

The Chorus Story

Chorus, an autonomous division of Lilly Research Laboratories, began in 2002 as an innovative R&D pilot by Eli Lilly and Company. Chorus was founded with the intent of transforming the existing drug development process by designing and implementing a lean approach to generating clinical proof-of-concept (PoC) data as quickly and cost-effectively as possible through the utilization of a more flexible virtual development model.

The pilot began with Lilly providing Chorus a handful of drug candidates not active in development, along with personnel and funding consistent with a lean model. Within two years, Chorus had provided Lilly with positive biomarker PoC data for one of the molecules. Over time, additional, active, early-phase molecules were directed to this group and Chorus demonstrated notable productivity improvements. The advantages of Chorus over traditional pharmaceutical development were significant in terms of cost and time savings to clinical PoC. Given the success of Chorus, this innovative early phase research engine has been strategically repositioned by Lilly to develop additional molecules and expand the company's early-phase pipeline.

In the seven years since its inception, Chorus has advanced two dozen molecules into Development from Discovery through early phase Clinical (typically through Phase IIa). Of those molecules, ten have been progressed and concluded through clinical proof-of-principle (PoP) or PoC, at a mean cycle time of 25 months and a mean total cost per molecule of \$3.8 million (direct plus indirect cost). Due to the more complex nature of recent additions from Lilly's mainstream portfolio, the mean cycle time for Chorus' contemporary portfolio is now 29 months to Clinical proof-of-concept at a mean total cost per molecule of \$6.0 million (direct plus indirect cost). In the context of industry benchmarks, data from a 2000 Tufts report place the cost of Phase I development without achieving PoC at US \$15.2 million¹. In a subsequent analysis published in early 2006, Adams and Brantner place the mean cost of Phase I development at US \$32 million².

1. DiMasi JA, Hansen RW, Grabowski HG. 2003. The price of innovation: new estimates of drug development costs. *J Health Econ.* 22:151-85.
2. Adams CP, Brantner VV. 2006. Estimating The Cost Of New Drug Development: Is It Really \$802 Million? *Health Affairs* 25(2): 420-428.



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1. INTRODUCTION

Chorus is a small group of experienced drug developers focused on establishing clinical proof-of-concept (PoC) as quickly and inexpensively as possible. Chorus designs and manages drug development plans on new chemical entities (NCEs) from the stage of candidate identification through Phase IIa clinical trials. Chorus has gained experience across all Lilly Research Laboratories therapeutic areas of interest, including, neuroscience, endocrine, cardiovascular, inflammation, women’s health, and oncology. Chorus offers extensive early-phase expertise along the entire development value stream, including manufacturing, preclinical, regulatory, and clinical operations. Chorus performance metrics exceed industry standards as a result of leveraging experienced internal talent and the adoption of a set of streamlined standard operating procedures and business processes similar to those of a small biotechnology company. Additionally Chorus benefits from Lilly’s FIPNet (Fully Integrated Pharmaceutical Network) strategy which leverages collaborations and service agreements with a broad network of global providers.

Chorus tests new molecule hypotheses in man by addressing key scientific questions at the earliest possible time, before embarking on the more expensive, late-stage development activities. In this model, traditional pre-PoC development—including large-scale manufacturing, extensive formulation work and long-term toxicology testing—are delayed until data are developed to support the testing of the key “gating” hypothesis. The Chorus approach alters the balance of risk across the portfolio and enables clinical study of many more candidates at a fraction of the time and cost, typically associated with traditional drug development. Additionally, Chorus advances molecules with an improved probability of technical success into later phases of development.

2. THE CHORUS ORGANIZATION

The Chorus operation is based on the campus of Eli Lilly and Company in Indianapolis, Indiana. Chorus operates much like a lean biotechnology company within the walls of a larger biopharmaceutical company. The Chorus team consists of talented and experienced industry professionals representing all of the relevant functions of pharmaceutical R&D. Chorus has a flat hierarchical structure consisting of approximately 30 experts in medical, CM&C, toxicology, regulatory, clinical operations, quantitative pharmacology, statistics, and quality.



