Pharmacometrics as a Discipline Is Entering the "Industrialization" Phase: Standards, Automation, Knowledge Sharing, and Training Are Critical for Future Success

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The development of drug models that incorporate characteristics such as pharmacokinetics, pharmacodynamics, pathophysiology, and genetics has gained importance in drug discovery, development, and innovation in recent years. Integration of drug models with disease progression models has been proposed but has been limited by the lack of contemporary and robust data.[1]

In 2004, the US Food and Drug Administration (FDA) Critical Path Initiative identified neuropsychiatric diseases and disease models as priority areas of active research opportunities.[2] The World Health Organization reached similar conclusions that same year.[3]

In such a context, precompetitive research, defined as collaborative scientific efforts by entities that ordinarily are commercial competitors, plays a central role.[4] To that end, data-sharing initiatives and the training of professionals with the abilities to tackle such tasks become key needs.

In the face of these challenges, industry, regulatory bodies, and academia need to collaboratively address the shared problem of lengthy and expensive medical-product development programs with high attrition rates.[4] This requires not only well-structured translational sciences and precompetitive research but also a workforce with the necessary training background, for which training and skill building are essential.

This article presents the advances being made with respect to developing standards and automation at the FDA, 3 data-sharing initiatives that focus on developing modeling and simulation as a useful tool for drug development, and a discussion about the training of future pharmacometricians.

DEVELOPMENT OF STANDARDS, AUTOMATION, AND KNOWLEDGE-SHARING AT THE FDA

Pharmacometrics has become an integral part of regulatory decision making. The Division of Pharmacometrics has reviewed more than 200 new drug applications (NDAs) and biologics license applications (BLAs) in the past 10 years. The early phase of pharmacometrics' application to key decisions has come to fruition. During this period, analyses have been predominantly tailored for each problem.[5,6] The discipline is now entering the "industrialization" phase, during which similar analyses will be performed over and over. Quality, consistency, and speed along with the ability to access prior knowledge are needed, as is knowledge sharing, to accelerate this phase. This section describes the advances being made with respect to developing standards and automation and sharing knowledge at the FDA.

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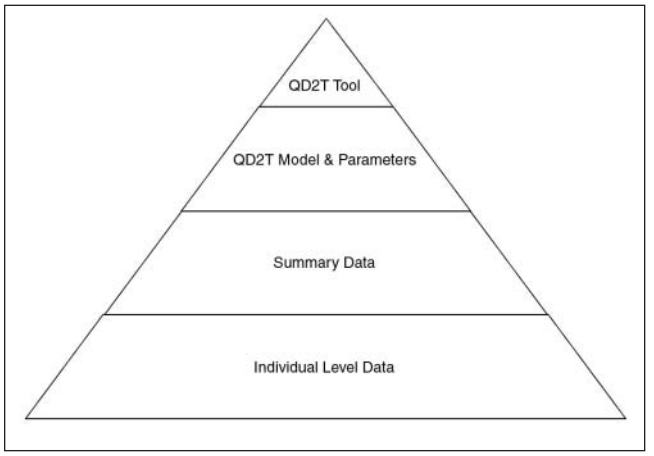

Figure 1. Knowledge pyramid.

Developing Standards and Automation

The workload for a pharmacometrician is ever-increasing, the number of experts trained per year is constant at best, and the collective experience to solve problems is increasing. Tailored modeling work leads to reinventing the wheel and diversity in analysis and reporting. A leading factor for the successful integration of disciplines such as statistics and engineering into the critical path of decision making is standardization. The result of a statistical analysis is always shown as mean or median with confidence interval for continuous data and a Kaplan-Meier plot for time-to-event data. Interdisciplinary scientists have gradually developed a comfort level in basing decisions on such summaries. Pharmacometricians should develop similar standards within their area.

