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REPORT



Benchmarking biopharmaceutical process development and manufacturing cost contributions to R&D

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ABSTRACT

This study aims to benchmark and analyze the process development and manufacturing costs across the biopharmaceutical drug development cycle and their contribution to overall research and development (R&D) costs. This was achieved with a biopharmaceutical drug development lifecycle cost model that captured the costs, durations, risks and interdependencies of the clinical, process development and manufacturing activities. The budgets needed for process development and manufacturing at each phase of development to ensure a market success each year were estimated. The impact of different clinical success rate profiles on the process development and manufacturing costs at each stage was investigated, with a particular focus on monoclonal antibodies. To ensure a market success each year with an overall clinical success rate (Phase I to approval) of ~12%, the model predicted that a biopharmaceutical company needs to allocate process development and manufacturing budgets in the order of ~\$60 M for pre-clinical to Phase II material preparation and ~\$70 M for Phase III to regulatory review material preparation. For lower overall clinical success rates of ~4%, which are more indicative of diseases such as Alzheimer's, these values increase to ~\$190 M for early-phase and ~\$140 M for late-phase material preparation; hence, the costs increase 2.5 fold. The costs for process development and manufacturing per market success were predicted to represent 13–17% of the R&D budget from pre-clinical trials to approval. The results of this quantitative structured cost study can be used to aid decision-making during portfolio management and budget planning procedures in biopharmaceutical development.

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Introduction

The pharmaceutical industry has suffered from declining research and development (R&D) productivity and increasing costs over the past few decades.^{1,2} The reported capitalized R&D cost to bring a new biopharmaceutical to market has risen from \$1.2 billion in 2007³ (\$1.6 billion in 2020 dollars US), with an average Phase I to approval success rate of 30%, to \$1.8 billion in 2010¹ (\$2.2 billion in 2020 dollars) and \$2.8 billion in 2016⁴ (\$3.1 billion in 2020 dollars), with average Phase I to approval success rates of 12%. Others have suggested that several companies may be experiencing even lower success rates resulting in R&D costs per market success of over \$4 billion⁵ (\$4.6 billion in 2020 dollars). These overall R&D costs and success rates have a direct bearing on budget planning for process development and manufacturing activities underpinning the supply of material for pre-clinical and clinical trials. Although published studies have evaluated the overall cost of R&D and the phase costs, they have not addressed the cost breakdowns across clinical, process development and manufacturing activities at each phase. This report is the first to provide benchmarks for the R&D costs associated with process development and manufacturing for biopharmaceuticals, such as monoclonal antibodies (mAbs), across a range of industrially relevant clinical success rates.

Pre-clinical and clinical trials, which lie on the critical path of biopharmaceutical product development, are underpinned by process development and manufacturing for material supply, also known as Chemistry, Manufacturing, and Controls (CMC) activities. Provisional budget allocations and planning are required to safeguard the smooth running of R&D activities. Previous work has either focused on total phase costs in drug development, cost of goods estimation for manufacturing or decision-support tools for portfolio management, capacity planning or bioprocess design.

On the drug development level, DiMasi and colleagues^{3,4} and Paul et al.¹ provided pivotal benchmark studies of the out-of-pocket and capitalized cost of R&D per approved biopharmaceutical, with a breakdown per clinical phase. Paul et al.¹ explore also the impact of factors such as transition rates and cycle times on R&D productivity and costs. Bodgan & Villiger⁶ provided rough estimates of out-of-pocket R&D costs per clinical phase for smaller biotech companies, as well as typical discount rates based on their experience. In addition to benchmarking studies, tools have been built to aid drug development decision-making for biopharmaceuticals such as mAbs. Rajapakse et al.⁷ and George et al.⁸ built decisional tools to simulate and optimize decisions related to drug candidate selection and build-versus-buy capacity sourcing for companies with portfolios of mAb candidates. These models captured the costs, durations, success rates and dependencies

for clinical trial activities, as well as for in-house and out-sourced process development and manufacturing, to illustrate the application of the tools.

On the manufacturing level, process improvements in the mAb sector over the past four decades have contributed to published commercial cost of goods (COG)/g values decreasing from over \$10,000 per gram to \$1000s per gram in the 1980-90s to \$10s-100s per gram in the present day.⁹⁻¹⁷ Process economics modeling and optimization studies provide further estimations of COG values and drivers for mAb processes for clinical and commercial stages across a range of different scenarios, with several also highlighting critical factors affecting the ranking of competing technologies. Examples include the impact of the following technologies or process improvements on COG for mAb processes: single-use or disposable components;¹⁸⁻²⁰ perfusion processes as opposed to typical fed-batch processes;^{21,22} continuous chromatography and end-to-end continuous processes compared to conventional batch processes;^{17,23,24} alternatives to Protein A purification;^{25,26} higher titers on facility fit and COG in legacy facilities;^{27,28} and very large production scales in the order of tons rather than kg.¹² The models used in these studies provide a basis for evaluating the overall cost of manufacturing in the development pathway under changing portfolio and hence production scenarios.

To date, these published studies provide useful benchmarks for overall phase costs and methods to determine COG which are built upon in this study. We focused on estimating the R&D cost contribution from process development and manufacturing activities for material supply to pre-clinical and clinical trials for biopharmaceuticals. A drug development cost model was developed capturing the clinical trials, process development and manufacturing activities, with their durations, resources, and success rates. The study bases the COG and process development estimates on mammalian cell culture-derived mAbs. The model evaluates the cost of R&D per drug, and per market success. Benchmarks of process development, manufacturing and clinical trial costs at each phase per drug and per market success are provided across a range of industrially relevant transition rates to assist with budget planning.