3. KEY COMPETENCIES

Chorus leads and supports pharmaceutical development due diligence, planning, and implementation services for a diverse portfolio of new chemical entities (NCEs). For effective planning, implementation, and partnership with external third-party providers, a number of key competencies, which are highlighted below, have been established within Chorus. Each of these focus on implementing the necessary targeted drug development experiments designed to answer critical scientific questions.

The service groups within Chorus are accountable for three objectives:

1. Designing creative approaches and using cutting-edge methodology and technologies to solve challenging drug development problems.
2. Providing the main point of contact for a vast network of external content experts.
3. Implementing activities efficiently and cost-effectively by coordinating with global collaborators and service providers.

Chorus is agile and operates as a single efficient unit, enabling seamless integration of all relevant activities.

The Chorus team leverages the following key competencies to accomplish its objectives:

- a. Clinical Design
- b. Clinical Implementation
- c. Regulatory
- d. Chemistry, Manufacturing, and Control
- e. Quantitative Pharmacology
- f. Toxicology
- g. Quality
- h. Voice Technology

Clinical Design

Clinical studies are the core of the drug development decision-making process, and thoughtful design of experiments is fundamental to effective testing of critical scientific hypotheses. Chorus focuses on answering key scientific questions in order to determine the safety and efficacy of a molecule. For each molecule, Chorus reduces the most important scientific issues into very specific questions that can be answered with focused clinical experiments. Examples of these key questions include:

- Can the molecule be safely administered at levels required to produce a measurable pharmacodynamic response?



- Can a biomarker be used to quantify the relevant pharmacodynamic response in order to facilitate dose selection for Phase II studies?
- Will the molecule demonstrate a measurable pharmacodynamic response in healthy volunteers through the disease state surrogate test?

Chorus focuses its attention on questions that will, at the earliest stages of development, either increase the probability of technical success of a molecule by discharging significant technical risk or determine with minimal investment that the risk is unmanageable and the molecule is not worthy of further development.

Once key scientific questions are identified, the clinical experiment is designed to answer those questions in the safest and most effective manner for healthy volunteers and patients. To supplement Chorus internal expertise, Chorus engages the most relevant published and experienced academic and industry researchers around the world. Their input and knowledge is leveraged to refine the questions and experimental strategies. At this point, the approach to hypothesis testing often incorporates the use of new and innovative technologies, unique biological markers that allow for early indicators of pharmacological response (safety and efficacy), novel surrogates/models for disease states, and adaptive clinical trial design.

Table 1: 5-year summary of Chorus molecules by therapeutic area expertise (2004-2008)

	2004	2005	2006	2007	2008	Total
Neuroscience	4	3	0	2	2	11
Endocrine	0	1	0	0	2	3
Oncology	0	0	0	1	1	2
Women's Health	0	1	0	1	0	2
Bone/Inflammation	0	2	1	0	0	3
Cardiovascular	0	2	0	1	0	3

Clinical Implementation

Chorus clinical operations has implementation experience ranging from small, local, and regional Phase I studies to combination Phase I and II studies and complex, global Phase II trials. Having started more than 30 clinical studies since 2004, Chorus has demonstrated some of the most impressive early-phase clinical cycle times and work flow in the pharmaceutical industry.



