Training the Next Generation of Pharmacometric Modelers - A Multisector Perspective

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Abstract

The current demand for pharmacometricians outmatches the supply provided by academic institutions and considerable investments are made to develop the competencies of these scientists on-the-job. Even with the observed increase in academic programs related to pharmacometrics, this need is unlikely to change in the foreseeable future, as the demand and scope of pharmacometrics applications keep expanding. Further, the field of pharmacometrics is changing. The field largely started when Lewis Sheiner and Stuart Beal published their seminal papers on population pharmacokinetics in the late 1970's and early 1980's and has continued to grow in impact and use since its inception. Physiological-based pharmacokinetics and systems pharmacology have grown rapidly in scope and impact in the last decade and machine learning is just on the horizon. While all these methodologies are categorized as pharmacometrics, no one person can be an expert in everything. So how do you train future pharmacometricians? Leading experts in academia, industry, contract research organizations, clinical medicine, and regulatory gave their opinions on how to best train future pharmacometricians. Their opinions were collected and synthesized to create some general recommendations.

Introduction

The field of pharmacometrics has changed considerably since 'pharmacometrics' was first coined in this journal in 1982 [1]. At that time, almost exclusively, scientists in the field came from a pharmacokinetics, drug metabolism, pharmacology, or pharmacy background. We considered ourselves 'Pharmaceutical Scientists' and the American Association of Pharmaceutical Scientists was one of the major professional societies we belonged to. When you went looking for a job you used the keyword 'pharmacokineticist'. Today, that is not the case. First, 'pharmacokineticist' as a profession has largely vanished and when it is seen, it is often in reference to noncompartmental analysis. Today we are split into two disciplines: clinical pharmacology and pharmacometrics. We use 'pharmacometrics' to reflect that what we do is so much more than pharmacokinetics. We are a much more diverse group in terms of background. Although people from the pharmaceutical sciences still enter the field, it's not unusual to see someone with an Applied Mathematics, Statistics, Engineering, or even Physics background. The training of those entering the field has changed over time, as well, probably as a result of the portfolio of drug companies changing over time. When pharmacometrics entered our lexicon, every drug company's portfolio consisted almost entirely of small molecules. At the time, knowledge of small-molecule-related aspects like drug interactions, drug absorption, drug distribution, CYP-mediated clearance mechanisms, were critical. Sometime around the early 2000s, things changed, and companies started developing monoclonal antibodies and other biologics. Today, company portfolios may include cell-based therapies, gene therapy, modified viruses, and a host of other technologies that are a far cry from the small molecules of yesteryear. It's not unusual today to see a portfolio where small molecules represent a small percentage of the pipeline. Hence, it makes sense that you might not need someone who understands the relationship between things like dose, solubility, ionization, absorption, etc., parameters that are important for small molecules, but not so important for biologics. It may make more sense to hire graduates who might understand the

biology/pharmacology and teach them modeling or it might make more sense to hire someone who is good at developing mathematical models in general, and then teach them the biology.

Not everyone knows everything coming into this field, even after graduate school and post-doctoral research, which prepares you for your career. There are often gaps, sometimes large gaps. A person might know a lot of the biology, but have little modeling experience, or vice-versa, they might know how to model, but know nothing of the therapeutic area. And when the word 'model' is used, it's 'model' in the broadest sense, which can include population pharmacokinetics-pharmacodynamics, physiological-based pharmacokinetics, systems pharmacology, machine learning, or statistics (and there are many others). Today, there is a lot of on-the-job training, particularly when you enter industry. It's difficult to accept, but finishing graduate school is just the beginning of your learning.

As editor of the Journal of Pharmacokinetics and Pharmacodynamics, this got me thinking, what will the next 10 years, 20 years, in this field look like? How can we best prepare students for their careers? What skills and skillsets should they know coming into the field and best prepare them for the next 30-odd years of their life? Recent editorials have raised the same issue [2]. With that in mind, I reached out to different leaders from all aspects of the field and asked for their opinion on how we should train the next generation of pharmacometricians from the point-of-view of the sector they worked in. I reached out to those who worked in academia, in contract research organizations, industry, and as clinicians, and asked their opinion (in about 1000 words) on what skills students will need 20 years from now to succeed in particular work sectors. What follows is their unedited opinions. In the Discussion, I will attempt to find some general themes to help guide training the next generation of modelers.

Academic Perspectives

Stephen Duffull, University of Otago

Pharmacometrics is not a discipline but rather a collective term that encompasses any activity relating to quantitative pharmacology. Whether this is limited, inclusively or exclusively, to any area of pharmacological modelling, systems approaches, design or simulation is very much a matter of opinion. The area is characterized by great diversity in approach and thinking with practitioners who primarily identify with pharmacy, medicine, statistics, engineering, mathematics or indeed from any numerically attentive discipline [3]. The current benefit of this collective term is its permissiveness and diversity.

Pharmacometric education has grown up under a research-intensive umbrella, mostly around graduate research qualifications (such as Doctor of Philosophy [PhD] or Doctor of Science [DSc]). The current state of play is characterized by one-on-one research training where the content is bespoke to the student and supervisor in order to advance the student's research expertise rather than any specific area of practice.

Many pharmacometrics laboratories, such as the Otago Pharmacometrics Group, enjoy the participation of graduate students from a wide variety of geoethnic and academic backgrounds. These research-intensive PhD programs are designed to develop attributes in its graduates that include critical thinking, problem solving, inquisitiveness, communication and domain specific expertise. While many research projects will involve a variety of practice elements, e.g. ability to develop a PKPD model, they are not limited to or required to have a core set of identical elements (whatever those elements might be).

The critical next step in the maturation of the education of pharmacometricians is for pharmacometrics to become an academic field and assume a practice element such that pharmacometrics can be both practiced and researched, rather than focusing specifically on research. A practice element therefore lends itself to the needs of end-users as it implies that a

training program can be established, is fit for purpose and that graduates will have the domain specific skills and knowledge required to undertake the many and varied roles in industry, regulatory, consulting, or clinical practice. Various training programs currently exist (examples; the University of Maryland Master's program and the North Texas distance Certificate program) but the curricular and educational devices are not yet set nor standardized.

Importantly, where will a curriculum of pharmacometrics sit in an academic institution? Such an offering would normally be housed in one of the "usual" divisions within universities (such as education, humanities, business, law, engineering, science, health science, …), with, arguably, the latter two being historically more likely. In addition, would it be a subdiscipline of an established department or faculty (e.g. a subdiscipline of pharmacology or pharmaceutical science or engineering)? While this may seem somewhat trite and organizational in nature it represents the first step to recognition by university bodies and academic institutions which would then promote its development.

Finally, if pharmacometric education is relegated to the rigor of an academic discipline in which a curriculum is defined and training follows a one-to-many setting (e.g. a classroom), then how will its graduates look and feel by comparison with current (research trained) practitioners. Graduate attributes may vary across various levels of training, for instance a baccalaureate as a first higher degree program, compared to a graduate entry masters compared to a graduate entry research-oriented PhD program. Note, the opportunity to assume a single qualification of the professional doctorate (e.g. M.D. or PharmD) may not be possible since pharmacometrics is not part of a regulated profession. All of these graduates (baccalaureate, masters, doctoral) might be able to perform the same basic functions and potentially assume the same roles, but will they be perceived based on their qualification (yielding a possible academic-based model for career progression) or will expertise be considered exchangeable irrespective of training level? These are difficult questions to answer but will lead to important distinctions and academic pathways in the future.

Over the next 20 years these issues will no doubt be debated and perhaps to some extent resolved. Our current and most pressing future issue is the supply and demand of pharmacometricians. We have seen no let-up in demand and indeed demand for pharmacometrics has been expanding rapidly in the last decade, since the term was first used formally in 1982 [4] (note it was used as early 1971 [5]). It is clear that the current one-on-one, bespoke research-intensive training paradigm is incapable of keeping up with demand with only a handful of academic institutions producing PhD scholars and indeed the number of global sites of academic excellence potentially declining. Whether this decline is due to the attractiveness of industry or a lack of grant funding, difficulties with promotion within academia and lack of succession planning (not a feature of academia) is uncertain but these elements continue to plague academic units. Whether demand will continue to outstrip supply leading to ever increasing opportunities for pharmacometricians or demand will eventually dwindle due to lack of sustainability of pharmacometric services or inequitable distribution of services across sectors relegating pharmacometrics as nice to have but not essential, lies in our hands.

The only way that we can hope to sustainably meet the future needs is by introducing university recognized fit for purpose training programs. Ideally these programs would be linked with end-users to maintain important practice links.

Mats O. Karlsson, Uppsala University

Most of the future pharmacometric modelers are likely to have their early pharmacometric education and training at an academic center. This naturally makes academia the most important sector for providing pharmacometric modelers with their relevant education and training. It has to do so with a view to provide the different sectors of society that has a need for pharmacometric modeling with suitably educated and trained individuals. These sectors include pharmaceutical industry, CROs, regulatory agencies, health technology assessment organizations, modeling tool developers, hospitals, and other care givers and, of course, also

academia. This perspective will focus on the skills and experiences needed for a career in academia, with regards to the next generation modelers.

Most academics have three basic missions: education, research, and interaction with the surrounding society. For educators, skills, experience, and training in teaching is important as well as a good understanding of the topics to be taught. It is naturally desirable, and typically required, that modelers wanting to take up a tenure track position in academia already have training, skills, and experience in teaching from previous positions. Universities often have ample opportunities for deepening those skills and additional teacher training and demonstration of skills is not seldom a requirement for promotion. As teaching formats are becoming increasingly diverse, so is the demand on communication and pedagogic skills. The teaching topics that academic modelers are providing may often be in areas related to modeling, such as basic pharmacokinetics/pharmacology, mathematics, or statistics. However, increasingly, pharmacometrics and related modeling topics have become the basis for formal undergraduate and postgraduate courses and also Master programs in modeling are increasingly being offered. Teaching in an applied science like pharmacometrics, requires not only a command over theoretical and methodology aspects and relevant software, but also knowledge and understanding of how pharmacometrics is being utilized in drug development and drug usage. To have teachers able to provide such a perspective is greatly facilitated by an academic environment open to collaborations with organizations that apply pharmacometric models in their knowledge-generation and/or decision-making.

Pharmacometric research concerns methodology, application and not seldom the combination of the two as when a new application requires methodological development. A research program may often be more narrowly focused compared to a teaching program, and requires a somewhat different skill set. To generate research results, hands-on capability in population modeling and statistics software is a basic necessity. Familiarity with many modeling methods, their implementation in software and their application in drug development/usage is a definite strength for a pharmacometric researcher. In the past, few programs from which

pharmacometricians were recruited included modeling to be part of the curriculum before the PhD-level. Now we increasingly see Master programs with large components of modeling applied to drug development being offered. Such programs provide not only a broad technical skill set in modeling, but also an understanding of the modeling ecosystem as it applies to areas relevant to pharmacometricians. For becoming an efficient academic researcher, understanding, familiarity and experience of the research process is important, and this is the purpose of PhD-programs. To be able to operate efficiently within it communicative, organizational, analytic, and creative skills are key. The research teams pharmacometricians contribute in are often multi-disciplinary and an understanding of the skills, mindset and expected contributions of colleagues of other disciplines are valuable to understand and appreciate.

Interaction with the society, such as the general public and peers in other organizations, is in general desirable, but in the case of an applied science such as pharmacometrics, it is necessary to operate well as an academic teacher and researcher. Familiarity with the applications is facilitated by close understanding of the drug development/usage processes and to address important problems, understanding the problems and inefficiencies in drug development/usage. Lastly, to make your research relevant, it requires interactions at multiple levels and not only within the academic field.