Drug development lifecycle description

The biopharmaceutical new product development process follows an established pattern. Exploratory discovery research identifies a new target of potential therapeutic use, then a number of molecules are developed and optimized, and the best one amongst them is selected to be the product candidate. This product candidate then goes through the pre-clinical study phase where a range of tests are run both *in vitro* and in animals to characterize the likely safety and effectiveness of this molecule in treating its target disease. Upon completion of the pre-clinical phase, the drug developer applies to regulatory authorities (e.g., US Food and Drug Administration (FDA), European Medicines Agency (EMA)) for approval to commence human clinical trials. Clinical trials are required to prove that the drug is safe and effective when administered to human patients, providing an acceptable

benefit-to-risk ratio. There are three major phases of clinical trials before the product receives approval for commercialization: Phase I tests the safety of the product in human, Phase II provides an initial assessment of its efficacy, and Phase III aims at definitively assessing the efficacy and dosage in a large number of patients. Upon completion of clinical trials, the drug developer is required to gather all pre-clinical and clinical data generated during the process, along with extensive details on the manufacturing process developed for the product of interest, and submit an application to the regulatory authority for market entry. Once granted, the product developer can legally manufacture and sell the product.

This study focuses on the development stages from pre-clinical to regulatory agency (e.g., FDA, EMA) review. The activities prior to the pre-clinical trial stage are not covered in this model because the costs generated at these stages are often shared with other compounds. Therefore, the stages from discovery to lead optimization are omitted, leaving pre-clinical and clinical trial stages as the major cost drivers in our model.

The development pathway described in this study assumed that only the pre-clinical and clinical trials are on the critical path. To avoid causing delays to the activities on the critical path, the supporting process development and manufacturing activities take place off the critical path, bearing the risk of clinical trial failure. As a result, these supporting activities are at risk, as they begin before the decisions to progress are made for their supporting clinical trials. This model assumes that for every development stage, the dependency exists that the occurrence of activities starts with process development, to manufacturing, and then to clinical trial.

Manufacturing and process development activities are designed to meet the need of the clinical trials. In order to produce the products efficiently and at the required quality, the developer must, through a series of process development activities, establish the manufacturing process and optimize it to meet regulatory requirements while ensuring that it is cost-effective and reproducible. Inter-dependencies between clinical trial, manufacturing, and process development activities are depicted in Figure 1.

Pre-clinical trial materials are produced through a cell line that provides products often with suboptimal titer at a small scale. For Phase I and II clinical trials, process development focuses on process scalability and improvement of productivity. Process development for Phase III and regulatory approval mainly focuses on process characterization and validation. Initial process limits evaluation and validation studies typically commence during process development activities prior to Phase III. Major characterization and validation studies run simultaneously with Phase III clinical trials in order to avoid causing any delay to submission to regulatory approval. These include at least three consistency batches that are also known as process validation (PV) or process performance qualification (PPQ) batches that can also be used to supply the market on approval. Typically, the manufacturing scale for mAbs increases from 100s of liters to 1000s of liters as the product moves from pre-clinical to late phase trials. Often process development efforts result in an increase in titer across the phases, for example, it can often double from pre-clinical to

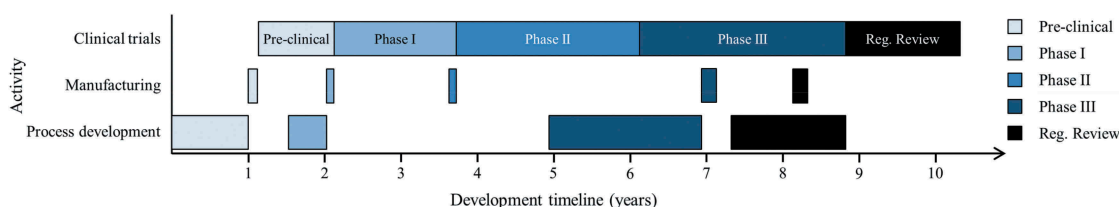


Figure 1. Timeline of new biopharmaceutical development activities, highlighting the dependencies between process development, manufacturing, and clinical trials. The process development activities establish the manufacturing process to produce material at small scale and low titer in order to supply for pre-clinical and early phase clinical trials. Then as the development of the product proceeds larger quantities of material are required for clinical and commercialization demand, hence the need for scale-up and optimizing the titer and yield. Late stage process development also focusses on regulatory compliance. The process parameters need to be characterized and process consistency validated before submission to regulatory approval. Because of the lengthy duration for patient recruitment, the actual need for clinical trial material in Phase III does not appear until 1 year after the success of Phase II.

Phase III supply. The scale and titer of manufacturing for commercialization are kept often the same as Phase III. This study focuses only on evaluating the costs of new biologic product development.

Drug development lifecycle cost model structure

A lifecycle cost model was built for biopharmaceutical drug development that captured the costs, durations, risks and interdependencies of the clinical, process development and manufacturing activities. The tool was designed to simulate and optimize both the drug development costs and project valuation based on profitability indicators such as expected net present value. This study focuses only on the tool elements required to determine the drug development costs. Here, the CMC activities refer to process development and manufacturing. The term ‘process development’ was taken to include all bulk process and formulation development, as well as the analytical effort for process characterization and validation studies. The term ‘manufacturing’ was taken to include the cost of manufacturing batches for supply of material to pre-

clinical and clinical trials, as well as the PPQ batches required for regulatory review and authorization.

Figure 2 summarizes the key model inputs and outputs to determine the drug development costs. This is split up across the portfolio and the core activities that occur across the development pathway as projects move from pre-clinical trials to market, namely process development, manufacturing, and (pre-) clinical trials.

The cost of process development activities were determined based on a breakdown of personnel involved on a full-time equivalent (FTE) basis and the duration of the activity at each stage. This was based on experience with mammalian cell-based processes producing mAbs.