The format and nomenclature of input and output data are seldom consistent across trials even within an organization. Analysts spend disproportionate efforts locating the data and creating analysis data sets, leaving relatively little time for interpretation and interactions with drug development teams. Speed is especially important if a company has 3 months to file an NDA! The first few exposure–response analyses that a typical pharmacometrician conducts for a given clinical end point are reasonably constant across trials and drugs. Additional tailored analysis based on the initial results from these default analyses might be necessary. From the FDA experience, trial data for a given disease are submitted in varying formats and initial modeling is reasonably constant for a given disease.[7,8]

Sharing Knowledge

Data are information and by themselves are of minimal utility. Quantitative analysis transforms information from data into knowledge, which is more generalizable and shareable. Figure 1 describes the "knowledge pyramid." Initiatives to share clinical data have made little progress in the past and might be overly ambitious, given that data are perceived to be a commercial advantage. At the other end of the spectrum is the sharing of model parameters, which routinely is done through publications and scientific meetings. However, it is hard to use this type of information because the level of detail often is insufficient to allow investigators to reproduce the results or update them with new data.

A more pragmatic deliverable could be sharing standards in addition to models. The authors propose that the pharmacometrics community align and share knowledge through a system that enables acquiring, storing, analyzing, and reporting information through the development of data standards, tools and script libraries, and report templates to maximize the use of knowledge.

The following proposal lists 5 elements that will increase productivity and quality of quantitative analyses:

1. Data standards: Data standards and templates with definitions and controlled terms for different diseases and types of analyses.
2. Input database: A relational database of raw data along with scripts to create analyses-ready data sets. This enables adherence to defined data standards for each drug and study in the database as well as version control.
3. Tool library: Library of tools and scripts for routine analyses: for example, population pharmacokinetic, exposure–response, and concentration–QTc analyses.
4. Output database: Automatic archiving of analyses results to leverage existing knowledge through pooled data analyses.
5. Report standards: Reporting templates for consistency and easier communication across disciplines.

Among the 5 elements, data standards, tool library, and report standards can be developed and shared across organizations. The following have been developed and shared by FDA:

- Data and report standards: The QT knowledge management system for automatic data analyses, storage, and reporting of QT interval (measure of the

time between the start of the Q wave and the end of the T wave in an electrocardiogram) is implemented as an R package called "QT" (http://cran.r-project.org).[9] The tool enables automatic creation of analysis-ready data sets. The QT–RR, QTc–time, and concentration–QTc analyses results are stored in a searchable repository and used for automatic reporting. The QT knowledge management system has improved the productivity, quality, and communication of regulatory review of thorough QT studies. The source code is furthermore made available as a Google code (http://qttool.googlecode.com), which is a collaborative space for community-developed tools.

- Tool Library
  i. PopPK: The population pharmacokinetics (PK) reporting tool ("popPK" R package, http://cran.r-project.org and http://poppk.googlecode.com) was developed to summarize population PK analyses and standardize reporting. The idea is to create a pharmacometric wiki page (http://pmetricopedia.org) and use it as a platform for the pharmacometric community to collaborate and improve on how population pharmacokinetic analyses are presented and used to influence drug development decisions.
  ii. Disease Models: The non–small cell lung cancer (NSCLC) quantitative drug–disease trial (QD2T) model is an exploratory tool to improve oncology drug development. The NSCLC model is intended to aid in go/no-go decisions early based on effects on tumor size and design of late-phase clinical trials including dose selection. This work has been shared at an FDA advisory committee[10] and in a publication.[11] Work is in progress to create a collaborative space for interested parties to share their knowledge and experience.

Development of standards can be undertaken collectively via consortia and initiatives that make model and data sharing a key priority. Strategically, it is best to start by developing a few standards and tools for demonstrative purposes, which then allow appreciation of their value. Individual organizations should come forward and share their standards to build a momentum. In summary, the development of tools and standards for quantitative analyses will allow the pharmacometric community to become more efficient, increase the quality of data, and ease communication across disciplines—to ultimately become more influential.

TI PHARMA MECHANISM-BASED PKPD MODELING PLATFORM

The TI Pharma Mechanism-Based PKPD Modeling Platform is a public–private partnership of 4 academic institutions in the Netherlands and 7 international leading pharmaceutical companies, under the auspices of the Dutch Top Institute Pharma (TI Pharma) established in 2006 (www.tipharma.com). The objective of the platform is to develop a mechanism-based PKPD model library plus a database of biological system–specific information to enhance drug discovery, development, and innovation research. To this end, the partners have agreed to share data, models, and biological system–specific information. The education of graduate students and postdoctoral fellows is an integral part of the activities of the platform.