2004-2008 Clinical Milestone Cycle Time Metrics

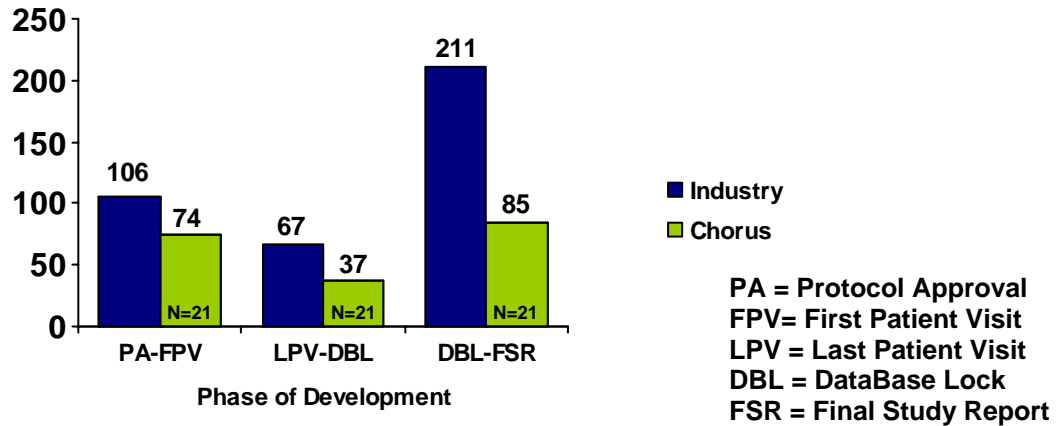


Figure 1: Chorus Clinical Milestone Cycle Times (Represents 21 clinical studies in the Chorus portfolio, starting between 2004 and 2008). Industry data reflects CMR composite industry data 2004-2006.

How does Chorus gain such efficiencies in the clinical trial process? Chorus achieves this benchmark performance by applying its unique RIGHT FIT concept:

- Appoint a single, skilled and experienced internal point of contact/project leader to each clinical project.
- Select accurate and appropriate global geographies for conducting Chorus clinical trials including the possibility of emerging markets
- Leverage a global therapeutic and scientific network of experts who have unique experience or technology tailored to fit the specific study design.

Chorus clinical best practices drive efficiency and are built on the Chorus philosophy of making intelligent business decisions and delivering on commitments with diligence:

- Chorus does not have preferred provider vendor relationships. This enables selection of only the most qualified providers for each clinical study in the targeted region, specific to the unique study requirements.
- Chorus has a single oversight committee that reviews all regulatory and patient safety documentation and, therefore, can move quickly and consistently through the review and approval process without being encumbered by multiple layers of internal governance reviews.
- Chorus can use third-party provider's templates, systems, and operating procedures to maintain efficiencies, both internally and externally.



To date, Chorus has implemented early-phase clinical trials in the following countries:

- North America: United States
- Central and South America: Argentina, Brazil, Columbia, Mexico, Peru
- Western Europe: Belgium, Denmark, Germany, Hungary, Netherlands, Switzerland, United Kingdom
- Eastern Europe: Romania
- Africa: South Africa
- Asia: India

Regulatory

The Chorus regulatory affairs group supports the regulatory needs of each molecule from nonclinical testing through first-in-man studies and proof-of-concept. Chorus activities are designed with emphasis on the Declaration of Helsinki and International Conference on Harmonisation (ICH) good clinical practices (GCPs), to meet the expectations of regulatory agencies worldwide as established by the

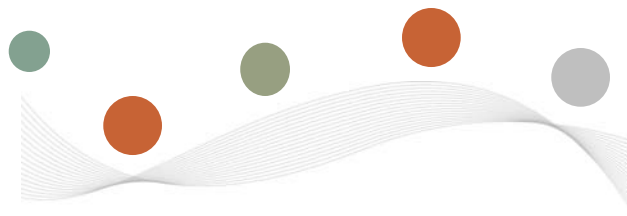
- World Health Organization (WHO)
- European Union (EU)
- U.S. Code of Federal Regulations (CFR)
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The Chorus regulatory affairs group has a broad understanding of global regulatory challenges and the requirements to conduct clinical studies around the world. Chorus has selected partners to assist in regional regulatory strategy development to ensure regulatory compliance from the outset. Chorus operates in alignment with directives, guidelines, and regulations of bodies such as the WHO, ICH, CFR, and EU, and by applicable specific country and state regulations.

Implementation of the regulatory work product (i.e., clinical trial authorizations, investigational new drug applications and clinical trial notifications) is also accomplished through collaboration with experienced partners.

Chemistry, Manufacturing, and Control

The chemistry, manufacturing, and control (CM&C) group at Chorus focuses principally on providing a fully integrated CM&C design and implementation strategy to support preclinical, first human studies and early proof-of-concept clinical testing.