Manufacturing costs for pre-clinical and clinical batches as well as PPQ batches were calculated using a bioprocess economics model developed at University College London (UCL) that was based on previous UCL models,^{23,26} but with a greater level of granularity and an updated cost database for resources such as raw materials and equipment. Manufacturing costs were derived for mAbs on a Chinese hamster ovary cell platform process where the main process and ancillary tasks are captured. The main input parameters

Decisional tool for drug development budgeting across process development, manufacturing and clinical trials				
	PROCESS DEVELOPMENT	MANUFACTURING	(PRE-) CLINICAL TRIALS	PORTFOLIO
KEY MODEL INPUTS	Per phase per drug: <ul style="list-style-type: none"> • Process development FTEs required • Duration • Timing dependencies 	Per phase per drug: <ul style="list-style-type: none"> • Over-production factor • Manufacturing demand • Number of PPQ batches • Process platform • Batch scale • Cell culture titre • Duration • Timing dependencies 	Per phase per drug: <ul style="list-style-type: none"> • Phase transition probability • Dose • Number of animals / patients • Duration • (Pre-) clinical demand • Timing dependencies 	<ul style="list-style-type: none"> • Total phase costs per drug • Target number of market successes per year • Cost of capital / Discount rate
KEY COST AND TIME OUTPUT METRICS	Scheduling of events Per phase per drug and per phase per market success: <ul style="list-style-type: none"> • Process development cost 	Scheduling of events Per phase per drug and per phase per market success: <ul style="list-style-type: none"> • (Pre-) Clinical manufacturing cost (direct and indirect) • PPQ manufacturing cost 	Timing of development milestones Per phase per drug and per phase per market success: <ul style="list-style-type: none"> • Clinical trial cost per phase 	<ul style="list-style-type: none"> • Number of projects required per phase per market success • Portfolio out-of-pocket cost • Portfolio capitalised cost • % cost breakdown across process development, manufacturing, clinical trials • Time to market

Figure 2. Decisional tool structure for drug development budgeting across process development, (pre-) clinical manufacturing and (pre-) clinical trials with key model inputs and key cost and time output metrics.

are the demand, flowsheet, batch scale, and cell culture titer. The model then draws on default values from the database with representative mAb process and cost data for the remaining model parameters needed for the detailed mass balance, sizing, and cost calculations. The output costs were split into direct costs per batch that include raw materials (e.g., cell culture media, chromatography resins) that increase with batch number and indirect costs that are annual facility-dependent costs (e.g., maintenance) that are spread over the annual number of batches in a facility.

At the portfolio level, the model requires the user to define the total phase costs per drug, the target number of successful market entries per year, and the cost of capital or discount rate.

For pre-clinical and clinical studies, the phase transition probabilities are required to calculate the required number of projects to achieve the user's desired target. Demand of materials at (pre-) clinical trial stages is determined based on patient (or animal) numbers, dose and over-production estimates. This then drives the number of (pre-) clinical manufacturing batches required using the batch scale and titer given as inputs at the manufacturing level. The clinical trial costs are assumed to be the total phase costs minus the calculated process development and manufacturing costs.

At the beginning of the evaluation, the model builds up the timeline of the development pathway according to the inputs on duration of pre-clinical and clinical trials. Then, based on their material requirements, the model generates manufacturing activities with the appropriate number of production batches. The timings of manufacturing activities are set to meet the clinical material requirement. The process development activities are planned to provide technical support for manufacturing at various stages. After the model plans all the clinical and CMC activities for developing a single product, it calculates how many products the user needs at each step to achieve the target number of market successes, based on the clinical success rates. With the number of products being developed and the cost of developing each one determined, the total cost is evaluated.

The outputs at the portfolio level provide the user with information concerning how much it costs to achieve their target in terms of total out-of-pocket cost and total capitalized cost. The total out-of-pocket cost is defined as the total cost required per market success and hence it takes into account clinical success rates and the cost of failed candidates in terms of (pre-) clinical trials, process development, and manufacturing activities. The total portfolio out-of-pocket cost per market success is determined as the sum of process development, manufacturing, and (pre-) clinical trial costs for the number of projects entering each stage. The out-of-pocket costs for each stage are presented as outputs and they serve a more practical purpose for budget planning. More specifically, the cost breakdown of clinical trials, manufacturing, and process development is also available for more detailed budget planning. This enables the percentage contribution of process development and manufacturing to the out-of-pocket R&D costs to be determined. The capitalized cost is the out-of-pocket cost

adjusted for cost of capital and to account for the time value of money. For this study, the methodology from Paul et al.¹ was used to find the capitalized phase costs, assuming a cost of capital of 11%.

Results

Case study setup

A case study was set to estimate the CMC budgets needed for process development and manufacturing at each phase of development so as to ensure a market success each year. The case study focused on mAbs made in mammalian cell culture systems. The impact of different clinical success rate profiles on the process development and manufacturing costs at each stage was investigated. The key assumptions were derived through a detailed review of literature and interviews with industrial experts so as to derive industrially relevant inputs for this study.

Clinical transition rates

The clinical transition rates at each phase in the drug development process can significantly affect drug development costs to ensure a market success. Three case study scenarios were built for the base case average outcome as well as best-case and worst-case outcomes. In this model, the clinical success rates were characterized by the phase transition rates of projects. Table 1 summarizes the key assumptions for the risk profiles for each scenario, namely, the phase transition probabilities, the overall (Phase I to approval) success rate and the number of products required at Phase I so as to realize a market success.

The best-case scenario considered the upper end of the range of phase transition rates published with an overall success rate of ~30%, for biopharmaceuticals in general, as well as for mAbs specifically.^{3,29} The average scenario used the more typical phase transition probabilities derived from Paul et al.¹ resulting in an overall success rate of ~12% to provide a more balanced evaluation. More recently, overall success rates for antibody therapeutics have been reported as 22%, falling within the bounds explored in this study.³⁰ The worst-case scenario used an overall success rate of 4% derived from using the industrial average phase transition probabilities for pre-clinical to Phase II stages whilst addressing the possibility that for some therapeutic areas, such as Alzheimer's disease, the phase transition probability of Phase III could be extremely low due to the novelty of the drug targets being pursued and to the lack of animal models with a strong capacity to predict human efficacy.³¹

Table 1. Risk profiles of new biopharmaceutical product development represented by phase transition probabilities.

Scenario	Phase of development					Overall success rate	N _{P1} ^b
	PC ^a	I	II	III	Reg. Review		
Best case	70%	85%	55%	70%	91%	29.8%	3.4
Average	69%	54%	34%	70%	91%	11.7%	8.6
Worst case	69%	54%	34%	21%	91%	3.5%	28.5

aPre-clinical stage.

bNP1 = number of Phase I products required for one market success.