The Concepts

The scientific basis of the TI Pharma Platform rests on the theoretical concepts of mechanism-based PKPD modeling.[12,13] Mechanism-based PKPD modeling considers the cascade of processes on the causal path between drug administration and response. In this context, mechanism-based PKPD models contain expressions to characterize: (1) the kinetics of target site distribution, (2) the target binding/activation process, and (3) the transduction mechanisms that govern the time course of the drug effect, using concepts from physiologically based pharmacokinetic modeling, receptor theory, and dynamic systems analysis. A pertinent feature of mechanism-based PKPD modeling is the strict distinction between "drug-specific" and "biological system–specific" properties that govern the response. In this context, drug-specific properties characterize the interaction of the drug molecule with the biological system. Drug-specific properties often can be predicted from in vitro bio-assays. In contrast, biological system–specific parameters can only be estimated from in vivo biological systems analysis. The values of these parameters can differ between biological systems (ie, species, subjects) and within biological systems (ie, nonstationarity, environmental factors; Figure 2). Pertinent information on the structure and functioning of the biological system in conjunction with the values of biological system–specific parameters constitutes the scientific basis for the prediction of (variation in) drug effects.

The most recent developments in mechanism-based PKPD modeling have been the introduction of novel concepts for predicting drug effects in nonstationary systems, in relation to aging[14] and disease progression.[15] In this respect, time-variant changes in the functioning of a system are treated as system-specific properties.

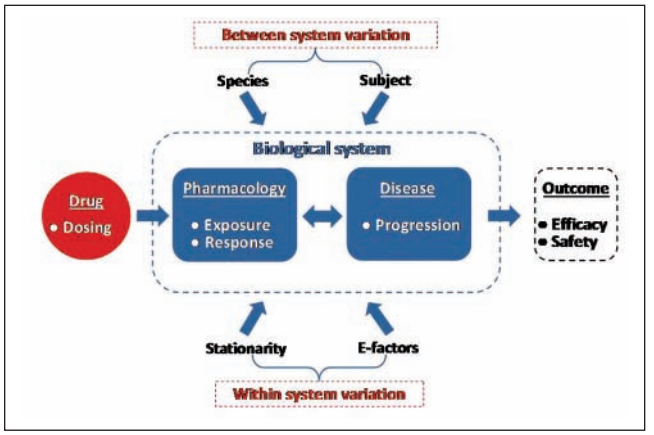

Figure 2. Mechanism-based PKPD modeling: modeling of the functioning of the biological system.

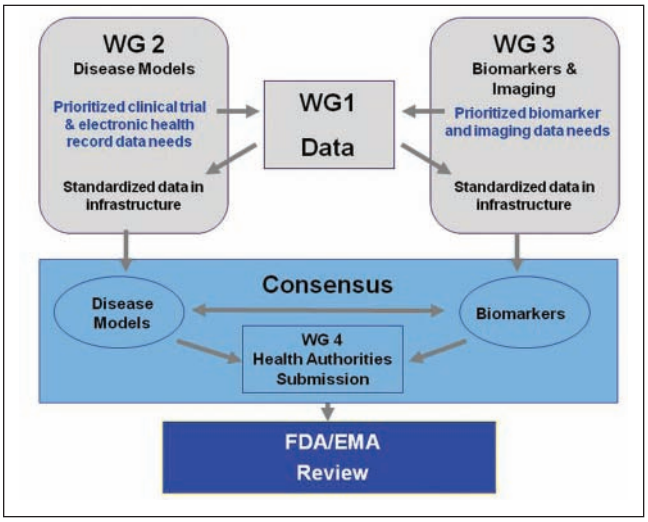

Figure 3. Work group workflow.

The Research Themes

The TI Pharma Mechanism-Based PKPD platform focuses on key aspects of drug discovery, development, and innovation research: (1) translational pharmacology, (2) developmental pharmacology, and (3) disease systems analysis.

Research in the field of translational pharmacology focuses on the interspecies extrapolation of pharmacodynamics with the aim of predicting the cardiovascular safety of novel drugs and the therapeutic effects of drugs for the treatment of schizophrenia and chronic (neuropathic) pain.