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Over the past decade, we have witnessed the discovery and design of new “smarter” targeted drugs such as bicyclic peptides, designed to penetrate tumors based on their smaller size compared to antibody drug conjugates. These smarter designs stem from transformative innovations like single cell RNA sequencing combined with computational tools to quantitatively understand the interactions between pharmacological interventions and

underlying biological networks. Continued innovations in the areas of imaging, omics, animal disease models, *ex vivo* and *in vitro* models have enabled us to gain targeted, in-depth experimental knowledge. Combining these innovations with a range of available modeling tools has allowed us to incorporate in-depth knowledge about biological systems. From increased awareness of transporters and metabolizing enzymes in individual organs to whole systems-based knowledge, these innovations have facilitated and enabled the rollout of improved bioconjugate cancer therapeutics, vaccines, and cell-based therapies. By contrast the lack of innovations at the same pace in areas like anti-infective drugs has resulted in the reintroduction of old treatment modalities like phage therapy that were once difficult to quantitatively describe. Pharmacometrics is a matured discipline that directs model-based methods to develop safer, more efficacious drugs in target populations [6,7]. Over time the focus of pharmacometrics has shifted from using modeling and simulation to "summarize" the knowledge gained during the routine course of drug development to making dosing recommendations for improved drug development processes also known as model informed drug development [8,9]. The ability of modeling to utilize new data, as well as leverage prior knowledge, has expanded the scope of modeling activities to play a key role in decision making at every stage of drug development.

There is now a routine need for precision dosing of existing drugs in post-approval landscapes, and mathematical modeling can help bridge the gap beyond late-stage clinical development [10]. Furthermore, clinicians and healthcare providers are becoming increasingly aware of the variable patient response to standardized dosing approaches and the impact that drug pharmacokinetic variability has on treatment outcomes especially in diseases like cancer, HIV, and tuberculosis [11]. Gaining access to increasing amounts of patient-specific digital health data with pharmacological and disease specific pathophysiological knowledge that is not collected through clinical trials is becoming easier. This data can be used with clinical endpoints to develop models that support clinical decisions for improved patient care and outcome. The continued growth of the pharmacometrics field both in terms of its core functionality in drug

development and its utility in the approval process, as well as expanding its use to newer areas such as clinical decision support or management of care, would require the development of an interdisciplinary infrastructure. This infrastructure would need to support 1) training and education of a new breed of pharmacometricians; 2) developing and adopting standards for a) assays that are used in preclinical and clinical studies and b) data reporting standards to enable data sharing across different drug development programs [12]; 3) best practices and workflows for developing modeling and simulation software tools and programs that support model development activity [7]; 4) a well-recognized authority with the necessary capacity and infrastructure to provide oversight, facilitate and establish standards for training, software development, and data sharing across drug development programs within industries, regulatory agencies, academic and other research centers [12]; and 5) adopting standards for development of therapeutic drug monitoring and clinical decision management tools that leverage developed *in silico* models.

New therapeutic treatment regimen design, as well as optimization or repurposing of approved drugs, will use the quantitative understanding of the underlying interactions between the pharmacological agent and the biological system. The integrated knowledge about this system requires multidisciplinary collaborations between clinical pharmacologists, experimentalists, clinicians, pharmacists, statisticians, big data analysts, epidemiologists, etc. Hence, pharmacometrics, as a field, is unique and attracts professionals with diverse educational backgrounds from pharmacists and clinicians to engineers and statisticians. It is important to develop curricula that supports the training of this diverse talent pool to equip them with skills and tools necessary to enhance and build upon their educational background. The access to pharmacometrics resources and training material is scarce [13], and furthermore well-trained pharmacometricians are a scarce resource unable to fulfill the current demand. The advances in experimental approaches have helped us gain more insights and in-depth knowledge about biological systems at a multi-scale level (e.g., tissue specific, single cell level). This also means that that the pharmacometrics curriculum needs to include training in other allied fields that

will prepare pharmacometricians to understand and incorporate this newer experimental data to further our understanding about the underlying biological interactions and pathways and their impact on treatment design and outcome. For example, understanding the contribution of the drug specific transporters and drug metabolizing enzymes would greatly enhance the predictive power of physiologically based pharmacokinetic models. Courses focused on newer systems-based modeling approaches that incorporate AI based algorithms and model based meta-analysis approaches will need to be included in addition to traditional modeling and statistics coursework.

Given the competitive nature of drug development, current restrictive data-sharing standards limit our ability to use this knowledge to further drug development and prevent the replication of ineffective drug discovery pursuits. Multi-institutional collaborations can provide a more cost-effective access to vast amounts of patient, disease- and/or treatment-specific data compared to single-institution clinical trials. Access to clinical data, combined with established mechanisms to share developed models, will transform drug development. In addition, standards for developing modeling tools that address the drawbacks of current estimation methodologies and the addition of tools that can handle complex analysis can provide the robustness necessary for the *in-silico* backbone for drug development [7].

It is easy to predict that over the next decade the trajectory of modern medicine will continue to evolve at a rapid pace with significant changes to the development and utilization of medicines necessitating shifts in healthcare team dynamics. Given our ability to iteratively incorporate diverse data sources, we are able to gain more knowledge and insights about the drug during the entire development process and beyond Phase 4. Additionally, the continued emphasis on personalized medicine further emphasizes the need to direct resources and efforts towards developing a robust infrastructure for data sharing [12]. Such a repository of real-world data will serve as a valuable resource for training the next generation of pharmacometricians [7,14,15]. This also emphasizes the need to develop cross functional teams that can leverage this real-world data to better understand disease patterns thereby developing newer,

personalized treatment modalities. As academic healthcare institutions are challenged to meet anticipated needs of individual patients and populations around the world, stakeholders such as pharmaceutical companies, regulatory agencies, payers, and healthcare systems need to be involved in the development of this infrastructure necessary to ensure the success of these training programs. Such a collaboration between these stakeholders will help shape these training programs to adapt to the growing needs of the field.

Richard C. Brundage, Metrum Research Group, University of Minnesota

In thinking about training pharmacometricians over the next 20 years, I believe the source of these scientists will continue to be from academic fields with a quantitative background. They will continue to be engineers, pharmacologists, statisticians, biochemists, physicians, pharmacists, physiologists, computer scientists, and the list goes on. This multi-disciplinary coalition has been the strength of the pharmacometrics discipline for the past 50 years and will continue to be for at least another 20 years. My contention is that a well-trained graduate from any one of these programs is not at all likely to be a “project-ready” modeler. Consider the minimum competencies desired for a project-ready modeler. One will want them to have skills in pharmacokinetics, statistics, clinical pharmacology, computer programming, higher level mathematics, physiology, regulatory science, and communication. Even with the addition of a minor to a graduate student’s course of study, it is difficult to imagine mastering more than two or three of these competencies. Given the narrow scope of study to become an “expert” in a doctoral program, the financial model for graduate education that relies heavily on project specific funding, and the hesitancy of academic culture to embrace collaborative reward systems, there has been and will continue to be little opportunity for a student to acquire the array of tools necessary to be a competent pharmacometrician.

The next step then is to look at some alternative ways of thinking about this. One could expand a graduate program to seven or eight years. I hope that is a non-starter. It isn’t any more

desirable to suggest multiple PhD degrees. After that we get to post-doctoral fellowships, and there are at least two problems with that. First is again the financial model. Post-docs are most often the worker bees funded to work on a specific project, leaving little time to explore the world of pharmacometrics. In addition, there is a trend for PhDs graduating in life science programs to skip the fellowship route and move directly to the job market. Bioscience companies in particular appear to be willing to seek out talented and ambitious graduates who are willing to learn. And this is the other side of that coin. The corollary is that the bioscience sector needs to be willing to teach. However, given the scope of the skillset desired for a competent pharmacometrician, this is no small task. It is understandable that the drug development sector doing the hiring, i.e., the pharmaceutical industry, regulatory agencies, academic institutions, and consulting groups are so frequently asking where the next generation of pharmacometricians will be trained. Academia cannot meet the demand. In-house training within any given bioscience organization is expensive. Time taken to train new hires takes time away from profit-generating projects. At some point, individual bioscience organizations will realize what it is costing to train pharmacometric scientists in house. It is my hope that they will stop asking where the next generation of well-trained pharmacometricians is coming from and ask how they can participate to make the training process more efficient.

So where do we go from here? It is possible to curate existing resources and consider the use of remote learning. However, consider the wealth of textbooks, journals, videos, tutorials, online materials, training manuals, and blogs that have existed for quite some time in support of pharmacometrics. Perhaps they are not being used effectively by individuals looking to break into model-based drug development, or perhaps processing separate pieces of a 10,000-piece jigsaw puzzle is not an efficient way to visualize the final picture. Independent learning lacks a facilitator to guide them through this highly complex, multi-disciplinary field. It is my contention that the opportunity to ask questions, discuss concepts, participate in hands-on exercises, and observe model-based drug development processes first-hand will lead to more rapid professionalization when in an immersive setting that assures dedicated attention to the why,

the how-to, and the why not….. Allow me to brainstorm on a paradigm-shifting alternative. My motivating assumption is that academia will continue to maintain its current culture and produce graduates who are well-trained in their field, some of which are relevant to pharmacometrics. I will also assume that for the foreseeable future, retrenchment will continue in major research universities and there will be no expansion in the disciplines of pharmacometrics and pharmacokinetics.

Proposal. An organization could hire a highly motivated, promising individual who desires to break into a model-based drug development career, but the hire is contingent upon successful completion of an intensive pharmacometrics bootcamp. This pharmacometric submersion experience could be three months and impart the competencies listed above, as well as impart the wisdom of communication skills, management philosophies, and negotiation tactics. The trainees could be entered as a cohort of ten, but that is scalable. Hands-on activities are essential. Shared struggles with difficult topics facilitate the integration of knowledge. Learning to learn and teaching others has hopefully occurred in a graduate program and that can be translated to the discipline of pharmacometrics. Is this three-month pharmacometrics immersion a sacrifice? Undoubtedly, both on the part of the trainee and the hiring organization. But think of the benefits for both if the bootcamp produces a (nearly) project-ready scientist. So where might this bootcamp occur? Regardless of the organizer, it must be contingent upon there being a critical mass of competent personnel and staff available to support this immersive training. And then it comes down to cost. If a new hire is only marginally productive for the first six months or more while they are onboarding and developing their skillset, that salary cost to the organization may be minimal compared to having someone hit the ground running after three months. Organizations sending the trainees to bootcamp would need to cover the costs of the bootcamp facilitators. That may not be as costly as one might think. It might require two full-time scientist equivalents and administrative support for the three months. Those FTEs can be shared across multiple individuals, and the cost is spread across perhaps ten organizations.

There are of course many variations of the above proposal, and my intent is to start the discussion that explores these variations. What I believe is critical is that our highly trained quantitative scientist coming from a wide variety of backgrounds will still need to learn what it is they bring to the table IF they choose a career path in pharmacometrics, and they need to learn several additional pharmacometric dialects in order to communicate at that table effectively. We need to acknowledge that pharmacometrics is not the only career path for which quantitative scientists are being trained in academic settings.

What if we invest in training the individual and they choose to leave?

What if we don't train them and they choose to stay?

INDUSTRY PERSPECTIVES

Brian Corrigan, Pfizer

The past quarter century has witnessed the increased acceptance and utilization of model-informed development approaches. Over this time, the deliverables of a "modeler" have expanded, growing from applications of population pk modeling of individual studies to PKPD, disease progression, PBPK, and QSP. Our sources of data have also expanded to include literature sources, real-world data/electronic health records (RWD/EHRs), genomics, proteomics, and data obtained from digital and wearable devices. We apply these analyses across an increasingly complex array of modalities including biologics, gene therapies and vaccines. And we do all of this with increase urgency to bring our medicines to patients even more quickly.