Cost estimations for developing a single product

Cost of process development

The definitions of process development and its associated costs in biopharmaceutical product development vary between sources and organizations. In this model, process development was defined as the activity that establishes and optimizes the manufacturing for biopharmaceutical products for clinical and commercial purposes, and provides knowledge for regulatory compliance. The cost associated with process development was therefore distributed across strain development, process synthesis, design, optimization, characterization, validation, and the related analytical development activities. It should be noted that the cost of manufacturing clinical material was not included in the cost of process development and instead was included under manufacturing.

The estimation of process development costs adopted a - FTE year-based approach. This approach first reviewed the necessary tasks for each step of process development in biopharmaceutical new product development, then derived the workload required to fulfill these tasks in terms of FTE year, and applied a fixed cost incurred to the company in every unit of FTE year to account for the actual cost of process development.

Table 2 contains the estimated FTE required for major process development activities in this model. The calculation of FTE was based on the number of personnel and their relative involvement in performing their function compared to a full-time employee. As an example of calculation, an employee working 2 h per working day on this project only accounted for 0.25 FTE. This principle applies to all the personnel working in regulatory support and quality control and quality assurance (QC/QA) functions that are not dedicated to any specific project.

The cost of the process development activity was determined based on the total workload required. On average, for every unit of FTE year workload, the cost incurred to the company was assumed to be \$250,000;³² this cost comprised the FTE salary plus overheads that included on-costs (e.g., pension contributions), management and infrastructure costs.

A breakdown was provided of employees by job function, shown in Table 2; this was used to ensure accuracy when estimating the total number of FTE required per phase. For every

step of process development, it was assumed that a project manager was required to work full-time in order to coordinate the work of the team and communicate with other relevant divisions of the company that facilitate the on-going process development. For the early stages of development, one project manager was assumed to be sufficient for the relatively small process development team, whereas for the late stages of development, the size of the team increases significantly so that one extra project manager was required. Process scientists are needed for upstream and downstream process establishment, optimization, characterization, and validation. Hence, they are needed from the start of the development lifecycle. Requirement of personnel in charge of technology transfer to pilot and large-scale manufacturing increases as the scale of manufacturing increases. The FTE required at a scale of 500 L, 2000 L, and 6000 L was set as 1, 2, and 4, respectively. The regulatory support required at pre-clinical and clinical stages is much less than that required at the regulatory review stage. The QC/QA personnel work on developing analytical assays for process development, but they normally work on multiple projects. The FTE figures for QC/QA were adjusted by the number of projects that one specialist can simultaneously handle and the number of specialists required for each process development step. The process development activities at the regulatory review stage were divided into two areas, with the original process development group working on the final process characterization, validation, and documentation for submission, while another group consisted of QC/QA and site support personnel working on preparations for commercial manufacturing. Given the definition of process development described earlier, the preparation of commercial manufacturing was considered as part of process development, and hence it was important to include the cost incurred.

Cost of manufacturing

The cost of manufacturing in pre-clinical and clinical development was calculated using an extended version of process economics models initially developed by Simaria et al.²⁵ and Pollock et al.²³ at UCL. The model receives inputs on the fermentation scale, titer, and clinical material demand. Estimation of material demand in clinical trials was based on the number of patients participating in each stage and the dose regimen. Table 3 presents the assumptions for patient numbers for clinical trials. With the assumptions that the average patient body weight is 86 kg and the approximate dosage per body weight is 7 mg/kg, one dose of treatment requires 0.6 g material. For Phase I, one dose per patient is sufficient to test product safety. For Phases II and III, the number of doses administered per patient is related to the length of test period and the frequency of administration. This case study assumed the frequency of taking one dose every 2 weeks and the average lengths of clinical treatment per patient for Phases II and III were 0.5 and 1 year, respectively. Typically, drug developers produce more product than needed for clinical trials to support CMC uses related to quality analysis and testing, as well as contingency inventory (e.g., in case of change in dosage or product loss). The ratio of overproduction applied to early phases is 250% and for Phase III is 125%, as the uncertainty of manufacturing decreases. The adjusted demand that takes into account the overproduction was therefore considered the target demand for the

Table 2. Estimated personnel and costs for process development (PD) activities in new biopharmaceutical product development.

PD Personnel	PC	Phase I	Phase III	Reg. Review (PD)	Reg. Review (Comm)
# Project manager	1	1	2	2	0
# Process scientists	3	6	10	12	0
# Tech-transfer	1	2	4	4	0
# Reg. support	0.5	1	2	10	0
# QC/QA	0.5	2	2	4	20
# Site support	0	0	0	0	20
Total # personnel	6	12	20	32	40
Duration (year)	1	0.5	2	1.5	1.5
Total FTE years	6	6	40	48	60
Cost (\$ million)	1.5	1.5	10	12	15

The process development activity in regulatory review stage is divided into 2 separate parts: Reg. Review (PD), with the original process development team working toward submission, and Reg. Review (Comm) with a team of QC/QA and site support personnel working on commercial manufacturing.

Table 3. Estimation of product demand in clinical trials.

Stage	Patient number	Doses per patient per trial	Total number of doses per trial	Clinical Demand	Over production	Adjusted demand
Phase I	40	1	40	24 g	250%	0.1 kg
Phase II	200	13	2600	1.6 kg	250%	3.9 kg
Phase III	2000	26	52000	31.3 kg	125%	40 kg

To calculate clinical demand, a dosage of 7 mg/kg body weight and an average body weight of 86 kg were assumed.¹⁷

process economics model to calculate the manufacturing cost. The target demand for the pre-clinical stage was assumed to be 0.5 kg.¹⁷

The adjusted demands for pre-clinical and clinical trials were then fed into the process economics model for calculation of the manufacturing cost. Assumptions related to the fermentation scale and titer are presented in Table 4. At the pre-clinical stage, the manufacturing process is established at a pilot scale of 500 L and a titer of 2.5 g/L. At Phase I and II, a 2000 L cGMP facility with a 2.5 g/L titer was assumed to be the standard set up for manufacturing. The fermentation scale and titer were further increased to 6000 L and 5 g/L at Phase III, as more material was required at this stage and the process is likely to be locked for commercialization. The improvement of the cell culture titer in Phase III is considered a result of process development. Three PPQ or consistency batches are included in the model, required to support the process characterization and validation package necessary for regulatory review for approval.