The research in developmental pharmacology aims at predicting age-related changes in pharmacokinetics and pharmacodynamics. With regard to pharmacokinetics, the emphasis is on modeling developmental changes in key pharmacokinetic processes such as plasma protein binding, renal function (glomerular filtration, active tubular secretion), (hepatic) blood flow, and the function of a diversity of drug-metabolizing enzymes (eg, uridine diphosphoglucuronate–glucuronosyltransferases, cytochrome P450-3A4). With regard to pharmacodynamics, the emphasis is on analgesic and sedative effects of drugs used perioperatively, anti-infective drugs, and drugs used in stem cell transplantation. The ultimate goal is to develop a systems model that can be used both for the initial dose selection of novel drugs in pediatric clinical trials and for individualized treatment with novel and existing drugs in pediatric clinical practice.

Finally, research in disease systems analysis focuses on the modeling of disease progression in osteoporosis and chronic obstructive pulmonary disease. As part of a systems approach, researchers attempt to model drug effects on relevant biomarkers in conjunction with effects on clinical end points.

The Operation

The platform aims to develop mechanism-based PKPD models on the basis of existing data that become available through the partners. It is important that data are provided by both the public and the private partners in the platform. Data are also provided by external parties.

For the purpose of data management and analysis, a dedicated, centralized computing network facility has been established. Within this environment, access to the pertinent, deidentified, merged data sets is restricted to those scientists who are directly involved in specific projects. However, as part of their membership, all partners in the platform have access to the resulting models and the corresponding biological system–specific information for use in proprietary research programs.

As models are being developed, the need for additional data has arisen: complete data to develop meaningful models and data required for the (external) validation of mechanistic PK and PKPD models. In a number of cases, the partners have agreed to generate these crucial data. An example is the generation of additional animal data in a number of translational projects. As well, prospective clinical trials have been started to validate novel dosing algorithms for individualized treatment in pediatrics.

Communication, Education, and Training

Within the platform, an effective network for communication between the partners has been established. Within the multidisciplinary project teams, frequent meetings and teleconferences are held with all partners to ensure maximum transparency and progress in all projects. Biannual plenary platform meetings are held to discuss strategy and progress of the platform as a whole.

Because education and training of PhD students and postdoctoral fellows are an integral part of the activities of the platform, an education and training program has been established. Within this program, advanced courses on PKPD modeling concepts, PKPD data analysis, epidemiology, and statistics as well as workshops on specialized topics are regularly organized. Participants in these courses are the PhD students and postdoctoral fellows in the platform as well as scientists from the partnering pharmaceutical industries.

All models resulting from the work in the platform are published in the international scientific literature.

Partners

The academic partners in the TI Pharma Mechanism-Based PKPD Platform are University of Leiden, State University Groningen, Erasmus Medical Center Rotterdam, and University Medical Center Utrecht, all in the Netherlands. The private partners, all of which are international pharmaceutical companies, are Astellas, GlaxoSmithKline, Johnson & Johnson, Lilly, Merck, Nycomed, and Pfizer.

COALITION AGAINST MAJOR DISEASES (CAMD)

Critical Path Institute, in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution, formed CAMD in September 2008.[16] This coalition includes the FDA, the European Medicines Agency (EMA), 2 branches of the US National Institutes of Health (NIH), academic scientists, patient groups, and leading global companies representing the medical product industry.[17]

Goal

The coalition's goal is to accelerate drug development in neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease (PD), through identification of biomarkers, standardization of common data elements, and the use of quantitative disease models for more efficient trial design.

The work of the coalition focuses on sharing precompetitive data that improve knowledge across disciplines, an important condition for developing treatments for PD and AD. Improved management of existing knowledge is aimed at qualifying novel imaging or biochemical markers (in this document both are referred to as biomarkers) and quantitative disease progression models to inform trial design. This in turn is expected to increase efficiency in decision making during the drug development process and decrease development failures during late-phase testing.

Longitudinal models that quantify changes in neurodegenerative diseases models allow for various trial designs to be tested and optimized for duration, visit times, patient inclusion criteria, and mechanism of action of the proposed interventions. These models can improve decision making in drug development.[18,19]

Based on the successful model from C-Path's other collaborative efforts (PSTC, PRO, AzCERT),[16] CAMD is establishing a process and executing a plan for compiling and evaluating the scientific merit of potentially useful candidate biomarkers for drug or diagnostic test development for AD and PD.