Areas of Work:

- pre-formulation
- biopharmaceuticals
- drug substance process development and manufacturing
- drug product formulation development and manufacturing
- analytical control
- packaging, labeling, and release of clinical material
- clinical distribution

Consistent with the overall Chorus model, emphasis is placed on conducting the minimum required CM&C work necessary to allow the key toxicology and clinical experiments to be conducted while deferring most, if not all, later phase parallel processing until the PoC has been established.

Quantitative Pharmacology

Quantitative pharmacology is a discipline within Chorus that builds and uses *in silico* models of drug effects and disease progression to design clinical and non-clinical experiments that inform dose/exposure relationships for safety and efficacy, in keeping with the principles of model-based drug development. *In silico* modeling and simulations are used to evaluate and optimize clinical study designs and establish a comparative understanding of the benefits and risks associated with a molecule in order to enable definitive proof-of-concept decisions.

Areas of Work:

- Nonclinical pharmacokinetic/pharmacodynamic (PK/PD) and translational pharmacology
- Nonclinical ADME
- Clinical PK/PD
- Modeling and clinical trial simulation
- Adaptive designs

Toxicology

The mission of Chorus' toxicology group is to creatively integrate multiple scientific disciplines to evaluate the safety of new drug candidates. With external partners, Chorus conducts the right studies at the right time in order to characterize important toxicities and to define a margin of safety. All work has scientific and operational excellence at its core.



Areas of Work:

- General toxicology
- Pathology
- Safety pharmacology
- Genetic toxicology
- *In vitro* toxicology
- Nonclinical formulations and analysis

Quality

Chorus is fully compliant with corporate policies as well as all applicable laws and regulations. Additionally, Chorus has created a streamlined set of purpose-fit, early-phase research standard operating procedures (SOPs) aligned directly with good clinical practices (GCP), good laboratory practices (GLP), and good manufacturing practices (GMP) requirements as described in International Conference on Harmonisation guidelines. For outsourced implementation work with third-party providers, Chorus has minimized routine process complexity by developing streamlined SOPs that permit delegation of authority. Once a vendor passes an in-depth vendor/site qualification and ICH audit, Chorus and the outsource partner may use the outsource provider's SOPs, templates, and/or information technology platforms for data management. For outsourced work that requires sponsor approval, Chorus uses quality checklists to confirm that regulatory guidelines are followed.

Information Technology and Portfolio Management with Voice

Chorus teamed up with an external IT solutions partner to develop a custom, web-based enterprise management system called Voice. Voice enables small, virtual, global drug development teams to securely collaborate on all aspects of a project—including broad planning, detailed implementation, document development and approvals—and provides administrative solutions to numerous internal portfolio challenges. The system facilitates quick, strategic decision-making by leveraging defined processes to integrate collaborative information across a development plan. There is currently no commercially available software product rivaling the integration and functionality of Voice.

Voice addresses the unique communication and management challenges associated with the Chorus business model and facilitates collaboration with third party providers (TPPs). All Chorus TPPs have secure and restricted access into the Voice system, which enables collaboration and efficient communication among virtual, global team members.



Voice provides:

- Robust security to control internal and external access to intellectual property and proprietary information
- Global access via the Internet, via any computer
- No special software requirements for external collaborator's computers
- Compliance to FDA 21 CFR Part 11 for electronic documents and electronic signatures (ER:ES)
- Integration of high-level project plan information with detailed implementation plans
- Role-based functionality for Chorus, vendors, and sponsor stakeholders (i.e., Lilly)
- Vendor management capabilities
- Financial management capabilities, including development of purchase orders and invoices
- Portfolio reporting capabilities

4. OUTSOURCING PHILOSOPHY

The Chorus business model is built on the foundation of flexible outsource staffing through TPPs, offsetting fixed internal costs. Tactical outsourcing such as staff augmentation, functional outsourcing, and full-service outsourcing is an increasingly common method used by most pharmaceutical and biotech companies to reduce R&D fixed costs. Rather than dealing with inefficient outsource models, such as relying on a small exclusive group of providers, Chorus recognizes the need to leverage a wider group of external global implementation expertise to deliver multifaceted services. This external network provides Chorus with the flexibility to match each project's unique needs and strategic integration requirements to a wider array of global and niche TPPs. To support this more inclusive model, Chorus developed and maintains a large and growing network of providers to support each function. The Chorus external network continues to grow and currently consists of more than 200 global providers.

