A pharmaceutical drug candidate's chances of both entering clinical trials and successfully reaching the market can be vastly improved with Attana's solution to characterise, validate and directly recommend modifications in pre-clinical studies. The R&D pipeline of the 77 candidates which have been analysed by Attana in pre-clinical studies is shown below. Of the validated candidates, eight have secured financing for clinical studies to date. Of these, six candidates have successfully completed Phase I, of which two have commenced Phase II studies and one has reached Phase III. In 2016, Attana conducted an analysis of Index Pharmaceuticals' drug candidate, *Cobitolimod*[4], which has now successfully concluded clinical Phase IIb and is entering Phase III[5] (other candidates are undisclosed due to confidentiality).

Track Record Illustrating Significant Impact in Short Time
To date, Attana-validated drug candidates have had a 100 per cent success rate in clinical trials. Six of six candidates have Phase I success, and one of one has Phase II success with an additional two candidates showing good promise. Conversely, of the 47 candidates which Attana determined as unqualified, none have entered clinical trials (0 of 47).

Pre-clinical validation with Attana can save, per average client, 50 per cent of historic clinical trial costs, by eliminating candidates which are highly unlikely to achieve clinical trial success and optimising those which show promise. The early identification of flawed candidates also ensures resources can be allocated to more promising candidates, which ultimately may lead to more pharmaceuticals reaching the market in less time.

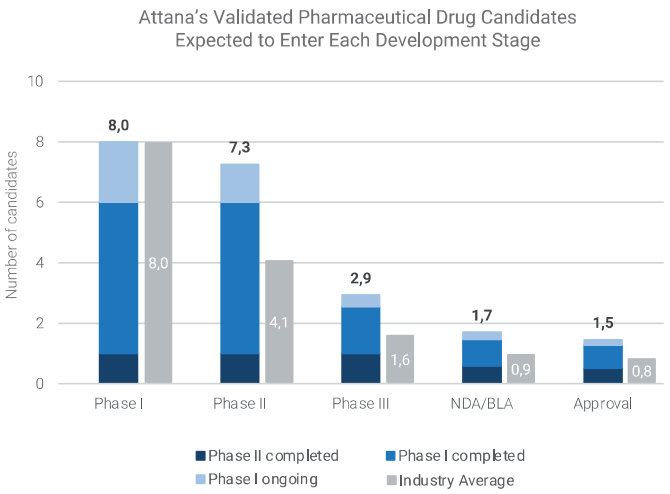

Figure 6. Attana's validated pharmaceutical drug candidates expected to reach the commercial market. The data is based on Attana's eight validated candidates in clinical trials and their current clinical phase. The industry average failure rates from Figure 2 are applied in all transitions between Phase I to approval.

Improving Clinical Trial Success Rates by 80 Per Cent
The Attana technology's ability to predict *in vivo* results helps to increase productivity in pre-clinical studies and improves success rates in clinical trials. By applying conservative market-based averages on failure rates in clinical trials from Figure 2, it can be illustrated how productivity can be increased in the drug development process. Attana's eight validated candidates have already improved clinical trial success rates by over 80 per cent by having an estimated 1.5 candidates reach the market instead of the industrial average of 0.8 candidates. By extrapolating the results to the pre-clinical stage, candidates that are validated by Attana will generate 4.8x more marketed pharmaceuticals than the industry average[6].

ATTANA'S VALIDATION PROCESS EXPLAINED

Predicting *in vivo* Results through *in vitro* Assays
Enabled by Attana's third-generation biosensor instruments and the expertise of Attana's experienced research professionals, the validation process begins with one or more pre-clinical drug candidates not yet evaluated *in vivo* (clinical trials). The Cell™ 250-instrument is easily calibrated to suit the type of analyte(s) being tested. In order to best mirror *in vivo* conditions, the