Data, Models, and Biomarkers

In the specific cases of PD and AD—given the complex nature of the underlying disease, uncertainty in differential diagnosis, and the need to understand the clinical outcomes that are typically used for registration—a top-down approach is being used that initially focuses on the registration end points. Four working groups were established, and the workflow is shown in Figure 3. The framework and considerations for the CAMD modeling and simulation plan are outlined in Table I.

Leveraging work from member companies and other collaborators, a longitudinal model has been developed based on clinical observations for the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) for mild to moderate AD, mild cognitive impairment, and normal controls, using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.[20]

This model is being refined and enriched with the incorporation of deidentified control-arm data from clinical trials conducted by CAMD member companies. To pool these disparate data sets, CAMD asked members to map their data to Clinical Data Interchange

Table I Framework and Considerations for the CAMD Modeling and Simulation Plan for Parkinson Disease and Alzheimer Disease

Framework for the Modeling and Simulation Plan	Considerations and Scenarios
Simulate clinical trial data sets based on: • Proposed model • Hypothesized drug effects • Candidate trial design options	Trial design considerations: • Magnitude and frequency of doses that are most informative • Sample size • Trial duration • Sensitivity for effects • Impact of patient inclusion criteria • Effect of attrition on analyses • Comparison of designs' efficiency (development stages) • Data analytic techniques
Compare operating characteristics based on the variation in results across simulated trial data sets	Design scenarios to test: • Drug effects: symptomatic, protective, both • Patient considerations: baseline severity • Design considerations: parallel, crossover, staggered start, 2-stage with adaptive dose selection • Data considerations: MAR, MNAR (efficacy or tolerability) • Data analytics dependent on design being simulated: MMRM, Hochberg, DM method, NHSS

CAMD, Coalition Against Major Diseases; DM, data mining; MAR, missing at random; MMRM, mixed modeling for repeated measures; MNAR, missing not at random, NHSS, natural history staggered start.

Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards, including new therapeutic-area standards developed by CAMD to accommodate these data types.

As of April 2010, a proposed approach to refine the existing model and incorporate placebo effects descriptions is being reviewed by FDA and EMA. Similarly, a previous PD model based on the Unified Parkinson's Disease Rating Scale (UPDRS), developed by FDA, is being used as the foundation to carry on the work in PD.[21]

Demographics and genetics, as well as the impact of biomarkers, are being tested in the models. Various trial design and data analytic methods for proof of concept, dose-ranging, and pivotal trials are also being tested and being optimized.

Biomarkers that are being studied as potential tools to be qualified for use in drug development include, among others, cognitive tests, cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$, P-tau_{181}, t-tau, and volumetric magnetic resonance imaging for AD as well as clinical scores, DaT-Scan (Ioflupane^{123}I), and β CIT SPECT–based imaging of the dopamine transporter system for PD.

Moving Ahead

Considering all of the above, CAMD will address the need for tools and methods that can result in a more reliable and predictable process of drug development for PD and AD. The combination of qualified biomarkers and quantitative disease progression models will provide tools for the pharmaceutical industry to accelerate drug development, learn more about how to terminate low-probability approaches sooner, and ensure that when a new therapy is found, it has a much higher probability to move through the development and regulatory system successfully and more rapidly.

OpenDiseaseModels.Org

In February 2009, Metrum Institute launched Open DiseaseModels.org (http://OpenDiseaseModels.org), a Web site and supporting organization that provide an open forum for collaborative model building and evaluation, driven by the following factors:

- Development of disease/systems models is an extremely resource-intensive effort.

- Precompetitive insights and resources shared across companies/institutions will lead to better systems models than could be developed by a single institution.
- Open models, which are transparently developed and publicly vetted, will be more widely accepted and will be better positioned to affect the entire scientific/biomedical/health community.

OpenDiseaseModels.org serves as a home for multiple disease/systems modeling projects. The approach is analogous to both open-source software development and wiki-based information sharing. Each individual project consists of 3 participant groups: a core model development team, an advisory panel, and the general public. The core model development team is made up of expert modeling and simulation scientists with experience in disease progression or systems biology modeling for the particular biomedical domain of interest. They serve as the primary developers and maintainers of the model source code and review input from the advisory panel and the general public regarding model revisions and improvements. The advisory panel consists of scientists, clinicians, policy makers, and patient advocates with demonstrated expertise or interest in the diseases of interest. This panel provides guidance to the core model development team regarding clinical and therapeutic utility, biologic plausibility, and, potentially, external research and funding opportunities. The general public includes other domain-relevant scientists, clinicians, policy makers, patient advocates, and anyone else with an interest in the modeling project. This group affects model development by exploring, challenging, and motivating through contributed examples and open discussion. All participants are allowed to download and review model documentation, data, and source codes; participate in open discussion groups; and contribute new models or data via discussion group uploads.

