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TUTORIAL

Communicating to Influence Drug Development and Regulatory Decisions: A Tutorial

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Pharmacometricians require three skills to be influential: technical, business (e.g., drug development), and soft skills (e.g., communication). Effective communication is required to translate technical and often complicated quantitative findings to interdisciplinary team members in order to influence drug development or regulatory decisions. In this tutorial, we highlight important aspects related to communicating pharmacometric analysis to influence decisions.
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Pharmacometrics utilizes biological, pharmacological, engineering, statistical, bioanalytical, and clinical theories or technologies (off-the-shelf components) to effectively analyze data for generating knowledge (generalizations) that can then produce intelligence (actionable knowledge).[1] The key goal of pharmacometrics is to influence drug development, therapeutic or regulatory decisions. Because of the multidisciplinary nature of the field, pharmacometricians interact with a variety of disciplines on the drug development team and, thus, need to have effective communication skills to successfully interface with clinicians, statisticians, and laboratory-based scientists.[2] For the purpose of the present tutorial, effective communication is defined as the process of conveying information with the sole goal of influencing a decision. Effective communication is a basic survival skill for pharmacometricians in drug development. Without impactful contributions, the field of pharmacometrics will not expand and provide opportunities for more pharmacometricians. A pharmacometrician who models without an effective communication strategy is less likely to influence decisions.

Modelers develop an analysis plan but often ignore planning for communications. Models are only a means to an end, and not the deliverable. In our experience, a successful pharmacometrician's real responsibility starts after the modeling because models perform exactly as they are programmed, but team members often do not. Postmodeling efforts are dictated by an understating of the business environment, regulatory policy, team composition, modeler's credibility, and clarity of the decisions and communication. We recognize that "one size fits all" communication strategy may not be feasible. One may need to tailor the communication style depending on the audience and the purpose of communication. As noted by Visser *et al.*,[3] in general, detailed technical and mathematical descriptions should be used only for documentation purposes and in a peer-to-peer learning environment, and not for cross-functional or management discussions. For the purpose of this tutorial, the primary focus is communication to an interdisciplinary audience with an aim to influence decisions.

The field of pharmacometrics has progressed over the years from a technical one to a decision-oriented discipline.[4–8] Though leaders from pharmaceutical companies acknowledge that communication remains a significant challenge for pharmacometricians and stress the need for technically skilled scientists who also possess good communication skills.[3] In a nutshell, pharmacometricians require three skills to be influential: technical, business (e.g., drug development), and soft skills (e.g., communication). Educational institutions continue to train pharmacometric scientists primarily in technical methodology. The lack of training in business and soft skills is preventing pharmacometricians from becoming high-level decision-makers.[1]

General concepts on preparing a presentation have been discussed elsewhere.[9,10] The goal of this tutorial is to build on those concepts in a manner that is tailored for pharmacometricians. Here, we will highlight the important aspects related to communicating pharmacometric analysis and recommendations to interdisciplinary scientists. Furthermore, we provide a few examples from the US Food and Drug Administration (FDA) reviews and advisory committee meetings and some hypothetical examples to illustrate the concept of effective communication. We also conducted a survey of current pharmacometricians and clinical pharmacologists working in regulatory agencies or pharmaceutical companies to identify the core skills pharmacometricians should possess to communicate effectively. The results of the survey are also discussed in this tutorial.

COMMUNICATION GOALS OF PHARMACOMETRICIANS

Table 1 describes why, what, how, to whom, and when pharmacometricians communicate. The communication goal of pharmacometricians is to achieve their desired response. To achieve their desired response, the communicator has to hone his or her skills from general to specific. The goals of communication can be stratified under the following tiers: (a) general objective; (b) actionable objective; and (c) communication objective.

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Table 1 Communication goals for pharmacometricians