The process economics model determined the cost per batch and this was split into two categories: direct and indirect cost. The direct cost accounts for the use of labor, consumables, chemical reagents, and direct utilities during the manufacturing process. The indirect cost accounts for the facility overhead costs, including maintenance, general utilities, and capital charges. These costs are linked to the fixed capital investment (FCI) for the corresponding bio-manufacturing facility derived using the Lang factor approach.^{33,34} The indirect cost per batch was determined by spreading the annual indirect cost over a representative number of annual batches (20 in the pre-clinical facility and 10 in the clinical facilities).

Cost of clinical trials

Clinical trials contribute most to the total cost of developing biopharmaceutical new products. Various sources have published stage costs of developing new products, which can be considered as the total costs of clinical trials,

manufacturing, and process development. Therefore, this model derived the costs of clinical trials using published total costs excluding the CMC components, namely the process development and manufacturing costs described in the previous sections, summarized in Table 5 after inflation to 2020 dollars (using the Bureau of Labor Statistics consumer price index). Paul et al.¹ were used as the basis for these calculations. Calculations based on DiMasi & Grabowski³ can be seen in Appendix I. Although more recent analysis has been conducted,⁴ this study was used since it focuses on biopharmaceutical R&D costs. As shown by the upward trend in development costs,⁴ it is important to note that these derived clinical costs may be conservative. For the regulatory review stage cost, the published figure refers to the pharmaceutical industry in general, not specific to biopharmaceuticals. The cost attributed to the clinical trials at this stage only accounts for the fees required for regulatory review of the submission application. For example, in the US this would be the license fee for the Biologics License Application, and in the EU it would be for the Marketing Authorization Application.

Development timeline and milestones

To establish the new product development pathway, durations of activities and their dependencies are required. Table 6 presents the durations of activities from three categories, based on published sources and industrial opinion. A duration of zero for an activity indicates that there is no activity from the category at the given development stage. Therefore, from Table 6 it can be seen that it was assumed there would be no process development for the Phase II stage, as the process would not be changed typically until the need for a commercial scale process for use in Phase III trials and launch.

In this model, the dependencies between these three categories of activities follow the rationale that: 1) clinical trials, including pre-clinical tests, require clinical material supply, which is the

Table 4. Estimation of batch cost and number of batches required in new product development.

	Model inputs			Cost per batch (\$ million)			Batches
	Scale ^a (L)	Titer (g/L)	Demand (kg)	Direct	Indirect	Total	
PC	500	2.5	0.5	0.43	0.14	0.57	1
Ph I	2000	2.5	0.1	0.98	0.38	1.36	1 ^b
Ph II	2000	2.5	3.9	0.98	0.38	1.36	1 ^b
Ph III	6000	5	40	2.51	0.61	3.12	3
Reg. Review	6000	5	40	2.51	0.61	3.12	3

^aScale corresponds to total bioreactor size.

^bMaterial for Phase I and II clinical trials is shared.

The direct cost per batch includes labor, consumables, chemical reagents, and miscellaneous materials. The indirect cost accounts for facility maintenance, insurance, local taxes, general utilities, and capital charges. These costs are linked to the fixed capital investment (FCI) for the corresponding bio-manufacturing facility. The Lang factor approach was used to estimate the FCI for each facility.^{32,33} The indirect cost associated with running the facility is calculated as an annual cost. Direct and indirect costs per batch are calculated by spreading their annual values evenly among the batches performed in a single campaign. The number of batches produced every year is 20 and 10 for a pre-clinical and a clinical facility, respectively.

Table 5. Assumption on cost structures and comparison to published total stage costs for biopharmaceutical new product development.

Cost (\$ million)	Pre-Clinical	Phase I	Phase II	Phase III	Reg. Review
Published total ^a	6	18	48	180	48
Model assumptions					
Process Development	1.5	1.5		10	27
Manufacturing	0.6	1.4	1.4	9.4	9.4
Clinical Trials	3.9	15.1	46.6	160.4	3 ^b

^aPublished total adjusted to 2020 dollars to account for inflation.

^bThis cost represents the fees required for regulatory review of the submission application; for example, in the US this would be the license fee for the Biologics License Application (BLA) and in the EU it would be for the Marketing Authorization Application (MAA).

Table 6. Duration of activities.

Stage	PC	I	II	III	Reg. Review
Clinical trial duration (year)	1	1.6	2.4	2.7	1.5
Process development duration (year)	1	0.5	0	2	1.5
Manufacturing duration (week)	6	5	5	10	10

Durations of clinical trials are from DiMasi & Grabowski;³ duration of pre-clinical trials is from Paul et al.;¹ durations of process development are from discussions with industrial experts, and durations of manufacturing are based on the number of production batches.

result of manufacturing activities; and 2) manufacturing is supported by process development. So, for any given development stage, the order of activities is from process development to manufacturing, and then to clinical trials, unless there is no such activity at that stage. Due to this set up, some activities have to run at risk of project failure, as depicted in Figure 1. This includes the manufacturing of Phase I and II materials, and the process development for Phase I. For Phase III, only part of the process development activity is scheduled to run at risk with the opportunity for a decision to continue once Phase II results are in; process development can then be completed in parallel with the Phase III clinical trial preparation stage, including trial set-up and patient recruitment.

Discussion

A detailed analysis is presented of the CMC or process development and manufacturing costs across the biopharmaceutical drug development cycle. The model constructed a full R&D portfolio with the number of projects required to achieve the desired target. The development pathway was established for each project and its corresponding manufacturing and process development activities scheduled. The costs along the development timeline were calculated for the three risk scenarios with average, best-case and worst-case profiles for clinical transition rates. The CMC budgets needed at each phase of development to ensure a market success each year were estimated, along with the effects of transition rates on these.