Some important characteristics of OpenDisease Models.org development projects are these:

- Models are developed with readily accessible (preferably open-source) modeling tools with model code openly available. Ultimately these models may be translated to a common model language (eg, an SBML-like language).
- Fully Bayesian modeling methods are encouraged in order to formally include prior information sources in the model development process and facilitate exploration of sensitivity of model-based inferences to parameter (and model) uncertainty.
- Models are developed using publicly available data, and those data sets will also be openly shared as part of the project.
- Documentation of modeling efforts, features, improvements, and bug fixes is transparently available within each project.
- All model code, data sets, and documentation are version controlled using a modern software development versioning system.
- Publication of modeling results in peer-reviewed literature must be allowed and is encouraged for all development projects.
- Public review, discussion, and extension of models are facilitated via a Web-based discussion board.
- All model code is distributed under the GNU General Public License.

To date, 3 open-model development projects have been initiated at OpenDiseaseModels.org.

- A systems biology model for calcium homeostasis and bone resorption
- An AD progression model based on the ADAS-cog end point
- A schizophrenia disease progression model based on the Positive and Negative Syndrome Scale (PANSS) total end point

Substantial content has been posted for the first 2 projects. OpenDiseaseModels.org projects are community driven. Suggestions for new modeling efforts are encouraged and collaborators are welcome.

The calcium homeostasis and bone resorption model is a systems biology model that describes rates of bone turnover due to natural disease progression and therapeutic intervention and describes time courses of the specific bone remodeling markers urine N-telopeptide, serum C-telopeptide, and bone-specific alkaline phosphatase.[22] The model is implemented in Berkeley Madonna 8.0. This physiologically based model allows evaluation of potential causal mechanisms for observed effects and prediction of the potential effects of proposed interventions. The model has been applied to the following disease states and therapeutic interventions: hyperparathyroidism (primary), secondary hyperparathyroidism caused by progressive renal insufficiency, hypoparathyroidism, once-daily parathyroid hormone therapy, RANK-L inhibition, and estrogen replacement therapy (initiation and withdrawal). The core model development team is Matthew M. Riggs (Metrum Institute), Mark C. Peterson (Biogen Idec), and Marc R. Gastonguay (Metrum Institute).

The schizophrenia disease progression model is under development by scientists at Metrum Research Group and Pfizer. The model will describe the time course of the total PANSS score as a function of time and selected covariates during placebo treatment. The model will be posted to OpenDiseaseModels .org once completed and vetted by the participating companies.

OpenDiseaseModels.org demonstrates the feasibility of an open, community-based, disease modeling collaboration. This paradigm also provides an opportunity for integration with other model-sharing initiatives, for example, sharing of nonproprietary components of models, data, and modeling tools from CAMD (http://www.c-path.org/camd.cfm), the FDA Disease Specific Model Library (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180485.htm), and TI Pharma (http://www.tipharma.com/home.html). Future goals include development of self-sustaining funding to support OpenDiseaseModels.org projects, construction of a single infrastructure for the shared model database (which currently relies on individual Google Code sites), implementation of advisory panels for existing modeling projects, and identification of new disease model projects and collaborators.

EDUCATION AND TRAINING OF PHARMACOMETRICIANS

The discipline of pharmacometrics has evolved over decades from an often ad hoc collection of straightforward analytical methods to a sophisticated, rigorous, and multipronged scientific discipline that uses mathematical models based on biology, pharmacology, physiology, and disease to quantify the interactions between drugs and patients.[23] In recent years, the impact of pharmacometrics has increased in all facets of drug discovery, development, and innovation, because the cluster of skills that define pharmacometrics provides powerful tools to maximize the information flow between different development stages and delivers crucial information for rational, scientifically driven decision making throughout the drug development process.[24] Today, a rigorous application of pharmacometrics in drug development is widely advocated by industry, academia, and regulatory agencies.[19,25,26]

