Assessing the Financial Impact of Translational Pharmaceutics®

A Platform for Accelerating Product Development

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EXECUTIVE SUMMARY

Pharmaceutical R&D activity continues to grow significantly year-on-year with increasing numbers of molecules in development. Yet despite increases in spending the industry struggles with poor R&D productivity, citing lengthy drug development times, increasing costs and high rates of molecule attrition. Tufts CSDD examined an innovative approach to accelerating drug development, Translational Pharmaceutics®, and quantified the savings to drug developers from applying the approach across the industry portfolio of investigational drugs. Translational Pharmaceutics integrates real-time manufacturing and clinical testing to make drug products available for clinical trials more quickly and flexibly than is the case for traditional drug development. Translational Pharmaceutics projects were compared to industry benchmarks, and the financial benefits were quantified on reduced industry R&D costs and increased returns from earlier sales. Data were obtained for different types of Translational Pharmaceutics projects and topline results included mean total benefits ranging from $102.6 million to $290.1 million and mean timeline savings of >12 months.

INTRODUCTION

The drug development process has been demonstrated to be highly costly, lengthy, and risky.[1] Despite long-standing efforts by drug developers to operate more efficiently, traditional drug development programs have become costlier on average.[1] In prior research, The Tufts Center for the Study of Drug Development (CSDD) has conducted studies demonstrating the economic significance in general from reducing drug development times,[2] and the financial impact from adopting alternative approaches to contracting for outsourced drug manufacturing activities.[3]

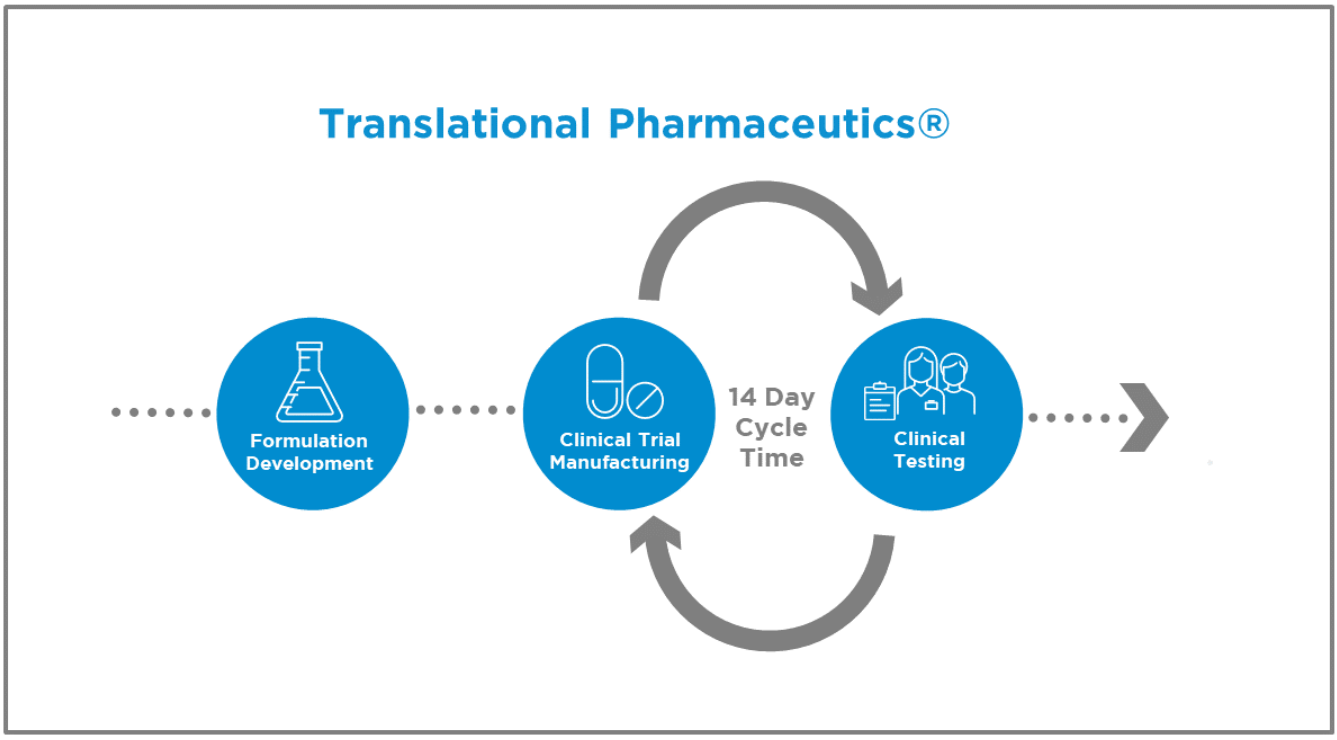
Quotient Sciences' signature drug product manufacturing and clinical testing platform is referred to as Translational Pharmaceutics and has been used over the last decade by pharmaceutical and biotech companies to accelerate product development.[4-7] It is defined as a process that integrates formulation development, real-time adaptive manufacturing and clinical research, to efficiently advance key stages of the drug development process:

- Transition of a molecule from First in Humans (FIH) to proof of concept (POC)
- Development and optimization of clinical formulations

One application of Translational Pharmaceutics is to fast-track the transition of a molecule from FIH to POC. While a FIH study can use simple formulations prepared within pharmacies, there will be an inevitable need to transition to a Good Manufacturing Practice (GMP) dosage form prior to the POC patient trials. With Translational Pharmaceutics® it is possible to bridge between formulations within the same FIH study as opposed to conducting an additional, separate trial.

Another application of Translational Pharmaceutics is the rapid development and optimization of new formulations for molecules post-POC and in life cycle management strategies. Hallmarks of this approach are single source, small batch manufacturing and integrated production and clinical testing in which numerous formulation prototypes or different technologies can be rapidly screened and clinically evaluated. This has been used extensively with drug molecules that have poor solubility and formulations that require modified release (MR). The programs can be further enhanced by the incorporation of a formulation design space, where a range

of allowable quantities of key ingredients is defined, from which formulation compositions can be selected, manufactured and dosed quickly, guided by clinical data emerging during the study.



Fundamentally, Translational Pharmaceutics reduces the time between production and dosing from months to weeks and, given that decision-making is driven by human data, reduces the probability that a drug will fail in later stage clinical testing due to sub-optimal formulation performance. Additionally, manufacturing activities can then be scaled up from small batch manufacturing to large volume manufacturing without the need for transferring the manufacturing process and methods to another Contract Development and Manufacturing Organization (CDMO), further reducing "white space" in drug development.

A traditional drug development approach to these processes would require engagement with multiple vendors including a Contract Research Organization (CRO), as well as at least one CDMO. Translational Pharmaceutics streamlines the management of outsourcing partners through assignment of a single vendor and a cross functional project manager. When comparing Translational Pharmaceutics to the typical approach to manufacturing and clinical testing, there are a range of potential benefits designed to save time and money, and that ensure that the formulation taken to clinical testing has a higher chance of success.

To inform drug developers of the potential financial impacts of such novel drug product development and trial designs, Tufts CSDD conducted a study comparing traditional drug development programs to Translational Pharmaceutics programs with respect to their impacts on development cycle times and their derivative effects on development economics. We conducted the study using actual data on completed Translational Pharmaceutics projects in comparison to benchmark drug product development durations determined by independent consultants with expertise in drug product development. These comparisons are incorporated in a drug development model and the financial benefits from applying these non-traditional development approaches are

determined using benchmark results on pharmaceutical R&D costs and net returns for new pharmaceutical approvals found in the published literature.[1,8]

METHODS

The base case for our model of the potential economic benefits from applying a flexible dosing and drug product manufacturing development plan, such as Translational Pharmaceutics, assumes a traditional drug development paradigm. Benefits are measured against that base case. For the model comparisons, we assume that both Translational Pharmaceutics and traditional drug development programs are applied across a diversified portfolio of investigational molecules that enter clinical testing. Thus, the results are to be interpreted on a per drug approval basis, taking into consideration failures during clinical development (molecules that are tested, but never reach the market).