With the increasing complexity of what is required from us to inform drug development, it is unreasonable to anticipate that any single individual would possess or be able to maintain the

knowledge and skills required in every type of application within a program. Analogous to athletes playing specific positions on a professional level sport team, modelers work as part of a team that supports various modeling approaches utilizing different tools, data sources and analytic methodologies. In turn, each set of unique skills augments the overall team effectiveness. The individual's modelers skills and experience required are unique to the specific role they play. As a result, each type of role has unique training requirements and expectations for degree of skill and training. Four common types of roles are described below

A) **Operational and automation roles:** With the advancement of specific health authority guidance and routine acceptance of pharmacometrics analyses, it is now possible to automate many basic types of routine analyses (e.g. NCA, QTC, myelosuppression, etc). Automation also enables increased efficiency (time and resources required). While the development of the automated tools often requires advanced skills, the application of these tools for routine analyses can normally be accomplished by BSc level scientists with quantitative backgrounds from engineering, physics, math, etc. coupled with on the job training and oversight from subject matter experts.
B) **Technical Expert roles:** Technical expertise roles can be divided into several different categories
    i) **Tools:** In the past, the focus of training has largely focused on analytic techniques related to specific tools (e.g., NONMEM, R). While still critical, tools routinely used in other disciplines like math/physics and engineering are of increasing value and having experts in the use of these tools can greatly who work with others with more drug development experience can greatly augment a modeling teams' effectiveness.
    ii) **Data:** the types of data that are utilized for modeling now include genomics, proteomics, RWD, biomarkers and biomarkers. Individuals with an informatics background are highly skilled in understanding the potential uses (and limitations) of this type of data and should be part of any modeling team.

iii) **Analytics and automation:** There is an increasing need for individuals who are technical experts in process automation and workflow automation.

C) Project-facing roles: The need for a human interface between analyses and interpretation by a clinical development team is perhaps the most critical role. These individuals must be experienced in analyses and drug development, and knowledgeable about the therapeutic area in which they work. They are capable communicators, listening to teams to understand the decisions that need to be informed, bringing development problems to the modeling team to identify solutions, and advocating for those solutions at the project team level. The individuals are normally highly skilled from a technical and interpersonal relationship perspective.

D) Teachers and mentor roles. Teachers and mentors are the mortar that hold the modeling teams together. As teachers, they provide training to technical experts and those in operational and automation roles on aspects of drug development. As mentors, coaches, and sponsors, they foster career growth in-role or across roles allowing colleagues to grow in-place or to expand into other types of modeling roles.

The Increased types of decisions informed by our work and the overall usage of model-informed approaches have increased the demand for our discipline. It is unrealistic to expect that current academic pharmacometrics (PMx) training centers can (or should) train for all types of modeling roles in the quantity now required by industry. Individual organizations must take responsibility to develop role-specific talent from other disciplines through industrial post-doctoral programs, studentships, and fellowships. For many industrial roles, individuals with a PharmD can provide excellent substrate for further quantitative and clinical pharmacology training as part of 1-2-year industrial fellowships, yielding individuals who have both a therapeutics and analytics background, ideal for many aspects of modeling work in drug development. For analytic and tool based expert roles, engineering, math, statistics, or physics background have proven highly effective. Those with backgrounds in informatics, genomics,

and proteomics complement existing modeling skill sets in our organizations to fully utilize new data sources. Biomedical engineers and software developers bring expertise in process improvement to allow for even further process automation in our field.

End-to-end MIDD is a team sport. Its successful application requires a variety of roles, each requiring unique skills and experiences. To be effective and to grow as a discipline, it is critical to bring skills from a variety for scientific and technical background together in an effective manner. It requires a culture of growth, a commitment to lifelong learning, and effective mentorship. The role of current modelers is to be the teachers and mentors that allow our discipline to continue to grow.

Peter Bonate, Astellas

As I approached this question, I asked myself, what will make a successful industrial pharmacometrician 10 years from now? As I started down the rabbit hole, this led me to ask myself, how do you define 'successful' because successful to one person might not be successful to another. One might consider themselves successful being the "technical expert", while another might consider being a team leader to be the definition of success. Are there skills that both need to succeed?

Schools tend to focus on the tangible things they can teach. They focus on the modeling, the lab skills, the course work. One of the difficulties with training the next generation of modelers is that much of what makes a person a success in industry is not necessarily their modeling skills. This holds true whether a person is a technical expert or a team leader. Modeling skill will only get you so far. Modeling skill provides the foundation for success, but is not the only thing that gets you there. There are many soft skills, which are personal characteristics and interpersonal skills that one exhibits in the workplace, that play a major role. I have said over and over that good communication skills are what separate a good modeler from a great one and I think that

message is finally being taught in schools. But there are other skills that also need more attention from graduate schools, things that are both harder to teach and harder to learn.

Trainee pharmacometricians will need to be more flexible. I've seen too often a student coming out of school knowing how to use NONMEM and thereafter every problem is solved using NONMEM. Students need to learn to be flexible in their problem solving – every problem has multiple solutions. Choose the one that gets you to the answer the fastest. Never forget that perfect is the enemy of good. It's easy to fall into the trap of searching for the perfect answer when a quicker approximation may be a better solution. To this end, I would suggest that schools assign problems that are open-ended and allow the students to find their own solution, be that NONMEM, Stan, or whatever. We must never forget that models are just tools and not the ends themselves.

Communication, Communication, Communication. I have stressed many times over the years the importance for good communication, and even wrote a book on it [16]. You can be the best modeler in the world, but if you can't communicate your models to anyone, you will have little impact in your role. Hence, the need to teach communication early and often in school. Every class a student takes should require an oral presentation (or a remote presentation) as part of their grade.

Pharmacometricians will need to learn quickly. Science is evolving at light speed. The amount of knowledge doubles in less than a year now. Companies change as well. Companies move into new therapeutic areas and modalities; it's important to be able to pivot to these new areas quickly. That's hard for some people. Areas that you know nothing about previously, you will quickly be expected to become an expert in. This flies in the face of most dissertations, which find a research problem and narrowly focus on that area. That might work in academia, but will not work in industry. Industry is more fluid. Schools can challenge students by having them give seminars in areas they know nothing about or write review papers in areas they are unfamiliar with.

Trainee pharmacometricians will need to draw across broad areas. I think the mark of a great modeler is to be able to see how to apply other learnings to current problems; learning to see things in other areas that may be applied to your own area. For example, the recent spate of machine learning papers published in the pharmacometrics literature is novel to our field, but these are really just adaptations of methods from another field applied to pharmacometrics. I don't mean to minimize the value of these papers (I've made a career of using methods from other fields and applying it to pharmacometrics); indeed, this is how science progresses. To this end, I suggest that schools assign more open-ended problems for student to solve or to assign a problem and then ask for a solution that is not the obvious choice.

Trainee pharmacometricians need to get more team experience. Although modeling is largely a solitary event, a large part of working in industry is being part of a team. Team projects in school largely suck for a variety of reasons: one or more members do not carry their weight, it's not clear why a team is even needed for a particular class assignment, and team projects increase student stress. But guess what, that's life. Just because you go to industry doesn't mean you won't encounter these issues there. And that's why students need more experience in the team setting. Learning how to communicate, mitigate stress, working as a team when one or members is not carrying their weight, working with difficult people, these are all skills that most recent graduates do not have enough of when they enter industry. Graduate school needs to assign more team projects that have team oral presentations when completed to better mimic working in industry. Problems should also be realistic, like given this set of data what would be a reasonable starting dose for a first-in-man study?

Trainee pharmacometricians will need to know Machine Learning, in addition to the skills we expect of them today. It seems likely that in the next decade, population-pharmacokinetic models will be largely automated as a result of machine learning methods like genetic algorithms. Physiological-based pharmacokinetic (PBPK) models will be expanded to handle population-level data, i.e., population-PBPK models will be routinely developed. And systems pharmacology models will also be automated, although probably not to the same the extent as

the other methods are. Machine learning will be the glue that brings these subdisciplines together. Industrial scientists will be largely model interpreters, with computers doing most of the heavy lifting, but will need to understand how these algorithms work and what their limitations are. It should also be expected that in some instances machine learning algorithms may overtake current methods. For example, using generative adversarial networks to simulate covariate distributions as opposed to current parametric or copula-based methods. Students don't get enough programming experience in school. Schools need to start more broad-based teaching of Python, R, or Julia, and give students experience in solving problems using machine learning.

Daniele Ouellet, Johnson and Johnson

This section provides my perspective on what it takes to be successful as a pharmacometrician working in the pharmaceutical industry. In this case, success is defined as a scientist who uses pharmacometrics to influence key decisions and strategy. The key to success depends on the confluence of three domains: 1) scientific knowledge and technical expertise; 2) ability to communicate and influence; and 3) leadership qualities. The training required for an entry level role will provide the foundation with the understanding that training is a life-long process. Many pharmaceutical companies will implement individual development plan to progress pharmacometricians from entry level to the different steps of the career ladder.

1. Scientific Knowledge and Technical Expertise: the 10,000 hours

Our pharmacometric toolbox has expanded over the last few years and now encompasses a diversity of analysis types ranging from mechanistic modeling (Physiological-Based Pharmacokinetics [PBPK], Quantitative System Pharmacology [QSP]) to population analyses of individual data (e.g., population pharmacokinetics, exposure-response, disease progression models), and summary level analysis (e.g., model-based meta-analysis).

By definition, the science of pharmacometrics combines knowledge of pharmacology, i.e., pharmacodynamics, pharmacokinetics, disease, on one side with knowledge of quantitative methods, i.e., statistics/mathematics/engineering, on the other. Prior to having programs dedicated to pharmacometrics, most scientists within that field would come from either of these backgrounds and filled the gap in expertise as their career progressed. With more specialization in pharmacometrics, academic training on the fundamentals of advanced pharmacokinetics, pharmacology/pharmacodynamics (PK/PD), and statistical principles, including nonlinear mixed effects, builds the foundation and is the most essential to success (Table 1).

Specific training in pharmacometrics should provide in-depth understanding of the methodological aspects in terms of

1) Data: Understanding of type of data to be analyzed with appropriate methods, how to handle missing data, outliers, etc.;
2) Methodology: model building principles, goodness of fit, variability, uncertainty, simulations; and
3) Best Practices: analysis plan, reporting, assumptions.

Pharmacometric analyses are often characterized in terms of the software they use, including but not limited to, NONMEM, R, SimCyp, Matlab, etc. A basic introduction is required while practical in-depth training is easily accessible for any specialized software by specific providers. Other expertise such as knowledge of drug development or regulatory application may take more time and require work experience, while a basic introduction will be helpful to a curriculum.

Table 1. The expertise required for pharmacometricians

Expertise	Skills	Training Opportunity
Scientific Understanding	Principles of Pharmacology/Pharmacodynamics, Pharmacokinetics & Biopharmaceutics, Statistics	Academic Training
Tools/Software	SimCyp, NONMEM, R, Monolix, Puma, Matlab, etc	Academic Training / Specialized Training/ Work Experience
Data Properties	Types (continuous, categorical, survival type, bounded), Missingness (random vs. non-random), imputation methods, time-variant variables, Outliers	Academic Training/Work Experience
Best Practices	Analysis plan, Assumptions, Best practices, Validation	Academic Training /Work Experience
Methodology	Model Development, Goodness of Fit, Understanding of variability and uncertainty	Academic Training/Work Experience
Drug Development/ Regulatory experience	Application of pharmacometrics in drug development, regulatory approval, regulatory requirements	Work Experience

In terms of technical expertise, an ideal candidate graduating from a pharmacometrics program would possess the fundamental technical and scientific knowledge, basic understanding of the methodologies, and overview of the different analytical tools. While building an adequate pharmacometrics model can be challenging, the value and relevance of pharmacometrics analysis resides in the interpretation of the model parameters, simulations of different clinical scenarios, and how the model can answer drug development questions. Relevant questions will depend on the project and can include any number of topics, e.g., time to reach steady state/target saturation, probability of meeting threshold for efficacy and/or safety, dosing recommendations, impact of missing dose(s), evaluation of study design options, guiding development strategy, etc. While a newly trained pharmacometrician can build the model, additional knowledge and experience will be required to increase its impact by engaging with other partners of the multi-functional clinical development team.