A successful contribution of pharmacometrics to increase the speed and efficiency of the drug development process, however, requires highly trained individuals—pharmacometricians. Pharmacometricians need to have considerable technical expertise, both with highly developed computational and algorithmic concepts that include advanced statistical techniques and numerical simulations and with the biological mechanisms of physiology, pathophysiology, and action of drugs and biologics, which must be summarized in relatively simple mathematical–statistical expressions amenable to computer solution. Pharmacometricians interact with a variety of different disciplines in the drug development team approach and thus need to have excellent communication skills to successfully interface with clinicians, statisticians, and laboratory-based scientists.[27,28]

The increasing demand for pharmacometricians in the pharmaceutical industry as a consequence of the widespread integration of pharmacometrics in the drug development process currently far exceeds the available supply, and the gap will only widen in the coming years. The major bottleneck responsible for this shortage is a stagnant or even decreasing number of academic sites for education and training of these highly specialized scientists. A major reason for this situation is the reorientation of many academic departments across universities during the last decades to a strong emphasis on molecular biological sciences secondary to the focus of federal funding opportunities in this area and the consequent fading of the academic disciplines of pharmacokinetics and clinical pharmacology as traditional feeder programs for pharmacometricians. In addition, a very limited number of graduate and postgraduate training programs in the United States and abroad have embraced the multidisciplinary scope of educating and/or training pharmacometricians and developed corresponding curricula. Tables II and III provide noncomprehensive lists of such programs.

Although the disparity between supply and demand for pharmacometricians may be viewed by some as positive in the short term because it provides job security and increased compensation, it will be essential to fill this gap in the near future to maintain the momentum for the implementation of quantitative, model-based approaches in the drug development process.

Increasing the number of individuals who are educated and trained in pharmacometrics will require a concerted effort from industry and academia. Most important, pharmacometrics needs to be accepted as a self-standing discipline with a defined and well-accepted core curriculum. Professional organizations and groups such as the American Conference of Pharmacometrics will be crucial to define the core competencies of pharmacometricians.

Pathways to become proficient in pharmacometrics have traditionally been graduate programs in

Table II Examples of Degree and Postgraduate Training Programs in Pharmacometrics in the United States

Institution	Director	Degree Program	Postgraduate Training
Children's Hospital of Philadelphia	J. Barrett	MS	Fellowship
Cincinnati Children's Hospital	A. Vinks		Fellowship
Indiana University	R. Bies	PhD	Postdoctoral
SUNY Buffalo	W. Jusko, D. Mager, J. Balthasar	PhD/MS	Postdoctoral
University of California–San Diego	E. Capparelli		Fellowship
University of California–San Francisco	H. Lee, N. Sambol, C. Peck		Fellowship
University of Florida	H. Derendorf, G. Hochhaus	PhD	Postdoctoral
University of Minnesota	R. Brundage	PhD/MS	Postdoctoral
University of Southern California	R. Jelliffe, D. D'Argenio	PhD	Postdoctoral
University of Tennessee	B. Meibohm	PhD	Postdoctoral
University of Washington	D. Chen		Postdoctoral
Virginia Commonwealth University	J. Venitz	PhD	Postdoctoral

Modified from Hofman et al.[30]

Table III Examples of Degree and Postgraduate Training Programs in Pharmacometrics Outside the United States

Region	Institution	Director	Degree Program	Postgraduate Training
Europe	University Paris Diderot	F. Mentré		
	Leiden University	M. Danhof	PhD/MS	Postdoctoral
	Martin-Luther-University Halle-Wittenberg	C. Kloft	PhD	
	University of Gothenburg	J. Gabrielsson, G. Tobin	MS	
	University of Manchester	L. Aarons, A. Rostami	PhD/MS	Postdoctoral
	University of Navarra, Pamplona	I. Troconiz	PhD/MS	
	University of Paris-Sud	M. Lavielle		
	Uppsala University	M. Karlsson	PhD/MS	Postdoctoral
Asia/Pacific Rim	Catholic University of Seoul	R. Y. Sun		
	PMECK/Yonsei University	K. Park	PhD	Postdoctoral
	Peking University, Beijing	W. Lu	PhD	Postdoctoral
	Auckland University	N. Holford	PhD, MS	
	University of Otago	S. Dufful	PhD, MS	Postdoctoral
	University of Queensland	B. Green, C. Kirkpatrick	PhD	Fellowship