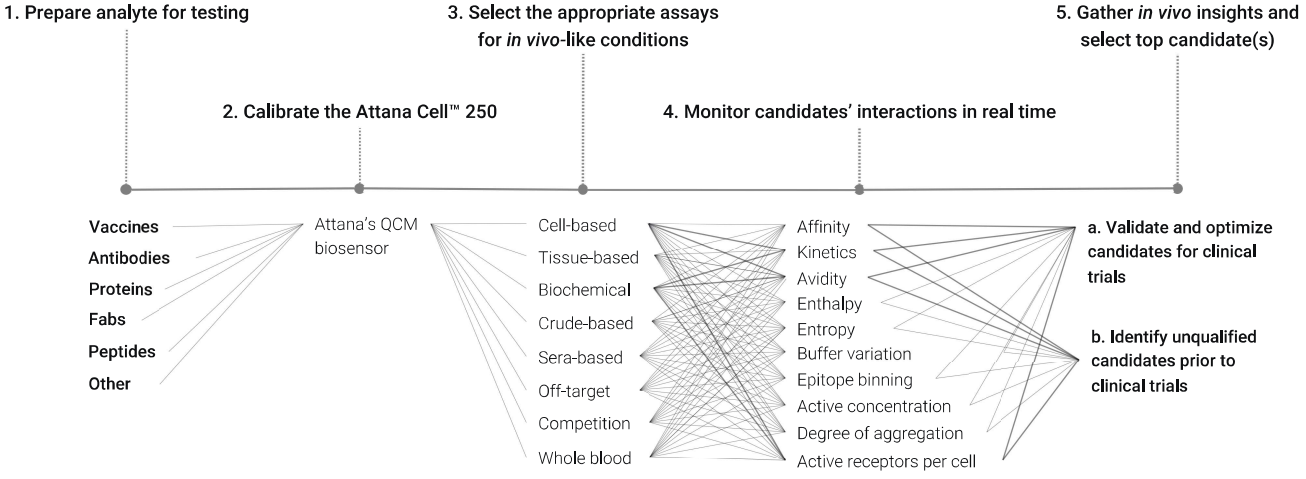

Figure 7. Step-by-step illustration of Attana's pre-clinical validation process, utilising the Cell™ 250 to mirror in vivo results through in vitro assays.

appropriate assays, including competition assays if needed, are selected. The assays are then performed and can be monitored in real time, creating a comprehensive interaction profile. From the insights generated by the interaction profile, Attana can (1) expose and understand any off-target interactions and (2) evaluate if the quality of the target interactions is sustained in the *in vivo*-like conditions.

Selecting the Best Candidates to Enter Clinical Trials

The evaluation of target and off-target interactions constitute the foundation of validating a candidate. Attana's off-target evaluations resemble GLP toxicity studies and is an essential precursor to clinical trials. The candidate's interaction profile exposes any off-target properties and Attana can attribute these unwanted interactions to a specific part of the antigen. For target interactions, it can be determined from the interaction profile whether their quality meets the requirement for the candidate's purpose and the desired degree of efficacy is obtained. Based on the degree of target and off-target interactions, Attana provides recommendations for selecting the appropriate candidate(s) to proceed with into clinical trials, along with further optimisation recommendations.

Optimising the Characteristics of Validated Candidates

The objective of increasing efficacy and minimising the off-target properties can be achieved in various ways. By attributing the off-target property to a specific part of the antigen, Attana exposes its modifiable characteristics and provides guidance on how to improve the molecular composition of the drug candidate (for case study on improving off-target properties, see Forssén *et al.*[7]). To improve the quality of target interactions, Attana can validate the suitable target, analyse the off-and association-rate characteristics and adjust the candidate's composition accordingly (for case study on target validation, see Bode *et al.*[8]).

Summary of Results

Pre-clinical validation of drug candidates by Attana has been shown to improve the efficiency and reduce the costs associated with bringing new pharmaceuticals to market. Clients have experienced considerable success both in contract research projects with Attana specialists, as well as by employing the proprietary Attana biosensor instruments in their own R&D labs. The versatility of Attana instruments combined with breadth of knowledge and experience possessed by the team of specialists, enables Attana to provide an unparalleled offering to clients seeking to maximise the returns of their R&D efforts.

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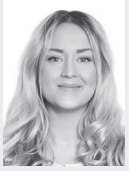

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