2. Ability to communicate and influence: the 5 min elevator pitch

The power to influence depends on the ability to translate all the complex work that has been done to an effective communication strategy to convince stakeholders. In the pharmaceutical industry, pharmacometricians will be required to present their work at multiple levels: 1) with

fellow pharmacometricians to present all the details of an analysis and ensure functional alignment, 2) at the clinical development team level to debate model assumptions, simulation scenarios, clinical criteria, and recommendations, and 3) at governance to lay out the proposed strategy devised using the model-informed drug development approach. As presentations move from the demonstration of functional expertise to influencing stakeholders, our ability to be effective communicator becomes more challenging and the presentation material, vocabulary used, and messaging content need to be adapted and simplified. In addition to learning how to communicate is also learning on how to gain allies, identify influencers and convince decision makers. Specialized training to become good communicator and negotiator exist in various forms while they are rarely thought as part of an academic program.

3. Leadership Qualities

A good training program and work experience will provide the foundation for the 'WHAT', while as importantly is the 'HOW'. Curiosity, teamwork, willingness to learn, humility, are key traits to be a life-long learner and grow within a large organization. Hiring managers will not only be interested in the ability to do the work, but fitting with a team environment, and having the ability and willingness to learn will go a long way.

Andreas Krause, Idorsia

Pharmacometrics has come a long way. Although it is one of the younger disciplines in drug development, pharmacometric contributions are now established in internal decision-making and health authority interactions. Model development is usually computer-intensive, and while methods were developed for about half a century, applications blossomed in the last decade with the availability of software and sufficiently fast computers. Some 20 years ago, only limited literature was available; nowadays there is systematic education and streamlined knowledge. The pharmaceutical industry joined the movement and started creating pharmacometrics

groups in the early 2000s (I joined the newly established modeling and simulation group at Novartis in 2001). Academic centers of excellence in collaboration with big pharma and consulting companies led the way.

When the United States' Food and Drug Administration established its Division of Pharmacometrics [17], it sent a signal to industry and academia that the discipline had matured. Evaluation of new drugs was expected to be accompanied by, and based on, pharmacometric activities. Population pharmacokinetic/pharmacodynamic (PK/PD) modeling became a core activity in health authority interactions. Physiology-based pharmacokinetic (PBPK) modeling is developing rapidly is nowadays frequently part of health authority interactions.

While the division of pharmacometrics at the FDA is located within the Office of Clinical Pharmacology, industry is still exploring the right place for pharmacometrics in the organigram. Pharmacometrics can be found in research, preclinical, or clinical departments, be associated with clinical pharmacology, biostatistics, data science or drug metabolism and pharmacokinetics (DMPK). A consequence of the search for the right location is that pharmacometrics groups are frequently moved around in reorganizations (a regular phenomenon in Big Pharma with similarities to weather tsunamis).

Functions and departments such as clinical science, biostatistics, data management, programming, and regulatory affairs are recognized by upper management as must-haves, while pharmacometrics or modeling & simulation are still considered optional. A clinical study could be conducted and evaluated, and a clinical program run without pharmacometrics. Decisions might not be ideal without quantitative support, but it might never be found out. Pharmacometricians, therefore, have a higher pressure to justify their existence, salaries, and expensive toys, i.e., computers and software. From this flows that pharmacometrics must place a focus on keeping the customers, pharmacologists, physicians, and managers, happy to come out unruffled in the next reorganization. This in turn will benefit the patients with better

characterization of drug effects and the organization with quantitative, rational, reproducible decision making.

A key aspect in pharmacometrics is that the pharmacometrician is part of a multidisciplinary team and generally not the decision maker. The pharmacometric contribution is in the development of a model that includes all available knowledge and data. The model is then applied to conduct simulations to produce quantitative results. The results are predicted outcomes: what happens if this dose is administered, if this population is treated, if this or that is decided, and what are the associated probabilities? In other words, the discipline is a *decision support* for physicians and managers to take the necessary decisions in the drug development program.

Customer orientation, therefore, must be taken seriously. It is essential that the pharmacometrician works very closely with pharmacologists, physicians, and managers (and other disciplines) from the identification of the question to the interpretation of the results and subsequent decision making. A great piece of work has no impact if the decision makers do not appreciate or misinterpret it. Clear, effective communication is key.

Key tasks of pharmacometrics include

- Integration into the drug development program (clinical study teams, life cycle teams)
- Spotting pharmacometric opportunities
- Identification of the question and the decision to be taken
- Precise definition of the question
- Understanding of the available data
- Development of a model in interaction with clinical scientists
- Conduct of simulations
- Communication of the results
- Fine-tuning in collaboration
- Helping with interpretation and decision making

In all these activities, the pharmacometrician must communicate in the language of the clinical scientists and decision makers, which is a skill that can be taught and learned. Physicians are

very good at grasping a complex object, such as a patient, but they might not be used as much to express themselves quantitatively. A typical communication between a pharmacometrician and a physician might develop as follows:

Pharmacometrician: what is it that you would like to know?

Physician: if the drug works with the selected dose.

Pharmacometrician: what does “works” mean?

Physician: that the blood pressure is lowered by (at least) 10 mmHg.

Pharmacometrician: Lowered compared to baseline or corrected for placebo?

Physician: Corrected for placebo.

Pharmacometrician: Lowering by 10 mmHg on average, in 80% of the population, or what else?

And so on, covering the target population, the effect of study inclusion criteria, variability, uncertainty, and more.

The precise definition of what is to be analyzed and modeled shows similarities to a current topic in statistics, estimands [18], and there are further similarities to topics in biostatistics [19-21]. Interaction is key to achieve common understanding of the question and the answer.

It is noted that while pharmacokinetics is important, the clinical impact is more often in the pharmacodynamics. Efficacy characterization is a focus in PK/PD modeling. However, modeling of safety parameters and optimization are clinically highly relevant and can be exciting pharmacometric topics. Examples include biomarker and joint efficacy and safety modeling [22] or development of an up-titration regimen to mitigate undesired drug effects based on model predictions [23].

There is no universally best way of communication, but the sender of the message must be aware of the recipient’s antenna. The same piece of work must be presented in different ways

to different audiences and readers. Conceptual teaching and learning of pharmacometric communication are highly relevant to help the discipline succeed. Ideas can be disputed, but it helps to seek inspirational sources to spark good ideas and develop one's own thinking and way of communication [16].

With technological progress, communication is not entirely verbal. With increasing remote working and collaboration across continents, non-verbal communications (sending PowerPoint slides or reports) means that the reader is on his/her own, the pharmacometrician cannot help with understanding and interpretation of the work after having sent the email. Physicians and managers will not ponder much over tables of parameter estimates, relative standard errors, or visual predictive checks, it will probably make them lose interest. They will not try to understand how exactly the model was developed. They will assess if the results match their intuition and what it means for them. Key results are commonly displayed in graphical visualizations of data and models.

Education and training in pharmacometrics have come a long way, and it is amazing to see how much young pharmacometricians have in their backpack after just having finished their studies. Communication skills still have room for development, a task for academic and industrial mentors. Focused training will integrate the pharmacometricians better into the drug development process and produce more job satisfaction stemming from appreciation of the work.

Teamwork and communication are particularly important in small and medium-sized enterprises where the pharmacometrics group is usually small and tightly integrated with pharmacologists and physicians, statisticians, and data scientists. Exposure to these colleagues is high and achieving good results as a team is a rewarding experience. The pharmacometrician should be clear about the expectations and enjoy the experience. Interaction should be sought actively, and clinical colleagues should be taught the relevant contributions of pharmacometrics from their perspective such that everyone benefits from a strong collaboration. A systematic

introduction to the topic of effective communication, exposure to non-pharmacometricians during internships and practicing critical thinking beyond pure pharmacometrics will help to develop impactful future pharmacometricians.

The topic of communication is highly relevant for the discipline as a whole. While it is good to have conferences and journals for pharmacometricians, it is naive to think that the message spreads from there to physicians or managers. Clinically impactful applications must be shown at the venues and in the literature where they meet the clients, i.e., pharmacologists' and physicians' conferences and journals and at times managerial platforms. The focus here must obviously be placed on the application and the decision making that is on solid grounds with quantitative pharmacometric support, technical details should be in the background. It is noted that this can yield two publications of a piece of work, one in pharmacometrics highlighting the technical aspects and another one the clinical application and its impact, highlighting the relevance to companies and patients.

The tools for visualization and interaction are available nowadays. Berkeley Madonna led the way in pharmacometrics, allowing for interactive visualization of models and clinical parameters with different scenarios by simply moving sliders around to change values. The system was not created for pharmacometrics though, and it lacks some functionality a pharmacometrician would wish to have [24]. Newer tools, such as the Shiny package in R or Simulx [25,26], provide more powerful interfaces to produce results on the fly, possibly in front of a clinical team. Pharmacometricians must have such tools in their toolbox.

Pharmacometrics is on a good way towards establishing itself in the pharmaceutical industry. After all, a pharmacometric model can contain all current knowledge about a drug and serve as a backbone of drug development, providing quantitative and reproducible results – if it is communicated clearly and the decision makers understand and appreciate the value. Integration of communication skills teaching and practicing into a curriculum will benefit the students as well as the discipline as a whole.

CONTRACT RESEARCH ORGANIZATIONAL PERSPECTIVES

Justin Wilkins, Occams

Pharmacometricians working at contract research organizations (CROs) find themselves in an interesting space. By the time we get involved, clients may need things done in a hurry, may not have sufficient internal resources, or may not have the time, skills or experience in-house to deliver within the desired timeframe. This implies that CRO pharmacometricians require a strong and diverse set of skills, and the experience to use them strategically, to deliver within what are often very challenging timelines.

First and foremost, consultants need to know their craft. Their technical base expertise needs to be in nonlinear mixed-effects (NLME) modeling of dynamic systems – population pharmacokinetics and pharmacodynamics (PK/PD), with a strong background in relevant biostatistics and pharmacology, as well as the therapeutic areas in which they work. If involved in early-to-mid phase projects, this will be particularly important. For late-phase work, knowledge of simpler exposure-response approaches for efficacy and safety commonly used in registration packages, like logistic regression and survival analysis, are often critical. (I expect this to be gradually superseded by more complex, more informative, more mechanistic modeling over time.) Population PK has become a central part of drug development and approval, and will remain so, as problems become more and more complex. Although consultants may find themselves specializing in physiologically-based PK and/or systems pharmacology modeling, NLME will remain a core skill. Machine learning and artificial intelligence (ML/AI) are becoming more popular, and although such approaches are probably unlikely to become more useful than those already in use, consultant pharmacometricians will need to understand what they are and how they work, so they can speak authoritatively about them.

Being able to understand and manipulate data is another key skill. In many circumstances, dataset structure is an integral part of the model being developed, and it will often be necessary to make changes, or at least direct that changes be made. Graphical analysis is another critical facet of pharmacometric analysis, and pharmacometricians need to be able to use tools that facilitate this, such as R and key libraries like ggplot2. Being able to exactly reproduce analyses years later, and documenting every data manipulation, plotting, and modeling step, is another key skill.