Contribution of CMC to R&D costs

The model was initially used to estimate the contribution of CMC activities to R&D out-of-pocket costs, focusing on pre-clinical and clinical development stages through to approval. Figure 3 shows the model predictions for the out-of-pocket costs per phase to realize one market

success across three risk profiles; a breakdown of the total costs per phase is shown for (pre-) clinical trials and the CMC activities, process development and manufacturing.

Analysis of Figure 3 provides the following benchmarks. The range in possible risk profiles for different indications suggests that for an average profile with an overall success rate of ~12%, nine molecules must enter Phase I annually so as to yield a single market success each year. Increasing the overall success rate to the more optimistic value of ~30% reduces the

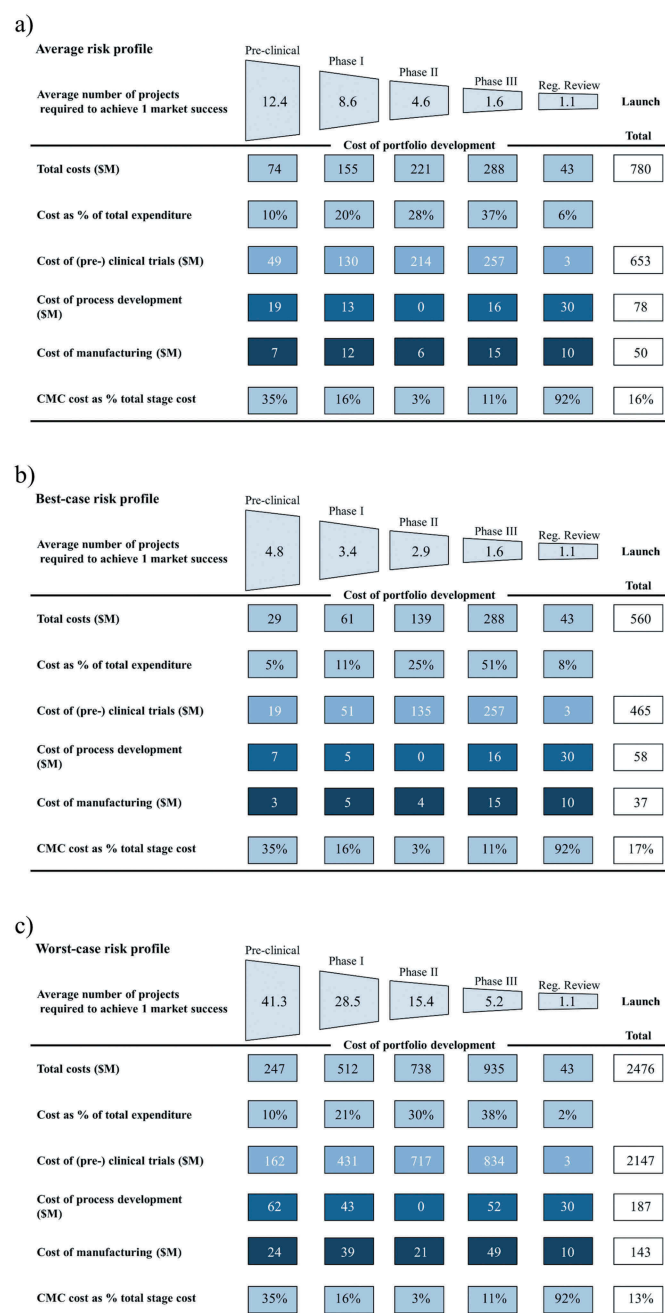


Figure 3. Cost evaluation of new biopharmaceutical product development for the (a) average, (b) best-case, and (c) worst-case risk scenarios. The three risk scenarios are presented, average (a), best-case (b), and worst-case (c). Using the phase transition probabilities the average numbers of projects required to achieve 1 market success at each stage are calculated. The costs of activities are based on the number of projects at the current stage, as typically early trial readouts allow the drug developer to plan for future stages.

number of molecules required to enter Phase I by more than a half to 4. In contrast, 29 Phase I entries are required to ensure a success when the overall success rate is decreased to ~4%, which is more representative of experience with indications such as Alzheimer's disease. Most companies would find it hard to sustain such a high number of Phase I entries per year, and this points to the importance of considering a mixed portfolio when targeting indications whose mechanism of action is less well understood.

Using success rates across a range, i.e., 30%, 12%, and 4%, has a significant impact on the total out-of-pocket costs from the pre-clinical phase to approval. The total out-of-pocket cost to have one market success was calculated by the model to be \$780 M (2020 dollars) for the average scenario, dropping to \$560 M for the higher success rate profile and rising to \$2476 M for the lower success rate profile. This is equivalent to capitalized costs of \$1880 M, \$1324 M, and \$5987 M, respectively. Total process development and manufacturing out-of-pocket costs are estimated to be \$78 M and \$50 M, respectively, for the average scenario. If the success rate increases from ~12% to ~30%, the out-of-pocket costs for process development and manufacturing decrease by 26%. If the success rate from Phase I to approval drops from ~12% to ~4%, the out-of-pocket costs for process development and manufacturing increase by 2.6 fold. Benchmarks for the ratio between process development and manufacturing costs can also be derived. Analysis of the average scenario suggests process development costs are 1.6 fold higher than manufacturing costs from pre-clinical to approval. The ratio of process development to manufacturing costs was found to vary from 1.3 to 1.6 for the worst-case scenario (\$187 M to \$143 M) and the best-case scenario (\$58 M to \$37 M), respectively.

The percentage of a biopharmaceutical company's R&D out-of-pocket costs from pre-clinical to approval that needs to be allocated to process development and manufacturing for each biopharmaceutical market success was found to vary between 13-17% for Phase I to approval success rates of 4-30%. For the most recent antibody overall success rates of 22%,²⁹ the CMC cost contribution to R&D was determined as 17%.