Over the past decade Quotient Sciences has completed more than 400 Translational Pharmaceutics programs. The current analysis was performed on a representative sample of 19 completed studies, covering three distinct types of Translational Pharmaceutics programs.:

1. FIH to POC transition
    - From initiation of a FIH trial to initiation of a POC trial where drug product is made available to initiate POC clinical trials sooner than otherwise
2. Modified Release formulation development
    - Where the drug product is optimized and made available to initiate pivotal clinical trials sooner.
3. Development of dosage forms to enhance solubility and bioavailability
    - Where the drug product is optimized and made available to initiate pivotal clinical trials sooner

Project cycle time data were quantified from executed project plans. These results were then compared to benchmark cycle times by type of program, as determined by independent expert consultants.

The model assumes that reductions in the length of the drug product development process from Translational Pharmaceutics results in the initiation of pivotal clinical trials sooner than it otherwise would, but that the lengths of subsequent clinical testing phases once initiated remain the same. This results in lower values for the time costs of new drug development (the monetized value of shorter development times). The base case pre-human and clinical phase costs are obtained from a recent study of biopharmaceutical R&D costs, updated for inflation.[1] The study also provides baselines for development times and the technical risks of drug development. The costs for both the traditional and new development paradigms are risk-adjusted.

A shorter clinical development process also means that net cash flows from an earlier launch can be brought closer to the start of development. Thus, there is a time saving that can be monetized by applying a net present value framework to future net returns from approved new products. We assume that net cash flows after approval remain the same, but they begin earlier according to the reductions in development phase lengths resulting from a different development model. We used data on the net present value of net returns found in a recent study of the rates of return to new drug development for our computations.[8]

All costs and returns are examined from the sponsor perspective and the benefits are thus considered on a sponsor after-tax basis. The financial results are all expressed in year 2018 dollars.

FINDINGS

The drug product development time benchmarking exercise yielded benchmarks of 26.5 months, 21.5 months, and 19.5 months for FIH-POC, Modified Release, and Solubility programs, respectively. In comparison, the average drug product development durations for the Quotient Sciences data are 11.5 months, 8.6 months, and 7.7 months for FIH – POC, Modified Release, and Solubility projects. Although average drug product duration times are longest for FIH – POC programs, average time savings are greatest for this application type (15.0 months vs. 12.9 and 11.8 months). The superior average time savings for FIH – POC applications is also evident for median, minimum, and maximum values.