Technical skills are taught. Pharmacometrics university curricula need to be developed in such a way that the nuts and bolts of pharmacology, technical modeling skills and data science are covered in a coherent and consistent manner within and between institutions, something which has so far been lacking – although a consensus proposal was put forward as part of the DDMoRe consortium's work almost a decade ago, it does not seem to have been widely adopted [27]. Focus needs to be carefully considered as well – many graduate and postgraduate training courses tend to neglect the needs of the pharmaceutical industry in favor of theoretical aspects (this is not necessarily bad, but does not prepare new graduates for what they will face in an industry or consulting job). With the advent of CROs attached to university departments, this may be improving.

Technical skills are only one part of the picture, however. Soft skills are crucial for pharmacometricians, irrespective whether they work in a CRO, industry or academia. Pharmacometricians need to be able to communicate complex science clearly and confidently to mixed audiences, need to do what they say they will (which means being able to "scope" problems properly, and realistically apply timelines to them), need to be able to collaborate effectively with colleagues and clients, need to be able to help clients think through what proposed analyses can do to support development objectives or label claims (and what they can't), and above all need to be a rock-solid anchor of calm, focus and expertise in any meeting in which their work is being discussed. This takes practice and experience, and is typically not learnt at university. Consultants need to be able to manage their time with iron discipline, and

they need to be clear-eyed about what can be achieved and what cannot, and they need to be able to defend their position if challenged, particularly when they pressured by the client to do something they disagree with.

Experience. This is the third pillar of consultancy, and is absolutely central. To be able to do their job, consultants need to be able to identify the central drug development question, to "scope" it (to determine what is needed and how long it will take, and how it will help sponsors make label claims or advance development), and then to execute on it. They need to be able to work independently, inside and outside of teams, under pressure, across different therapeutic areas, and deliver an analysis at the requisite level of quality at or before agreed deadlines. This cannot be taught – it is learned over time, whether from more experienced colleagues or inside a pharma company. It is being comfortable saying "no" or "I don't know". It is being able to diagnose and fix obscure technical problems under heavy deadline pressure. It is being able to convincingly answer unexpected and challenging questions from senior managers in client meetings. It is being able to translate clinical drug development questions into a model-based analytical strategy. For less experienced consultants, the ability to lean on and learn from mentors is very important.

So, to summarize – consultants in pharmacometrics need:

- Hard technical expertise in pharmacometric model development, data management, scripting, data visualization and reproducibility, as well as in pharmacology and relevant therapeutic areas – ideally, learned during graduate programs.
- Soft skills – communication, collaboration, problem assessment, time management, the ability to work independently under pressure – usually, learned on the job.
- Experience – knowing when they are right (and wrong), and being able to robustly defend their work and opinions when called upon to do so.

Mark Lovern, Certara

Key Challenges in Training the next Generation of Pharmacometricians:

1. "Classical" PMx Training Programs are not producing enough graduates to keep up with demand
2. Many academic training programs focus almost exclusively on teaching analytical skills. While necessary, these skills are not sufficient to ensure that pharmacometricians will be successful in industry. Communication and collaboration are at least equally important.
3. Pharmacometricians are coming from increasingly diverse educational and experiential backgrounds. As such, many have little or no understanding of pharmacology/biology or the drug development process.

A proposed plan for addressing these challenges:

Step 1: Establish a governing body (i.e. certification board) whose initial remit is to define the core competencies that EVERY pharmacometrician should possess in order to be board-certified. These core competencies should not be purely technical, but should also encompass communication and collaboration skills. Furthermore, a working knowledge of biologic/pharmacologic principles and the drug development and approval process should also be key components of the curriculum.

Benefit(s): Defining the core competencies will allow us to better identify resources and gaps within existing education programs. For example, there may be engineering or applied math programs that are teaching most of the core curriculum. It may be that we could engage with such programs to offer pharmacometrics specializations that would fill in the informational gaps by taking electives in other university schools. However, a prerequisite to such engagements would be to have clear definitions of what the skill set of a "classically-trained pharmacometrician" should be.

Step 2: Develop a standardized examination and certification process for pharmacometricians.

Benefit(s): Board certification should provide a conduit for migration from other fields into pharmacometrics, while ensuring that these emigres are able to hit the ground running upon arrival. It would also serve to elevate the maturity of our discipline similarly to that of engineering, law, or clinical medicine. Finally, defining the certification process would also allow educational institutions to tailor curricula toward helping students successfully obtain board certification. This could potentially broaden the field of schools that would be willing offer such programs.

Step 3 (Could be implemented in parallel with Steps 1 and 2): Conduct a discovery exercise focusing on early career pharmacometricians (≤ 3 years in the field). The discovery exercise should include both a survey and 1:1 interviews. Key objectives of the Discovery phase would be to characterize the following with regard to the early career PMx community:

- Educational background and previous career history
- Motivators for pursuing a career in PMx
- Struggles/challenges experienced during the first few years in the field
- Suggestions for improving training programs and/or educational curricula

Benefit(s): Data from this survey should help us better understand the needs and challenges of neophyte pharmacometricians. Ideally, this would facilitate segmentation of the labor pool for entry-level pharmacometricians, and definition of “user personae” for training programs and curricula.

Step 4: Design training programs and curricula to fit the needs of the “user personae” identified in Step 3. In all likelihood, data from the Discovery exercise will indicate that there are several different pathways and entry points for embarking on a career in pharmacometrics. For example, the educational needs of a mid-career engineering professional seeking to transition

to a career in PMx will be quite different than those of a junior candidate who has recently completed a Bachelor's of Science in Pharmaceutical Science.

Benefits: Offering more training options should allow "fast tracking" of experienced candidates into pharmacometrics positions.

Step 5: Engage with academic and professional institutions to expand the pool of providers offering programs identified in Step 4.

Benefits: More providers = more candidates.

Elodie Plan, Pharmetheus

"How is it that we and our peers enjoy our job so much?" It was a warm evening at the European pharmacometrics conference PAGE's social event, and this talented and ambitious student exploring options for his future was bringing in the discussion the refreshing aspect of happiness at work. Generally, job satisfaction for knowledge-intensive workers [28] is linked to a meaningful purpose [29], a caring organization, and to possessing the skills necessary to succeed [3]. While the first two are in the hands of the employer (such as pursuing a clear mission like bringing the right dosing regimen to patients and upholding values like competence development and corporate citizenship), the latter requires the involvement of the entire community.

Identifying the skills necessary to succeed as a pharmacometrician in the next decade, with an emphasis on the consulting workplace, is the objective of this section. We propose that these skills reflect the characteristics required for pharmacometrics deliverables to have an impact, in other words, for model-informed drug development to be utilized to its full potential. These skills can be broadly categorized into three main areas: 1) technical competence, 2) contextual knowledge, and 3) communication abilities.

Firstly, technical competence lays a solid foundation for the pharmacometrician to succeed in their work. Handling complex data, influencing high-stakes decisions, and facing regulatory scrutiny - the pharmacometrician's quality of work needs to be of the highest standard. A prerequisite, for the model-informed drug development consultant to be able to select the appropriate methodology and conduct timely analyses, is a strong technical expertise. In addition, a proficiency often required in consulting is problem-solving, which research studies contribute to expand. Today, many academic institutions, spread worldwide, offer programs that produce highly skilled graduates, and non-academic organizations provide training to professionals through workshops, tutorials, and online materials. As the demand for pharmacometricians grows and the field evolves, it would be beneficial for there to be *more* educational curricula in *more* parts of the world and them to focus *more* on enabling the scientists to master pragmatic yet gold-standard analyses.

Secondly, contextual knowledge provides a concrete structure for understanding the rules and realities of the industry. The field of drug development needs to be learnt instead of realized on the job. A model-informed drug development consultant with a strong grasp of this environment will be able to suggest solutions in an effective manner. Moreover, while benefiting from working with a range and variety of projects and companies, the level of influence and impact a consultant can have may vary between different contexts, even if the challenges are similar. Today, pharmacy education often places a low emphasis on the pharmaceutical industry behind dispensary pharmacy and clinical pharmacy, the low emphasis likely holds also true in disciplines such as bioengineering, bioinformatics, or biostatistics. While some industries already invest in academic programs, a beneficial evolution would be more established *partnerships* between universities and organizations that can contribute with providing hands-on exposure to real-world applications and extend practical awareness.

Lastly, communication abilities constitute the overarching element in making pharmacometrics succeed. A drug development program involves a team of experts with diverse knowledge, commonly including external partners, who need to collaborate and exchange information [30].

As a model-informed drug development consultant, effective communication is instrumental to discuss the relevant information supporting the analysis and deliver the pertinent results informing decision-making. Furthermore, this skillset facilitates a service-oriented approach to consulting - providing expert advice to other professionals. Today, communication skills are referred to as soft and assumed to be natural, although there is a recent recognition of their importance in the overall advancement of the field, which led to applauded initiatives such as communication sessions at international events. To support this positive development, a progress would be more *integrated* trainings that include both theoretical components and situational cases.

In conclusion, pharmacometricians need to possess a range of skills - the main ones being technical competence, contextual knowledge, and communication abilities. By developing and mastering these skills, model-informed drug development consultants can be well-equipped to thrive in the rapidly evolving field of drug development. While it is today possible to acquire these skills to some extent, further enhancement of the educational offering, specifically focusing on these three areas would be highly beneficial for these knowledge-intensive workers. It is assumed that a continuous update of the skillset, facilitated by a lifelong learner attitude, will remain more than ever necessary in this fast-pace environment. In this aspect, consulting companies often provide this internally to their employees as well as externally to their clients. By helping these professionals develop the skills necessary for success, we can help shape the next generation of pharmacometric modelers and ensure that their contributions have the desired impact in model-informed drug development, leading to increased job satisfaction and aiding the discipline to realize its full potential.

Marc R. Gastonguay, Matthew M. Riggs, Metrum Research Group

Training future generations of quantitative scientists in pharmacometrics is an essential endeavor for sustained growth and impact of the science of pharmacometrics. Although the future talent pool is a primary concern, this commentary would be incomplete without

acknowledging that continued training and development of all quantitative scientists, independent of experience level, is a requirement for the success of the discipline.

Delivering safe and effective therapies to patients in need has and will always begin with quality science. Pharmacometricians of the future will face uncharted ground given the advanced understanding of disease biology, novel treatment modalities, tremendous volumes of heterogeneous data, and advanced analytical methods; all within the constraints of potential drug pricing controls, increased competition and innovation, and increased regulatory expectations. Accordingly, effective training and continued development of pharmacometricians are necessary to maintain quality and integrity of the science.

The key characteristics and skills necessary for future success in biomedical modeling and simulation must be timeless, transcending a variety of use cases and problem settings to address the ever-evolving challenges and opportunities in the life sciences and the growing role of data and quantitative analytics. Successful pharmacometricians will be life-long learners, with a desire to seek insights and think independently, while developing resourceful problem-solving skills. Excellent observational and listening skills will be critical to fully comprehend the problem at hand and any relevant constraints or conflicts. Effective written and verbal communication skills will always be important in navigating the problem space and quantitative results with both technical and non-technical stakeholders. Furthermore, the ability to collaborate as a part of a multidisciplinary team with an authentic desire to understand collaborators and seek diversity in perspectives and experiences will become increasingly important.

Solid technical and scientific skills will also be essential, although it is anticipated that only a subset of these skills will be gained during an individual's formal educational path. Specific coursework and curricula have been previously proposed for training pharmacometricians [31-37], clinical pharmacologists [38], and quantitative systems pharmacologists [39]. Rather than viewing these curricula as formal course requirements, it may be more appropriate and

effective to view these as knowledge categories to be gained throughout education, training, and work experiences.

Fundamental components of any pharmacometrician's technical development include training and education in applied quantitative sciences, mathematics and statistics, and the life sciences (e.g., biology, pharmacology, physiology, pharmaceutical sciences). In addition, rigorous training in a programming language with an excellent understanding of coding best practices and reproducible research methods is becoming increasingly important. With the increased availability of structured and unstructured real world data sources, an understanding of and facility with novel methods of data handling and advanced analytics, such as: artificial intelligence/machine learning, causal inference, and evidence integration, will be extremely valuable.