Analysis of key cost drivers

Figure 4 indicates the breakdown of the portfolio costs for the three scenarios. The results indicate how total R&D budgets and CMC budgets are distributed across the phases when striving for one drug market success per year under different risk profiles. The total costs for each phase are summarized and their proportion to the total out-of-pocket cost calculated. In Figure 4a, the division of new product development R&D spending is presented for the three risk profiles. For the industrial average it shows that in terms of total R&D costs, Phase III is the major cost driver in biopharmaceutical new product portfolio development (37%) while the spending on regulatory review stage is only 6% of the total cost. However, when focusing only on the CMC activities (Figure 4b), in the average scenario, the process development and manufacturing activities for the regulatory review stage consume the highest proportion of out-of-pocket CMC funds per success (31% of

total CMC costs), followed by phase III (24%), the pre-clinical stage (20%), phase I (20%), and then phase II (5%). The best-case scenario follows a similar trend, with the regulatory review stage and phase III dominating. In contrast, for the worst-case scenario, the CMC costs for the pre-clinical stage and phase I increase significantly given the high number of entries required to achieve success.

Impact of clinical transition rates on CMC budget planning

The model indicates how process development and manufacturing budgets should be distributed across the various phases. Figure 4c highlights the model predictions on how CMC budgets should be distributed across early (pre-clinical to Phase II) and late-stage (Phase III to regulatory review) development. To ensure a market success each year with an average overall success rate of 12%, the model predicts that a biopharmaceutical company needs to allocate process development and manufacturing budgets in the order of \$57 M for pre-clinical to Phase II material preparation and \$71 M for Phase III to regulatory review material preparation. For the best-case success rate of 30%, these values are \$24 M and \$71 M, respectively, and for the worst-case scenario, of 4% success rate, \$189 M, and \$141 M.

For the industrial average risk profile, the cost of manufacturing was estimated to be approximately 64% of the cost of process development. As the risk increases, a greater cost burden falls on early-stage development. This could be attributed to the increased portfolio size required in these stages. For companies with large development portfolios, cost reduction methods such as streamlined technology platforms for process development and manufacturing should be employed as early as possible.

The distribution of process development and manufacturing costs across the development stages differs as the risk scenario changes. All early-stage process development and manufacturing are running at risk; therefore, costs of process development and manufacturing from early-stage increase faster than late stage as the development risk increases, shown in Figure 4c. The impact of lower success rates and the resulting higher numbers of candidates at each phase on capacity requirement must also be considered in order to ensure sufficient process development labs are available, as well as pilot and large-scale GMP manufacturing facilities.

In conclusion, this study benchmarks the cost to develop and manufacture therapeutic biopharmaceuticals across the drug development lifecycle, emphasizing the cost distributions across both development stages and clinical and CMC activities. This was achieved with the biopharmaceutical drug development lifecycle model that captures the costs, durations, risks and interdependencies of both the clinical and CMC activities. The CMC activities were broken down into process development and manufacturing. A detailed analysis is presented of the process development and manufacturing costs across the biopharmaceutical drug development cycle on a single drug and portfolio basis. The CMC budgets needed at each phase of development to ensure a market success