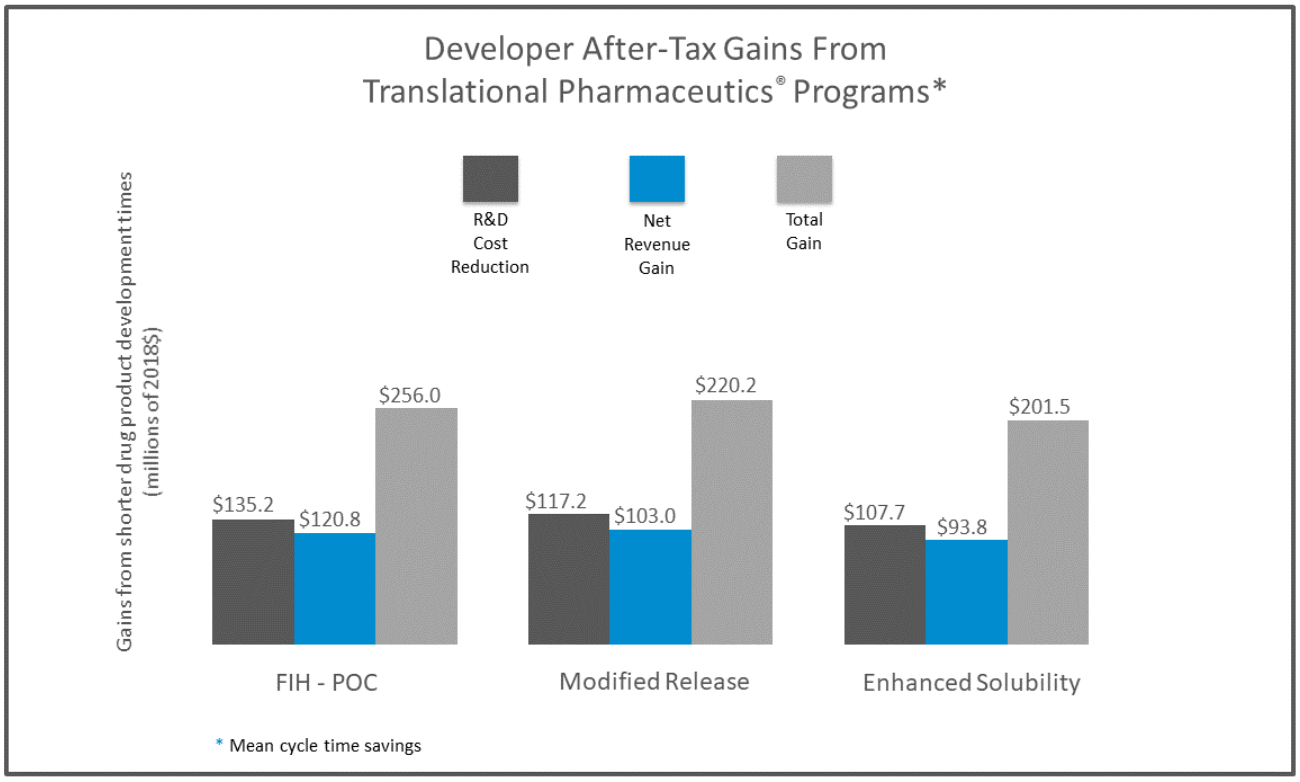
Drug Product Development Time Savings from Translational Pharmaceutics® Programs

			Time Savings Relative to Benchmark (Months)			
Program Type	N	Benchmark Duration (Months)	Mean	Median	Minimum	Maximum
FIH to POC	3	26.5	15.0	14.5	13.5	17.0
Modified Release Formulation	5	21.5	12.9	12.5	11.5	14.5
Enhanced Solubility Formulation	11	19.5	11.8	13.0	6.0	14.5

Reducing the length of the drug development process translates into lower time costs (the cost of the delay between when development investment costs are incurred and when returns are earned). Applying mean time savings for each application of Translational Pharmaceutics we find that sponsors would receive a mean pre-tax cost reduction of $193.1 million, $167.4 million, and $153.9 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. The mean after-tax cost reductions are $135.2 million, $117.2 million, and $107.7 million per approval for the three application types. Median after-tax cost reductions are $130.9 million, $114.0 million, and $118.1 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. The ranges in after-tax cost reductions are $122.4 million – $152.0 million for FIH – POC, $105.1 million – $130.9 million for Modified Release, and $56.1 million – $130.9 million for Solubility applications.

If Translational Pharmaceutics shortens the development cycle, sponsors can expect financial gains from having their products reach the market sooner. Utilizing the underlying data for the most recent product launches in the published rate of return study noted above,[8] we found the after-tax net present value of post-launch net returns (exclusive of pre- and post-approval R&D costs) from traditional drug development to be $1.14 billion in 2018 dollars. With this figure as a base and results from the above referenced R&D cost study for post-approval R&D costs,[1] we calculated increases in the net present value of after-tax net profits from moving from a traditional drug development program to a flexible dosage design and real time manufacturing model (inclusive of post-approval R&D costs). The mean gains are $120.8 million, $103.0 million, and $93.8 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. Median gains are $116.6 million, $99.6 million, and $103.8 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. The ranges in the net present value of after-tax net profit increases are $108.1 million – $138.1 million for FIH – POC, $91.3 million – $116.6 million for Modified Release, and $46.5 million – $116.6 million for Solubility applications.