For employers considering where to find such a talent pool, it is unrealistic to expect that any formal academic educational program will prepare individuals with a complete skill set. Formal training in a variety of quantitative disciplines with emphasis on the timeless skills defined earlier will serve as a foundation. With such a basis, individuals will be prepared to contribute to biomedical modeling and simulation projects, without necessarily being an expert authority on all aspects of the problem.

Traditionally, the field of pharmacometrics has held a specific niche and is relatively unknown outside of the discipline. Inspired by other quantitative sciences, future strategies aimed at awareness and talent development should include outreach to educational programs at the secondary school and undergraduate levels. Direct connection to related quantitative disciplines at the graduate school, postdoctoral and early professional levels may also prove to be fruitful in growing the talent pool.

The successful modeling and simulation enterprise in the contract research and consulting space will acknowledge and align with the diversity of abilities and breadth of experience levels in the available talent pool. Efforts will be focused on assembling teams which, collectively,

provide the complete skill set necessary for the problem at hand versus identifying a single individual with all the necessary expertise. In addition, project execution plans will be designed to allow for real-world learning opportunities specific to each team member's training and development needs. With such a strategy, the problem-solving effort naturally becomes a collaborative endeavor, optimizing specific talents and expertise across the team to deliver on the needs of the project while driving the professional growth and development of each individual. When firms adopt a business philosophy that prioritizes investment in employee development, the contract research and consulting setting is well suited to provide tremendous learning experiences for current and future pharmacometricians.

Non-traditional development opportunities driven by on-the-job problem-based learning will be particularly important and practical for the future pharmacometrics workforce. Despite the pressures to deliver on often unrealistic project deadlines, management functions across the industry must create opportunities and time for continued learning and development for each team member. Within an appropriately resourced multidisciplinary project team, this can be accomplished in the day-to-day execution of ongoing modeling and simulation projects or on less time sensitive platform modeling activities.

Another opportunity for problem-based learning is in the pre-competitive quantitative understanding of disease mechanisms and disease progression. Open partnerships across the discipline could drive new scientific insights for the community while providing rich and relevant learning experiences. Collaborations with trainees and their academic mentors augmented by expert guidance from scientists in industry, contract research, and government settings would drive learning. These types of collaborations paired with open sharing of non-proprietary data and access to computational resources and tools could be supported with open courseware, open models, and open-source tools also curated by community stakeholders.

Although training of pharmacometricians may begin in academia, learning and development must continue in subsequent career settings in order to build deeper and broader capabilities and expertise. This will be essential to maximize the discipline's impact on problems in biomedical research, development, and therapeutics. Stakeholders across academia, industry, contract research, and government settings have a responsibility to serve as advocates and active participants in the training, development, and education of pharmacometricians now and in the future.

Clinical Perspectives

Michael Neely, Children's Hospital Los Angeles

As of yet, a rarer application of pharmacometric skills lies within practitioners of direct patient care. More commonly seen in clinical pharmacists who hold a PharmD, occasional MDs are also clinical pharmacometricians [40,41]. This is the practice of "therapeutic drug monitoring", also known as "therapeutic drug management ", to infer a more active role, but which now is perhaps most often termed "model-informed precision dosing" (MIPD) [42,43]. Although "MIPD" only includes the word "precision", i.e., reproducibility, MIPD also embodies the concept of accuracy, implying reproducible target achievement as the endpoint. MIPD involves the use of pharmacokinetic/pharmacodynamic models, created almost exclusively by use of population methods, in combination with individual patient characteristics, dosing history and available measured drug concentrations to achieve target plasma drug exposures with maximum accuracy and precision. As such, the range of skills needed lies within those listed in Table 2, to the degree that the clinician is involved in model building vs. model application.

Clinicians may be involved in building pharmacometric models, but it is not strictly necessary, as it is likely more common in the patient care setting to apply a model provided within a software tool. Nevertheless, clinicians who are involved in model building should possess a number of skills that require training. First, they need a solid understanding of, and preferably, experience with the conduct of clinical trials. This is necessary to optimize the collection of sufficiently informative data to build useful models. Measuring only trough concentrations just before the next dose is a classic example of poor study design that is likely to lead to biased results and PK/PD models. Understanding how to negotiate with local or central Institutional Review Boards and maintain the necessary certifications, such as Good Clinical Practice (GCP) and Human Subjects research training, is necessary to conduct even simple Phase I PK studies that are necessary to build pharmacometric models that can be used for patient care.

Second, a basic grasp of statistical methods used in modeling is important, but a detailed understanding of the algorithms and extreme mathematical prowess is not necessary for the construction of most models if one is aiming for practical application like MIPD, rather than innovative algorithm development. Concepts such as Bayesian statistics, Monte Carlo simulation, regression, and hypothesis testing should be part of the curriculum for any clinician who is learning to build models. Inclusion of cost-benefit analysis in statistical training is desirable, as MIPD in the clinical setting is still the exception due to perceived costs and uncertain benefits. The ability to better define the benefit of a model in the clinical arena is crucial to increasing MIPD practice.

Third, of critical importance, is comfort with computers. There are many software tools available to perform the data processing and numerical analysis which are necessary to build a pharmacometric model, but all of the tools are complex and require training to use. The model-building practitioner should also possess a willingness to engage in some basic programming. Most pharmacometric tools currently are in R, while Python is typically used more in the machine learning domain, which is a major future direction for the field of pharmacometrics. Other languages such as Fortran, C++, Julia, and Stan all have representative software

applications in pharmacometrics. While expertise in any of these languages is not required, for clinicians who want to build their own models, increased programming proficiency offers greater flexibility and power in the kinds of models which they can build.

Fourth, and perhaps most obviously, is training in clinical pharmacology, with expertise in fundamental equations and biologic processes that describe pharmacokinetic and pharmacodynamic behavior. Non-compartmental equations are important for differing models of the same drug, perhaps validating a model under development to one previously published. Non-compartmental parameters, such as area under the concentration time curve (AUC), total clearance, half-life, maximum concentration, time to maximum concentration, and minimum concentration all describe the shape of the pharmacokinetic profile, which is the combined output of all model parameters. These non-compartmental parameters therefore provide a more relevant comparison between models with differing parameters that cannot be directly compared, e.g., because of compartment number or clearance vs. elimination. Compartmental pharmacokinetic equations are at the heart of the "structural" model, which define the relationship between input, e.g. dose, and output, e.g. concentration. The variables within the compartmental equations become the parameter values to be estimated in the population. Thus, a solid training in clinical pharmacology and pharmacokinetics is required to understand how to choose and customize the proper equations to describe drug behavior.

In contrast to the above requirements for a clinician-scientist, for clinicians who wish to apply but not develop models, i.e. to perform MIPD with pre-existing models within a software application, correspondingly fewer skills are needed in the areas of mathematics, statistics, and computer programming. Some comfort with computers is still required, as MIPD is implemented through an increasing number of software applications, even though they are more and more user friendly. Although some applications are connected to hospital medical record systems to permit automated data extraction, most are not, and therefore require manual data entry.

Interpretation of the MIPD software application output means that a background in clinical pharmacology, perhaps as a secondary specialization, is still important. MIPD experts may have a primary specialty within a particular branch of medicine, such as infectious diseases or oncology, or they may have broader expertise across multiple branches and practice as a clinical pharmacologist. Clinical pharmacology training is necessary to understand the assumptions, limitations, and characteristics of any given model and properly translate the computer output to the patient's drug prescription. For example, what happens when the model doesn't fit the data well? What is the proper response? Training a clinician to use MIPD tools must include such scenarios.

Finally, seamless practice of MIPD requires cooperation between physicians, pharmacists, and nurses, regardless of who is actually performing the MIPD calculations. Therefore, on the softer side, strong skills in communication, teaching, and coordination are essential.

Jeff Barrett, Aridhia

The pharmacometrician supporting clinical practice must first and foremost understand the patient population(s) that their work supports. This should include, but not be limited to, knowledge of the disease progression including comorbidities, the standard of care including pharmacotherapeutic options and the therapeutic window of relevant drugs in class used to treat the disease or condition both from a treatment and prophylactic perspective. More specialized training from this background depends on the nature of the pharmacometrics support to benefit clinical practice. There is an increasing understanding the quantitative sciences can contribute to the clinical care of patients in both an in-patient and out-patient setting. The specific nature of these roles is varied and can include the development and deployment of decision support tools and systems to allow individualized dosing, service on institutional review boards (IRBs) that decide the suitability of investigator-initiated trials in patients, service on hospital-based committees that inform and guide the formulary (e.g., drug

use evaluation or therapeutic standards committees) or as a member of an academic medical center that designs and analyzes patient trials (either as a Primary Investigator, statistician or pharmacometrician). From a training perspective, the prerequisite knowledge can be very different foreach one of these roles. Table 2 below highlights some of the expected core knowledge areas that would guide pharmacometricians in each of the clinical practice roles described above.

Perceived “soft skills” are also extremely relevant in clinical practice. Actual dialogue with patients represents a minority of the roles mentioned in Table 2. Still, the necessity of appropriately and effectively communicating the interpretation of the quantitative approaches to inform clinical practice to a diverse stakeholder community exists. These include both written and oral communication skills applied to the needs of collaborators or stakeholders with diverse baseline knowledge possibly including co-investigators, prescribers, patients, and caregivers. Pharmacometric approaches and outputs need to be demystified for many of these stakeholder types often in an impact-prioritized manner with humility and confidence. They must be excellent translators of the clinically-meaningful interpretations of their efforts and not get mired into touting the technical difficulty of their efforts over delivering a succinct explanation of the impact of the quantitative approaches on the clinical outcomes, explaining both the assumptions and the limitations while giving confidence in the analysis. Having access to strong mentorship in this capacity is extremely beneficial as these experiential skills need to be witnessed and practiced. As more opportunities are generated for pharmacometrics scientists in clinical practice, the demand for these skills will grow. Topics including precision medicine and more specifically precision dosing represent future drivers for the grow of clinical practice opportunities.

Further recommended reading on these topics can be found in [44] [3] [31] [45].

Table 2. Training Pre-requisites essential for various Pharmacometrics Roles Supporting Clinical Practice

Clinical Practice Role	Expected Pre-requisite Knowledge or Skills
Clinical Decision Support	Computer sciences and application development knowledge¸ regulatory requirements on applications (devices) that inform patient dosing, clinical pharmacology and therapeutics
IRB Member	Clinical drug development, bioethics, biostatistics, regulatory requirements
Hospital-based Committee Service (i.e., TSC or DUE)	Clinical Pharmacology and therapeutics, bioethics, clinical pharmacy, bioequivalence, regulations
Clinical Research Team	Drug development, bioethics, biostatistics, regulatory requirements, and science
TSC refers to therapeutics standards committee while DUE stands for drug use evaluation committee	

Joseph F Standing, Great Ormond Street Institute of Child Health, University College London and Department of Pharmacy, Great Ormond Street Hospital for Children

The direct use of pharmacometric models in clinical practice is limited to a few niche cases mainly in hospitalized patients. These include interpretation of therapeutic drug monitoring (TDM) results, dose determination for the unlicensed or off label use of a medicine, which occurs relatively frequently for example in pediatrics, and making risk assessments around drug-drug interactions. Whilst a great deal of current interest surrounds model-based Bayesian TDM, there are very few use cases to have proven to improve clinical outcome [46,47]. with prospective antimicrobial trials in particular being largely negative [48,49]. Whilst the adoption if Bayesian TDM is relatively limited however, there is still a strong case for clinical pharmacologists and pharmacists working in hospitals to possess pharmacometric skills [50].