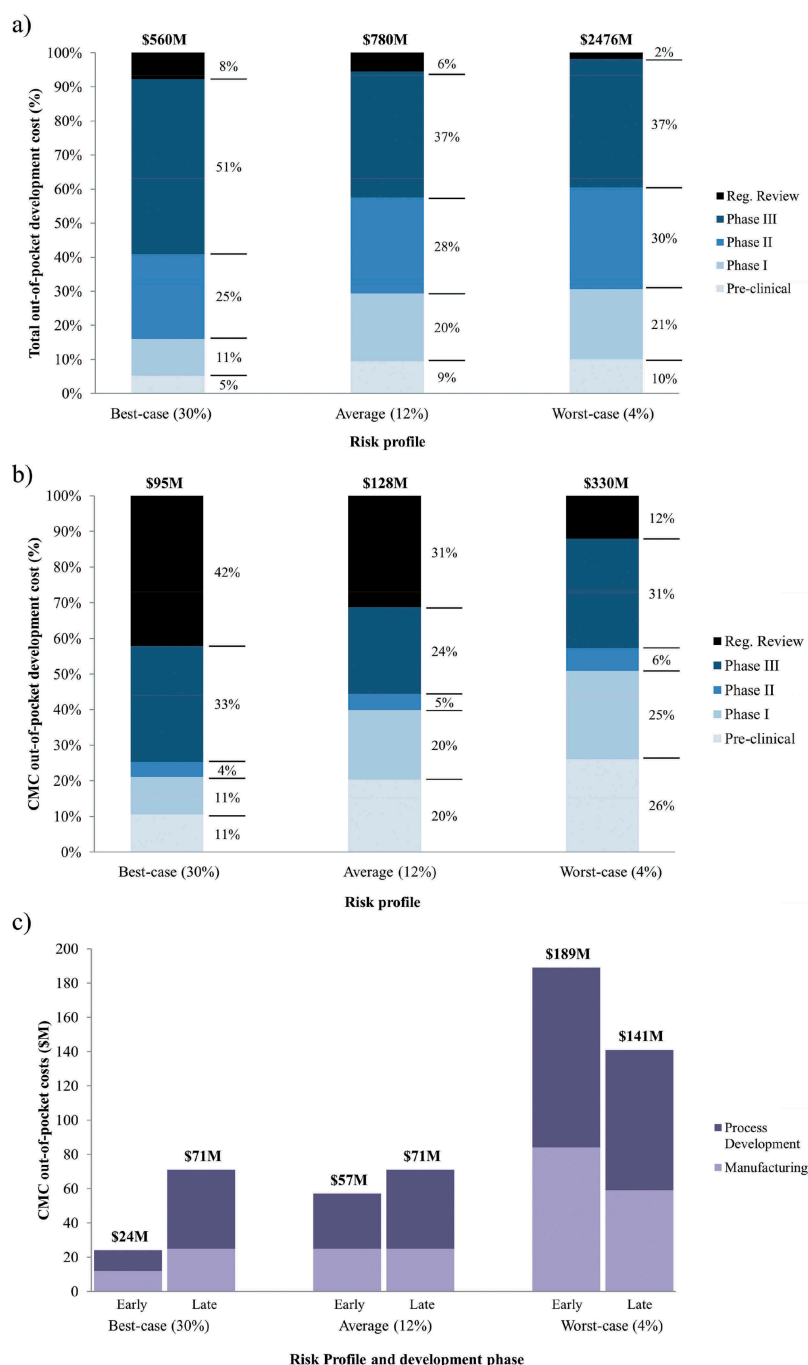


Figure 4. (a) Total out-of-pocket development cost distributions across development stages presented under the three risk scenarios. Each scenario is annotated with the percentage contribution from each stage along with the total out-of-pocket cost. (b) CMC out-of-pocket cost distributions across development stages presented under the three risk scenarios. Similarly, each scenario is annotated with the percentage contribution from each stage along with the CMC out-of-pocket cost. (c) Early and late phase CMC budgets required to ensure one market success under the three risk scenarios. Each phase is broken down to process development and manufacturing activities that form CMC, and annotated with the total CMC budget.

each year were estimated for three representative clinical risk profiles and two industrially relevant average stage cost alternatives. The costs of process development and manufacturing activities at each stage and their proportions of the total cost were further investigated in a sensitivity analysis with changing risk and cost scenarios. This study lays down the foundation for quantitative cost structure analysis of pharmaceutical product development under various clinical trial risk scenarios. The results can be further exploited in portfolio management and budget planning procedures.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Appendix I

Figure A1 displays the cost to market breakdowns, as seen in Figure 3, using the phase costs from DiMasi & Grabowski.³ Total phase costs were \$43 million for Phase I, \$50 million for Phase II, and \$127 million for Phase III after inflation to 2020 dollars. The pre-clinical cost was

sourced from Bodgan & Villiger at \$8 million (inflated to 2020 dollars);⁶ As with the previous calculations, the Biologics License Application cost at \$3 million was used for regulatory review clinical trials costs.

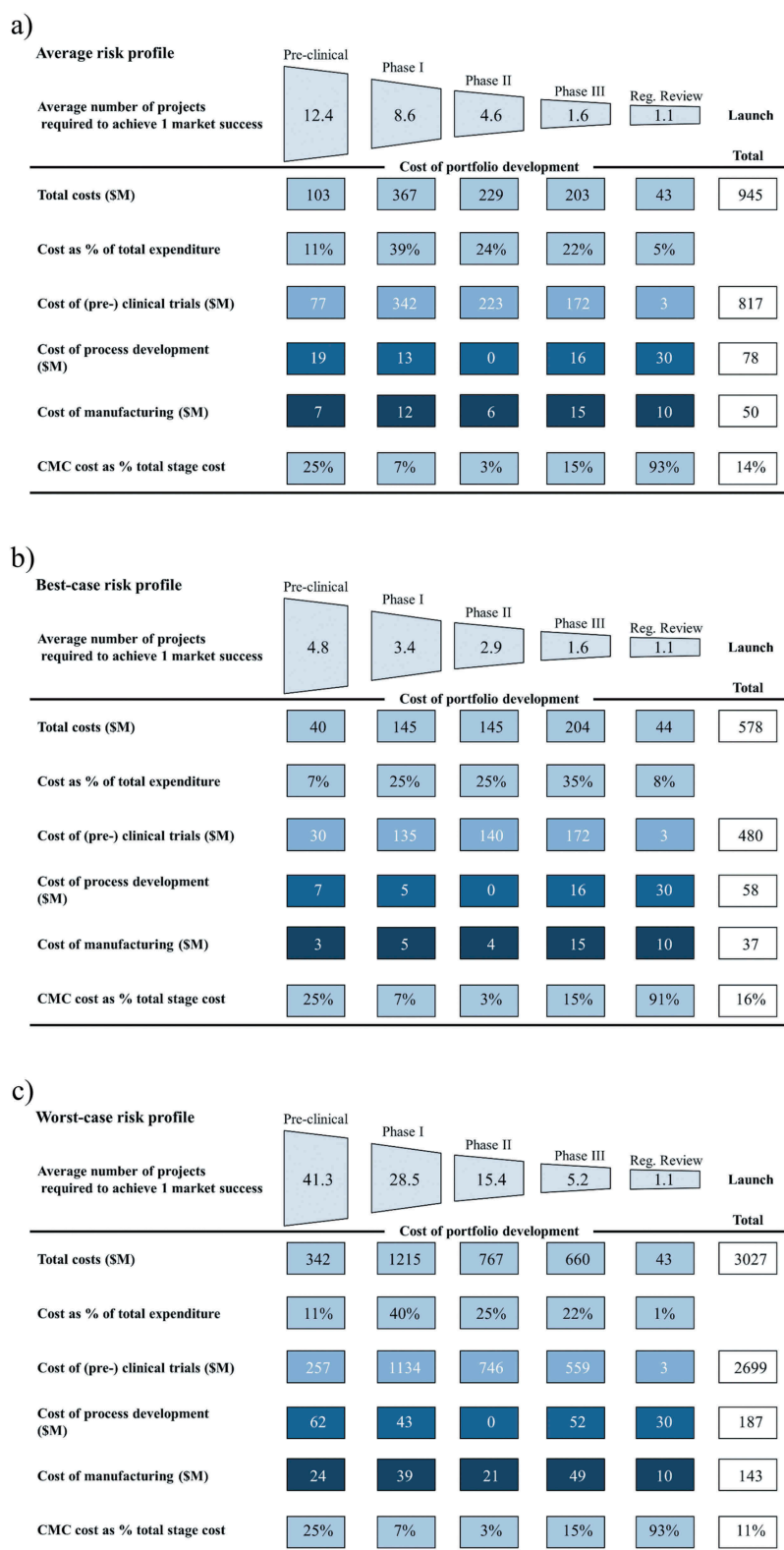


Figure A1. Cost evaluation of new biopharmaceutical product development using the study of DiMasi & Grabowski as reference for the (a) average, (b) best-case, and (c) worst-case risk scenarios.