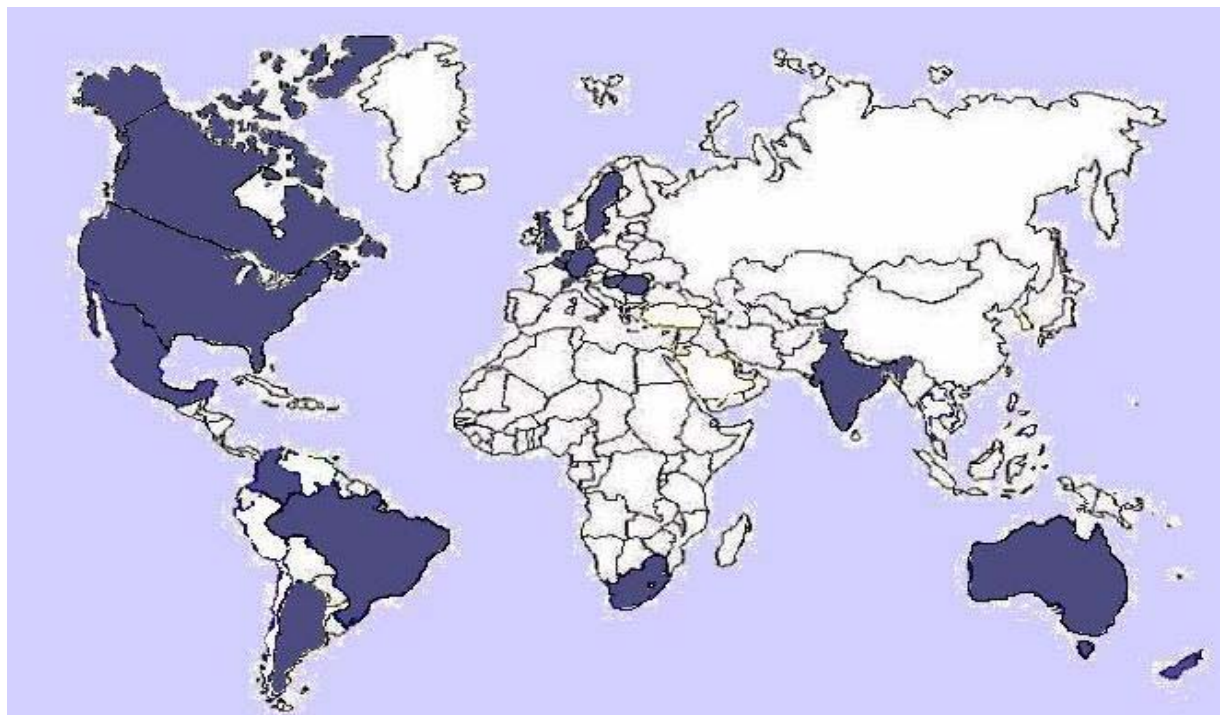
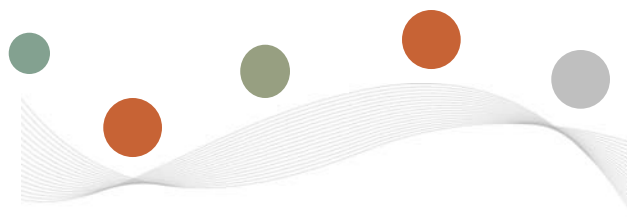


Figure 2: Global Reach of Chorus External Network

In Chorus, selection of the right vendor goes beyond standard requirements such as therapeutic area expertise, geographic presence, and big pharma references. The right vendor also has to have close alignment and strategic fit with the Chorus business philosophy. Since selecting an appropriate vendor is often pivotal to the success of the Chorus implementation model, Chorus devotes significant time to ensuring vendors are of the highest quality, are ethical and compliant with local laws and regulations, and are the top leaders in their field.