A statistical programming language and statistical literacy

The first skill required by a pharmacometrician is to be able to manipulate and analyze data computationally using an object orientated programming language. An object orientated programming language is one in which data and code form objects, with data with certain attributes (e.g. numerical, date, character) being manipulated by code in the form of data manipulation or statistical analysis. With this skill, a tool for reproducible data manipulations, plotting and statistical modelling will be available. For most pharmacometricians R is currently the preferred language [51-53] but there are several other alternatives.

The population mixed effects modelling approach firstly requires one to be able to define terms such as parameter, dependent variable, independent variable, and covariate. A working knowledge of parameter estimation principles, at least through an understanding of the principles of linear regression, a knowledge of statistical distributions, and a basic appreciation of structural identifiability are important. Pharmacometricians should appreciate the

assumptions made when choosing parameter distributions, or indeed when deciding to use a nonparametric approach, in addition to ensuring chosen models are identifiable before attempting to estimate parameters.

How are pharmacokinetics described and modelled, and relating the two

A fundamental piece of knowledge required by a pharmacometrician is to understand the basic descriptive approaches to the analysis of a pharmacokinetic (PK) curve. This includes the ability to calculate area under the curve for the observed period (AUC(0-t)), the elimination rate constant using three or more terminal concentrations and an assumption of first order decay, the total AUC (AUC(0-inf)) and how to report maximum concentration (Cmax) and the time to reach Cmax (Tmax).

Whilst this is covered in the early years of most medical and pharmacy courses, modelers from other disciplines may not have come across this may need to be revised or taught afresh to students without such background. A useful skill is to be able to calculate these parameters from rick PK data using an object-oriented programming language rather than relying on point/click software. Knowing how to calculate these parameters, and crucially how these relate to pharmacological effect via PKPD relationships, is vital for setting the dose.

The next step is to appreciate the usually nonlinear compartmental models used in PK, and how the primary parameters of clearance and volume of distribution in these models relate back to the secondary parameters of AUC, Cmax and half-life. Since nonlinear regression algorithms can terminate in local minima, understanding the physiological plausibility of parameters is also crucial. For example, knowing a water-soluble drug cleared by glomerular filtration is likely to have a volume of distribution close to total body water and clearance matching usual glomerular filtration rate will allow the modeler to gauge whether parameters are physiologically plausible.

In particular it is this understanding of how PK parameters relate to biological processes that will be a key skill for modelers of the future. Machine learning algorithms are increasingly being proposed to describe concentration-time data, but this neglects the fact that individual concentrations are driven by a number of known physiological processes and values. Without relation back to physiology so that parameters can be interpreted, and doses to reach concentration targets defined, it is unclear how useful these will be [54].

Designing pharmacometric studies and interpretation of covariates

Clinical pharmacometricians will often be required to design studies and here the balance between what is mathematically optimal in terms of parameter estimate precision and what is clinically feasible needs to be made. Opportunistic PK sampling can lead to an inability to estimate key parameters [55] whereas precise parameter estimates can be derived from well-designed studies using optimal design [56] or prior simulation-estimation studies [57]. These principles need to be understood in order to design clinical studies [58].

A notable issue in pharmacometric modelling is the lack of standardization in covariate parameterization. Modelers are encouraged to test any covariates available using linear or nonlinear functions to describe parameter-covariate relationships and include these based on purely statistical criteria. Whilst this approach may derive a model best fitting the data at hand, it results in difficulties in comparing parameter estimates across studies [59], typographical errors [60,61] and models which cannot be extrapolated outside the narrow range of covariates used [62].

REGULATORY PERSPECTIVES

Hao Zhu, United States Food and Drug Administration

Pharmacometricians at FDA have played critical roles to support the application of innovative modeling and simulation tools to facilitate drug development, to inform rational decision-making, and to assist new policy development that may further advance efficient drug development and patient care. Besides routinely reviewing materials submitted in investigational new drug applications, new drug applications, abbreviated new drug applications, and biological license applications, pharmacometricians actively engage in various review meetings with multidisciplinary review staff and industry scientists on issues critical for improvement of clinical development programs, such as selection of optimal dosing for patients or patient subgroups and identification of evidentiary facts necessary for regulatory decisions. FDA has also initiated several programs, such as Model Informed Drug Development Paired Meeting Program and Fit-for-Purpose Initiative, to promote early interactions in drug development programs. Pharmacometricians are key players in these programs that facilitate incorporation of novel tools and quantitative approaches into drug development. Furthermore, FDA pharmacometricians are always active in conducting regulatory research projects, and engaging scientists in the community to expand the applications of pharmacometrics tools for the benefit of patients.

To fulfil roles as a regulatory scientist focusing on the application of innovative quantitative modeling and simulation approaches for drug development, we anticipate several key features/skills for future pharmacometricians.

- *Be patient-centric*: Pharmacometrics is the application of various quantitative tools with the goal to facilitate drug development and improve patient care. The development and application of a novel pharmacometrics tool should always be centered around practical benefits that can be brought to patients. For instance, pharamcometrics analyses may

provide insights on the evidence of effectiveness, allowing patients' earlier access to an effective therapy. Some pharmacometrics work may inform better selection of a treatment for or identification of optimized dosing in patient subgroups. Future pharmacometric analyses should always address patients' needs. Identifying the best way to serve patients should always be the top priority for pharmacometricians working at the FDA.

- *Be active in learning novel technical skills*: Pharmacometrics is fast evolving. The concept of using quantitative mathematic models to understand a biological process and to improve drug development has been built upon explorations over the past century. Early pharmacokinetic and pharmacodynamic models tend to capture the mean changes over time. From 1950 to 1970, Dr. Sheiner applied non-linear mixed effects modeling, which led us into the world of population analysis with the capability to characterize variability and identify the source of variability. Since then, the community has witnessed a rapid growth of pharmacometrics tools and their applications in drug development as the result of joint efforts among scientists from industry, academia, and regulatory agencies. Common pharmacometrics tools include population pharmacokinetic models, physiologically based pharmacokinetic models, and exposure-response models. In recent years, disease progression models, model-based meta-analysis, quantitative system pharmacology models, quantitative-structure-activity models, and even artificial intelligence/machine learning models have been applied to support various activities in drug development. Real world data/evidence provides new information source, as a supplement to the learnings in drug development programs, to improve appropriate use of a drug in patients or patient subgroups. The emerging techniques largely broaden the scope of future pharmacometrics. Pharmacometricians at the FDA are expected to be on top of emerging techniques and work with the community to drive changes. Because no existing training program can provide all the needed techniques to cover the rapidly increasing scope of pharmacometrics, the

willingness and capability to learn new techniques and explore their applications will be key to the success of future pharmacometricians.

- *Thoroughly understand medical science and pharmacology:* Pharmacometric analyses rely on mathematic and statistic tools to identify useful information and to improve drug development and patient care. Domain knowledge of medical science and pharmacology is essential to establish a model structure, to build covariate relationships, to assess plausibility of parameter estimates, and to integrate information obtained from alternative sources for model building. The understanding of the underlying disease progression and pharmacology is especially critical for mechanistic models. Additionally, the work of a pharmacometrician goes beyond quantitative analysis itself. The impact of pharmacometric findings largely relies on the pharmacometrician's capability to interpret the results and derive decisions in an appropriate context. A thorough understanding of relevant medical science and pharmacology is the basis to communicate with and to seek buy in medical professionals.
- *Be a good communicator:* Critical decisions for drug development programs and regulatory actions are always made as a joint effort from multidisciplinary teams. The value of pharmacometrics can only be recognized when the analysis results are fully appreciated by the team and the recommendations are factored in to decision making. To accomplish this, it is important that pharmacometricians understand how to communicate the findings through plain language and avoid jargons whenver possible. More importantly, pharmacometricians should be integrated as part of the collaborative team decision making effort. Being an active listener, seeking questions and concerns, addressing identified issues, balancing different opinions based on solid scientific evidence, and seeking alignment are the features of a good communicator who are effective in driving rational decisions.
- *Be a good strategic planner:* Pharmacometrics analysis is a powerful tool to extract information and a platform to integrate findings from various sources. However, the

value of pharmacometrics would be limited if it was only applied to salvage trials with controversial outcomes. To maximize value, pharmacometrics analyses should be integrated throughout all aspects of drug development. The ultimate objectives for pharmacometrics analyses, the timing for data acquisition, the strategy for fine tuning the models during drug development, the capability to adjust the program based on interim pharmacometrics analyses, and the plan to communicate with multidisciplinary teams should be strategized when the development program is initiated. Pharmacometricians should bear a whole picture of the drug development program with a reasonable understanding of the final targeted risk and benefit profiles. In addition, pharmacometricians at FDA are expected to work closely with industry colleagues to optimize the pharmacometrics program as part of the effort to streamline drug development.

Shinichi Kijima, Japan Pharmaceuticals and Medical Devices Agency

Knowledge of clinical pharmacology, understanding of statistical modeling and analysis, and programming are fundamental skills for pharmacometricians. However, regulatory pharmacometricians must also be knowledgeable in regulatory science. The regulatory pharmacometrician must not be a simple “modeler.” Pharmacometrics is generally considered a tool for answering questions by integrating the existing information. The basic idea is the same for regulatory authorities. Regulatory science is employed for most regulatory decision-making by relevant authorities. For example, when pharmacometrics is utilized to make regulatory decisions in drug approval reviews, we must understand the data package, that is, the data required to develop a drug with assured efficacy and safety. Statistical and programming excellence in the absence of thorough understanding of the information required for regulatory decisions could prove ineffective, as it is difficult to provide team members and

stakeholders with the knowledge that contribute to the drug review or regulatory consultation process.

Communication skills are also essential. To appropriately conduct regulatory decision-making that involves the interplay of various factors, cooperation with the relevant parties is necessary. For example, reviews of drug approval are conducted from various perspectives; therefore, inputs must be collected from experts on clinical pharmacology and pharmacometrics, and also from experts in clinical practice, CMC (chemistry, manufacturing, and controls), toxicity, and post-marketing surveillance (PMS). Communication with non-experts in pharmacometrics and clinical pharmacology is important. Regulatory pharmacometricians must clearly and accurately present information to these collaborators and stakeholders. Even with the "correct" analysis results and information, complex and incomprehensible information may not be utilized appropriately.

Therefore, the following three points are essential for fostering regulatory pharmacometricians. Considering the individual background, all pharmacometricians must be trained in regulatory science and appropriate communication while filling in gaps for basic and critical skills (knowledge of clinical pharmacology, understanding of statistical modeling and analysis, programming, etc.).

1. Supplementing the missing basic and important skills, such as knowledge of clinical pharmacology, understanding of statistical modeling and analysis, and programming.
2. Learning regulatory science and understanding regulatory principles for drug development and regulatory decision making
3. Acquiring communication skills to utilize the output from pharmacometrics for regulatory decision making

Regarding point 1, training in academic and professional institutions can be considered, because systematic training within the regulatory authority may be difficult to provide. In addition, the actual implementation of analysis in the course of operations can provide practical

and continuous training. In the experience of the Pharmaceuticals and Medical Devices Agency (PMDA), a review using electronic application data submitted at the time of application is suitable on-the-job training to help improve technical knowledge [63, 64]. The relevant theories and techniques are continually being updated; therefore, periodic revision is required.

Regarding point 2, the general content related to the review and approval process and pharmaceutical administration for drugs should, in principle, reflect the regional situation for training at an early stage. However, with regard to the acquisition of practical knowledge and experience, responding to routine training that provides generalized content has limitations, because regulatory decision-making often involves considerations on a case-by-case basis with attention to complicated situations with varied points of information. Working on numerous cases can help improve regulatory decisions. However, accumulating knowledge and experience with on-the-job training alone can be time-consuming, because a person experiences only a limited number of cases during a given period. Therefore, sharing many cases experienced as an organization is an effective means of reducing training time. Practical case-based experience can be acquired via the organized and timely documentation of cases; this will allow any employee to refer to the factors that affected judgment in a case, even after the actual case has been closed. Creating a framework that encourages sharing of cases among persons in charge and using it to continue sharing and discussing cases could serve as training in practical knowledge and experience.