Total financial benefits to drug sponsors from employing Translational Pharmaceutics will be the sum of gains from lower after-tax R&D costs and increases in after-tax net returns. If we add the results we have obtained with respect to R&D costs and returns, we obtain mean total financial benefits of $256.0 million, $220.2 million, and $201.5 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. Median total benefits are $247.5 million, $213.6 million, and $221.9 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. The ranges in total benefits are $230.5 million – $290.1 million for FIH – POC, $196.4 million – $247.5 million for Modified Release, and $102.6 million – $247.5 million for Solubility applications.



The results presented here are dependent on the extent to which employing flexible dosage design and real-time manufacturing approaches can speed up the initiation of pivotal clinical trials. We conducted sensitivity analysis of the model by examining the outcomes for time savings of one to 18 months in one-month increments. The percentage increase in benefit declined with successive one-month increments, falling from a doubling in benefit from one month to two months in time savings to a 6% increase from 17 to 18 months. However, the absolute increase in incremental benefit was nearly constant at $17 million per month. The incremental reduction in after-tax pre-approval R&D costs decreased slightly by the number of months saved, but the increment in net revenues increased slightly by the number of months saved. The net effect was an approximately constant increase in financial benefit for each additional month in time savings.

Sensitivity Analysis: Financial Gains From Translational Pharmaceutics® Programs
(millions of 2018 dollars)

Months Saved	R&D Cost ($ M)	Net Revenues ($ M)	Total Gain ($ M)	Months Saved	R&D Cost ($ M)	Net Revenues ($ M)	Total Gain ($ M)
1	9.5	7.6	17.1	10	92.0	78.9	170.9
2	19.0	15.3	34.3	11	100.8	87.1	187.9
3	28.4	23.0	51.4	12	109.5	95.4	204.9
4	37.7	30.8	68.5	13	118.1	103.8	221.9
5	46.9	38.6	85.5	14	126.7	112.3	239.0
6	56.1	46.5	102.6	15	135.2	120.8	256.0
7	65.2	54.5	119.7	16	143.6	129.4	273.0
8	74.2	62.6	136.8	17	152.0	138.1	290.1
9	83.1	70.7	153.8	18	160.2	146.9	307.1

CONCLUSIONS

This modeling study compares the financial impact of a flexible dosage design together with real-time manufacturing of new dosages and formulations to a traditional development paradigm. Substantial financial benefits are found when a Translational Pharmaceutics® approach is applied in early-stage clinical drug development across a large portfolio of development projects. Mean after-tax pre-approval R&D cost benefits from quicker initiation of proof-of-concept and pivotal clinical trials are $135.2 million, 117.2 million, and $130.9 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively. The shorter development times also mean that drugs that make it to marketing approval will be on the market sooner. Using results on costs and sales from a recent published rate of return analysis, we found that mean after-tax net present values of an earlier launch results in gains per approved new drug of $120.8 million, $103.0 million, and $93.8 million per approval for FIH – POC, Modified Release, and Solubility applications,

respectively. The cumulative benefits in mean after-tax gains from flexible dosing design and real time drug product manufacturing of $256.0 million, $220.2 million, and $201.5 million per approval for FIH – POC, Modified Release, and Solubility applications, respectively.

All projects considered for this report are for small molecules administered orally and were conducted from 2009 to 2017. Future research could be undertaken to ascertain whether the benefits from Translational Pharmaceutics are similar for biologics and other routes of administration. The results here and for other molecule types and routes of administration in future studies will also depend on whether there are changes over time in development cost cash flows, development timelines, regulatory approval risks, company costs-of-capital, and the level and pattern of sales for new drugs that do make it to market.

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