5. CHORUS EXPERIENCE

Chorus is the only research and development engine of its kind that has managed the development of two dozen NCEs within five years with approximately 30 employees (2004-2008 data). Of the projects undertaken between 2004 and 2008, five were transferred back to Lilly for continued Phase II development, and five were terminated. The remainder resides in development within the current Chorus portfolio.

Chorus' past five years of drug development experience is summarized in Table 2. This table highlights the experience of Chorus staff exclusively with Chorus molecules and does not include other company development information.



Table 2. Summary of Chorus Development Experience (2004-2008)

Molecule ID	Therapeutic Area	Indication	Molecule Type	Program Management and Implementation			Territory: US, South America (SA), <u>Africa</u> , <u>Europe</u> , <u>Asia</u> , <u>Australia</u>	No. of Trials
				Pre-Clinical	Phase 1	Phase 2		
LY# 02	CV	Atherosclerosis	Small	✓	✓	✓	EU	3
LY# 04	CV	Stroke, Neuroprotection	Peptide			✓	US/ AS	1
LY# 01	CV	Venous Thromboembolism	Small		✓		EU	1
LY# 06	Endocrine	Chronic Kidney Disease	Small	✓			N/A	0
LY# 03	Endocrine	Diabetes	Antibody			✓	US	1
LY# 05	Endocrine	Diabetes	Protein		✓		AUS / AF / AS	2
LY# 07	Inflammation	RA	Antibody		✓	✓	EU / AUS / SA	1
LY# 08	Inflammation	RA	Antibody			✓	EU	1
LY# 10	Inflammation	RA	Small	✓	✓		EU	2
LY# 23	Neuroscience	Alzhiemers Disease	Small		✓		US	1
LY# 17	Neuroscience	EtOH Dependency	Small			✓	US	1
LY# 09	Neuroscience	IBS	Small			✓	US	1
LY# 11	Neuroscience	Migraine	Small		✓	✓	US	2
LY# 12	Neuroscience	Migraine	Small	✓	✓	✓	US	2
LY# 13	Neuroscience	Migraine	Small	✓	✓	✓	US	2
LY# 25	Neuroscience	Migraine	Small			✓	US	1
LY# 15	Neuroscience	Pain	Small		✓		EU	3
LY# 16	Neuroscience	Pain	Small	✓	✓	✓	EU	0
LY# 24	Neuroscience	PET	Small		✓		EU	1
LY# 14	Neuroscience	Schiziphrenia	Small	✓	✓		EU	1
LY# 18	Oncology	Advanced/ Metastatic Ca	Peptide	✓	✓		US	1
LY# 19	Oncology	Lymphoma	Small			✓	US / SA / AUS	1
LY# 20	Women's Health	Hot Flashes	Small	✓	✓	✓	EU	3
LY# 21	Women's Health	Uterine Leiomyoma	Small	✓	✓	✓	EU	0



6. CHORUS PERFORMANCE METRICS

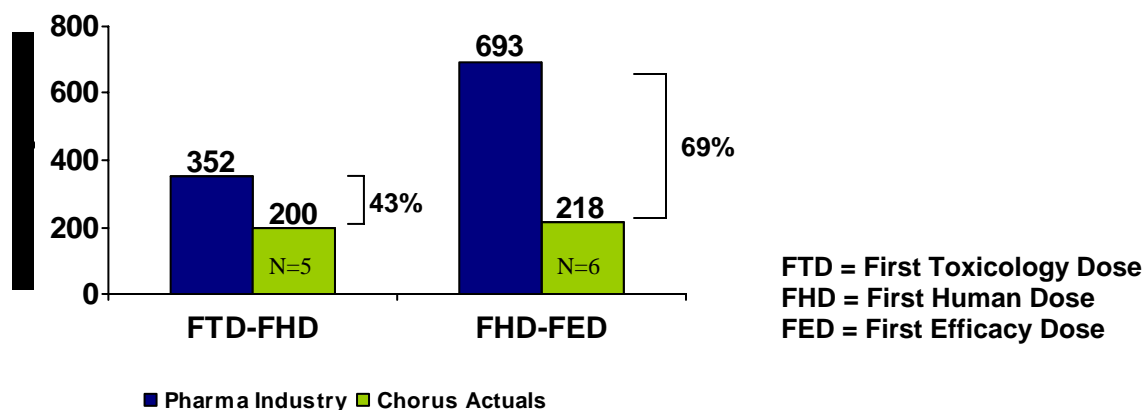
Chorus continues to demonstrate some of the most efficient drug development metrics (quality, speed, and cost) in the industry.