Because point 3 is a common issue, not only for pharmacometricians but also regulators, appropriate training can be decided upon by each organization, and most of them can handle this issue. However, separate training might be required to provide an explanation that is concise and understandable to non-experts on pharmacometrics and clinical pharmacology.

Finally, both the training provider and trainee should be reminded that the information from pharmacometrics must be adapted and used for the purpose, and that regulatory

pharmacometricians must accumulate knowledge and experience that is relevant to the use of pharmacometrics.

Discussion

There were many differing opinions regarding training future pharmacometricians, but there were some common themes and ideas. In order to help improve clarity around the many messages, an augmented word cloud was created (Figure 1) to help identify words or phrases that were repeated many times from the contributors. Some of the themes that were identified:

- Academic institutions cannot keep up with the demand for pharmacometricians and this is unlikely to change in the near future. Currently the focus has been on pharmacometrics as an advanced PhD degree. Some of the contributors suggested the need for non-PhD degrees and others pointed to their emergence in academia.
- Many stated that there were 3 areas of expertise a pharmacometrician should possess: technical competence, contextual knowledge, and soft skills (Figure 2). All of these should be provided to some degree in graduate school. While not emphasized too much in its beginnings, the importance of soft skills today is recognized and schools are working to include that as part of a student's training.
- Pharmacometricians, whatever their specialization (PopPKPD, PBPK, QSP, ML), will continue to need a solid foundation in pharmacokinetics and pharmacodynamics, and to understand the principles of pharmacology. They will also need solid training in quantitative methods, although there was less agreement on what those methods should be. Being able to solve problems quantitatively is a major core competency.
- Although academia is the major provider of trained pharmacometricians, across both academia and industry, it was agreed that industry needs to take on a greater

responsibility for training new pharmacometricians. This was perhaps one of the biggest outcomes of this paper – industry cannot entirely rely on academia to meet this job need and provide a sufficient stream of project-ready modelers. A solution to this is for industry to start funding graduate and post-graduate education to increase the pipeline of pharmacometricians. Another solution is “On the job training“, which came up alot in different forms. Companies could start investing in their own internal training curriculum or have dedicated employees whose job it is is to teach new employees those skills needed to succeed.

- New pharmacometricians need to realize that graduating with an advanced degree is just the start of their education. Experienced pharmacometricians also need to realize that the field is evolving and updating their skill sets throughout their career is needed to remain relevant. Further, at least for industry pharmacometricians, it is unlikely that someone will remain in a single disease therapeutic area. In fact, it is not uncommon for someone to work in multiple disease areas during their career. This means that constant learning of new areas will be required. The idea of a pharmacometrics mentor, sponsor, coach, or teacher to help fill in those gaps new employees have was mentioned. Some companies are already starting to hire such internal “teachers“ for new employees. Some contributors also mentioned patient-centricity, which is putting the patient first in what we do (which in itself is a noble goal but may be hard to define how to do in practice).
- One contributor mentioned certification as a pharmacometrician. This has not really been raised before by any of the professional societies but may come in the future. The American Statistical Association argued for years about the need for a ‘Certified Statistician‘ before launching the Accredited Professional Statistician program in 2010.
- There were parallels between the training requirements for industry and for CROs. All the CROs representatives emphasized the need for seasoned, experienced pharmacometricians with strong hard skills, like technical expertise and contextual knowledge, and soft skills, like time management, being able to scope problems

properly, and provide calm, focused expertise. Many consultants are already experienced when they enter the sector and rely heavily on those skills they developed in their previous employment, but they too require continual on-the-job training to remain current and fill in previous gaps in training. While employment in industry usually provides linear experience in drug development, employment in the CRO sector can be a tremendous learning opportunity for future pharmacometricians as it typically provides a wider experience.

- In terms of specific skills, the contributors did not focus on particular things, instead stating that new pharmacometricans needed a foundation in modeling and analytical skills. The phrase ‘problem-solving‘ was used alot. Pharmacometricians need to be able to solve problems for which there is no predefined solution. It was suggested that more open-ended, independent problem solving be done in graduate school. Some discussed the need for knowledge of population pharmacokinetics modeling, but this was probably the result of their own individual focus, as clearly there are many pharmacometricians who do not have these skills and work in other areas like PBPK or QSP. Also, no one said that those entering the field did not have the technical skills to succeed; most said that further training was needed to fill in gaps in education.
- Communication skills came up often. Everyone needs to learn to present the results of their analyses to teams, both internal and external, and to groups of other modelers and to nontechnical experts in other disciplines. Good communications skills were universally seen as an important skill. It was recommended that every class in graduate school have a communication component, either oral or remote, to help improve communication skills.
- The words ‘team‘ and ‘multidisciplinary‘ came up a lot. Pharmacometrics is a team sport; we play it with individuals from many disciplines: statistics, clinical pharmacology, medicine, toxicology, pharmacology, biomarkers, etc. Many discussed the need for individuals to have the soft skills to interact and communicate with their coworkers and external vendors.

- There was surpisingly not a single word said around ‘remote work‘ and how that might play into training and working. Pharmacometrics is a surpisingly flexible profession that could allow for its workers to work remotely and train remotely. It’s not clear if this is being accounted for by the sectors.
- There was not a lot of discussion around particular software. The most commonly used softwares were mentioned, but not in the sense that this particular software much be learned. There was a general consensus that modelers needed to be comfortable with computers, being fluent in at least one scientific programming language, be that R, Python, Matlab, or Julia, and have experience in data wrangling and graphical analysis. Some contributors brought up that machine learning is on the way and everyone should start to get prepared for the impact that might have on the field.

It is our hope that this manuscript will help those who are responsible for creating the next generation of pharmacometricians, that these thoughts and ideas can guide and improve currently in-place training programs.

Declarations

At the time of writing this, Steve Duffull has a shared position with Certara and the University of Otago. Hao Zhu’s section reflects the views of the author and should not be construed to represent FDA’s views or policies.

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Disclaimers

Shinichi Kijima: The views expressed in this article are the personal views of the author. The content of this article does not reflect the views or policies of the Pharmaceuticals & Medical Devices Agency (PMDA) or its staff.

Figures

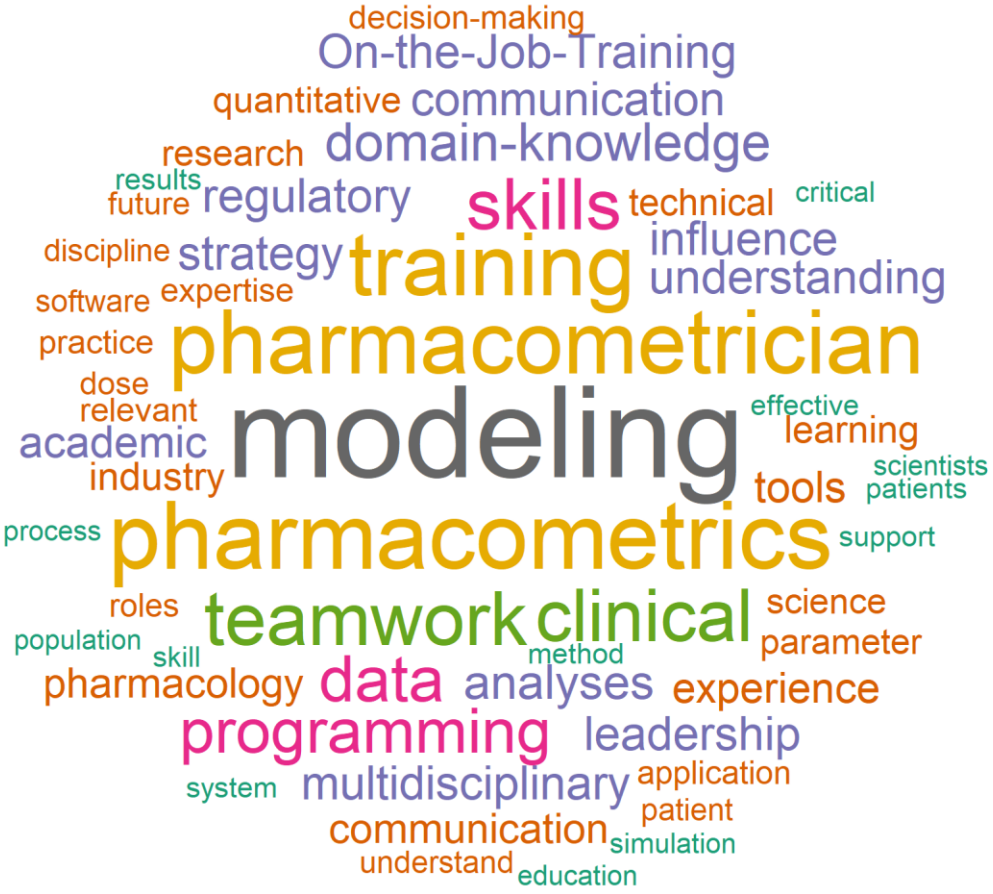

Figure 1: Augmented word cloud of text from the contributors.
In general, the size of the word represents the number of times the word is used in the text.

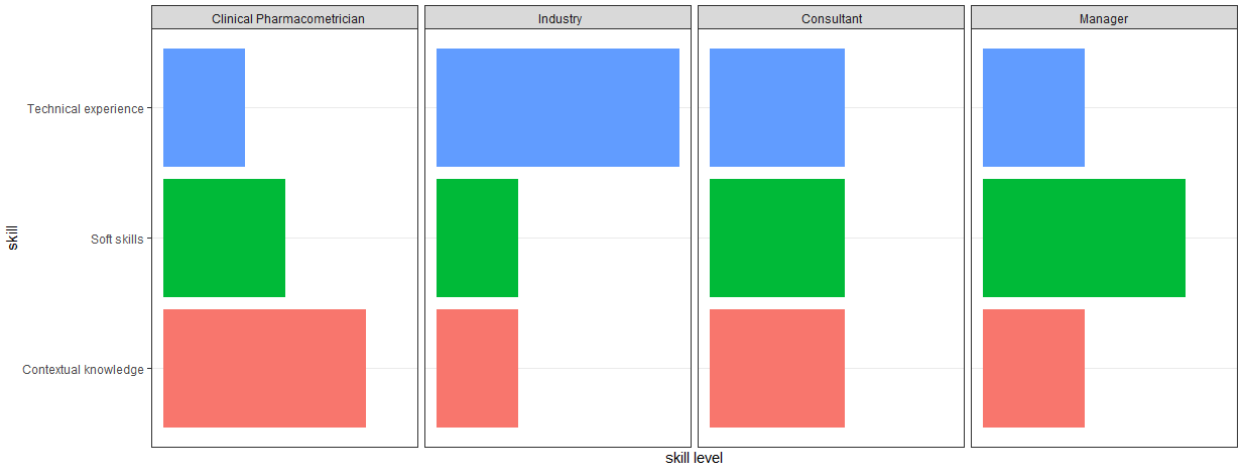

Figure 2: Skills needed for a pharmacometrician may depend on sector or position. All contributors agreed that technical experience, contextual or disease-specific knowledge, and soft skills are needed for success. Most people are unbalanced. Different ratios may be useful for different sectors. For example, A clinical pharmacometrician may need a greater ratio of contextual knowledge to technical experience. Someone in industry may need greater technical experience than contextual knowledge, whereas someone working as a consultant may need an equal mix of technical experience, contextual knowledge, and soft skills. A manager may need greater soft skills than contextual knowledge or technical experience.

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