Modified from Hofman et al.[30]

(bio)pharmaceutical sciences or biomedical engineering with focus on pharmacometrics or postgraduate pharmacometric training programs. To foster these pathways, academic–industry partnerships can provide financial support for academic programs either directly through unrestricted educational support or indirectly via industry-supported research projects. Industry will need to create additional postgraduate training opportunities, either through joint programs with academia or as their own, independent program. Professional organizations as well as regulatory agencies should contribute to this process by facilitating the establishment and support of these programs. Beyond bilateral agreements between a specific academic program and a company, consortia-type pharmacometrics programs between multiple industrial and academic partners have been suggested. This suggestion is especially intriguing in an era of Web-based instructional delivery because it would allow programs to pool instructors from participating institutions and to accept students from different geographic locations.

Besides forming partnerships and supporting collaborative approaches, professional and other nonprofit organization can supplement training opportunities, especially for individuals already in

the workplace who wish to refocus their work or add pharmacometrics to their portfolio of skills. A recently announced pharmacometrics certificate program based on live and/or Web-based courses offered by Metrum Institute is a prime example for such an approach.[29]

As happens in any applied science, however, learning on the job may always be a mainstay of the learning path for pharmacometricians.[27] Thus, corporate internal training and exchange of ideas will likely remain a substantial element in training pharmacometricians, and companies should strive to establish formal venues for interaction and mentoring programs to grow an in-house talent base.[26]

In summary, major efforts and intense academic–industry collaborations are necessary to resolve the pharmacometrician shortage and ensure a supply of well-trained, versatile, and competent scientists who can support the discipline of pharmacometrics and move it to the next level.

DISCUSSION

The development of integrated quantitative models that add value to the drug discovery, development, and innovation processes requires reliable databases that contain sufficient data. More often than not, such databases are best built with data from different sources, hence the importance of data-sharing initiatives. To be successful, such initiatives require the implementation of data standards and searchable databases that allow for easy and efficient access to information.

Data standards are mandatory for the success of precompetitive collaborative efforts. The need to remap legacy data to common standards in order to create an operational database is labor and resource intensive, but at the same time, precompetitive research provides the framework to develop universally accepted standards for data collection and storage, which are useful to not only remap legacy data but to increase the data-sharing efficiency to incorporate prospective information.[4] In this context, collaboration with organizations such as CDISC is essential, not to mention buy-in from industry and regulatory authorities.

For these types of efforts, the distinction between public versus private and pre- versus pro-competitive databases becomes a crucial issue. In the case of the TI platform, both public and private databases are used. For example, this initiative has access to the Rotterdam Study, a prospective cohort study in 8000 elderly subjects with repeated electrocardiographic measures and pertinent information on sudden cardiac death.[31] The use of public databases also extends to TI Pharma's pediatric research. In contrast, for the disease projects TI Pharma relies more on proprietary databases.

Similarly, CAMD pools data from publicly available sources like ADNI and precompetitive proprietary data from member companies (patient-level data from control arms and active treatment groups from failed trials), which are being remapped to existing and newly developed CDISC standards.[16,17] The deliverables from the work will be made publicly available by CAMD itself and also through collaborations like OpenDiseaseModels.org and through peer-reviewed publications.

OpenDiseaseModels.org focuses preferably on publicly available databases but does not preclude the use of proprietary data sets, as long as the deliverables can be made publicly available through this Web site.

Considering all of the above, standardization of legacy data is certainly important but should be accompanied by the development and adoption of standards for collection of prospective data, which in turn facilitate future collaborative efforts. One clear advantage is that collaborative environments allow multiple users to develop models and codes.

Such collaborative environments provide a unique opportunity for seasoned pharmacometricians to increase their experience and for future ones to develop critical skills in a "work force" environment. The combination of data sharing with education and training provides a unique opportunity not necessarily available in standard academic environments.

Standards, automation, knowledge sharing, and training with an applied focus are critical for the success of pharmacometrics as a discipline. The interplay of these factors will make possible the application of an integrated drug development process that incorporates drug models, quantitative disease progression, and trial models as well as biomarkers that provide useful and significant insights into the nature of neurodegenerative diseases and their response to pharmacological interventions.

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