Major Milestone Cycle Time Metrics

Typically, Chorus accepts new chemical entities (NCEs) into their portfolio at any stage between candidate identification and end of Clinical Phase I. Molecules are advanced through the Chorus portfolio to PoP or PoC within 29 months (planned and actual median data from 2004-2008 with a portfolio of 21 NCEs).

The following graph depicts major milestone, median cycle times for molecules that entered the Chorus portfolio between 2004 and 2008, at various stages between candidate identification and end of Phase I.

Median Cycle Times



Sources: CMR composite industry data 2004-2006; Chorus data 2005-2008 for assets achieving both FHD and FED in Chorus (actual data).

Figure 3: Major Milestone Cycle Time Metrics (2005-2008)

The first two bars in the above graph depicts median cycle times in days for Chorus molecules (green) between first toxicity dose (FTD) and first human dose (FHD), compared with industry benchmark data (blue). For this phase of development, benchmark data indicate Chorus performance is 43% faster than the industry median.

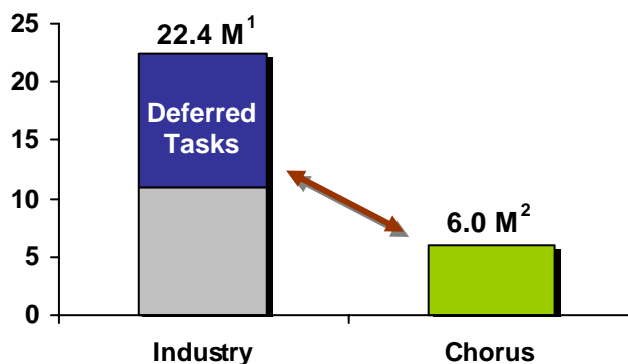
The third and fourth bars in the above graph depicts median cycle times in days for Chorus molecules (green) between FHD and first efficacy dose (FED), compared with industry benchmark data (blue). For this phase of development, benchmark data indicate Chorus performance is 69% faster than the industry median.



Cost Metrics

In total, the median cost for molecules that advanced through the Chorus portfolio between 2004 and 2008 was US \$6.0M (direct plus indirect costs), compared to the industry benchmark data indicating a cost of US approximately \$23M.

**Development Spend in Millions
(Ph I thru Ph II) PoC**



1. Sources: DiMasi et al, Journal Health Economics 22 (2003) pp 151-185 (cost to PoC estimated as half of Ph II spend)

2. Chorus Data – Total direct plus indirect cost for 21 molecules in the Chorus portfolio from 2005-2008 and one from 2004; Costs are actual + projected spend. Assets entered portfolio at different stages of development (i.e. with Tox, CM&C, or limited clinical work already completed).

Figure 4: Chorus Cost Metrics

It is important to note the difficulty of comparing Chorus drug development costs with industry benchmarks given the Chorus “truth-seeking” versus industry “success-seeking” business model.

- Truth-Seeking Model: to design minimum experiments that absorb maximum risk and all scale-up work is deferred until a positive PoC is achieved
- Success-Seeking Model: scale up is paramount with the assumption the program will be a success

Chorus is able to achieve considerable productivity gains compared to the industry, predominantly as a result of the organization size, integrated internal professional staff, and extensive global network of service providers, which together execute the truth-seeking business model. The Chorus model is the ideal approach for establishing PoC for drug candidates as quickly and as inexpensively as possible. Even more importantly, the Chorus model enables compounds to fail faster pre-POC, as 60 to 80 percent are destined to do so between first tox dose and first registration dose³ - thus saving precious resources for more promising molecules.

³ R&D Performance 2008 Success Rates and Cycle Time, Pharmaceutical Benchmarking Forum, Public Information prepared by KMR.