Communication goals of pharmacometricians		
1.	Why we communicate?	i) To seek input or provide information
		ii) To persuade stakeholders on the decision
		iii) To develop trust and credibility
2.	What we communicate?	i) Technical details of the analyses: the purpose is to seek concurrence on the methodology, expert advice on challenging analyses and to ensure consistency within the group.
		ii) Recommendations to stakeholders, such as drug teams, regulators, advisors, and investors, to influence a decision: the primary focus is on the recommendations and not on the model. The purpose is neither to educate the interdisciplinary team on modeling nor to demonstrate our modeling dexterity.
3.	How we communicate?	i) The primary mode of communication could either be written or verbal. Written communication can serve as the official record and can be fine-tuned, whereas verbal communication can help build rapport and is an efficient way of a two-way dialogue that allows negotiations. In our experience, verbal communication brings emotions and the ability to reason into the mix and is generally more powerful than written communication to influence decisions.
		ii) The approach of communication could either be deductive or inductive. Deductive approach focuses on stating the conclusions upfront, whereas in the inductive approach, the thought process or the method is stated first followed by the conclusions. We recommend pharmacometricians to use an inductive approach when the goal is to gain concurrence on the model, and to use deductive approach when the purpose is the decision.
		iii) Communication style could be either tell, sell, consult, or join. The first two communication styles are generally followed if the communicator has enough information regarding the project and wants to control the message. The latter two communication styles are more collaborative and are followed when the communicator needs input from other team members to make a decision.[10]
4.	To whom we communicate?	We communicate the recommendations based on pharmacometric analysis to statisticians, clinicians, marketing teams, and investors. Understanding the audience helps to frame the pharmacometrics reports and presentations. The key aspects of the audience to be kept in mind are:
		i) Who are they?
		ii) What are their expectations?
		iii) What will persuade them?
5.	When do we communicate?	The three key milestones for communication during the lifecycle of a pharmacometric project are:
		1) Scoping meeting: the purpose is to identify the decision to be influenced and frame key questions accordingly.
		2) Department approval meeting: the purpose is to get concurrence from peers regarding the analysis performed and decision taken.
		3) Decisional meeting: the purpose is to obtain concurrence from interdisciplinary team on the decision.

The general objective can be thought of as the broad overall goal of the project, the actionable objective is specific, measurable, and time bound, and the communication objective is what the audience will decide as a result of the communication of the findings. For example, if a pharmaceutical company is developing a new chemical entity, the general goal would be to decide whether or not to move forward with the new chemical entity (go/no-go decision), the actionable objective would be to compare the potency of the new chemical entity with competitors by a certain date, and the communication objective would be to present the findings to the drug development team. The goal of the communication is not only to present the findings of the analysis performed but to focus on key decisions (i.e., whether or not to move forward with the new chemical entity).

STATE OF AFFAIRS

In order to evaluate the current state of communication in pharmacometrics, a strength, weakness, opportunity, and threats (SWOT) analysis was conducted. Strengths and weaknesses are internal to an individual or organization, whereas opportunities and threats are external factors. Strengths and opportunities are helpful to achieve the objective, whereas weaknesses and threats are detrimental for attaining an objective. Consider that we are able to influence the key decision of an interdisciplinary management team based on a pharmacometrics project. **Figure 1** shows the results of our SWOT analysis for an average pharmacometrician. In general, pharmacometricians possess strong technical skills and a good understanding of clinical pharmacology principles. Pharmacometricians generally lack sound understanding of drug development and clinical therapeutics and an understanding of statistical principles underlying the clinical trials. Furthermore, in general, clinical pharmacology and pharmacometrics departments do not have the final authority in high-level decisions. Pharmacometricians do not need mastery of all disciplines and favorable power structure, but recognizing our weaknesses will aid in approaching the challenge in a smarter way. Pharmacometrics attempt to optimize the solutions by understanding the underlying science and, thus, is more of an engineering-type discipline. For example, the choice of the right dose range to be tested in a registration trial is an open-ended question. The conventional statistics attempts to apply the most precise methodology to provide a yes or

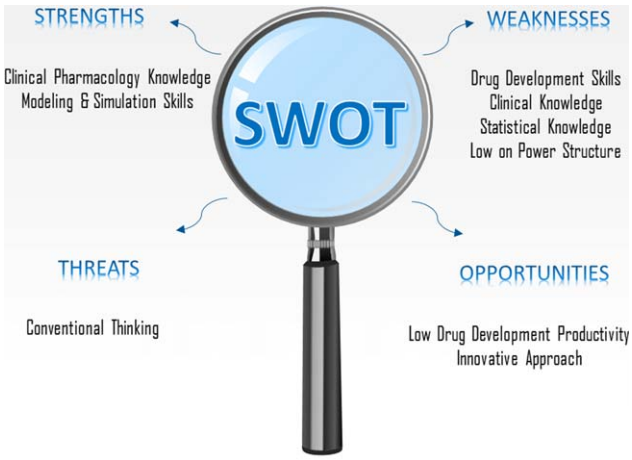

Figure 1 Strength, weakness, opportunity, and threats (SWOT) analysis in context of an average pharmacometrician responsible for influencing key drug development or regulatory decisions.

no answer. Whether a drug exhibits superior efficacy to placebo or not is a yes or no question. We tend to learn from data and apply that knowledge to decisions. The conventional approach tends to focus solely on confirmation, assuming you know the correct question. These philosophies often result in a conflict when they try to answer the same or a similar question. Therefore, conventional thinking is a formidable threat. The low productivity rate of drug development coupled with our ability to offer an innovative approach is the single most important opportunity.

In order to procure feedback from our colleagues, we conducted an anonymous survey of pharmacometricians and clinical pharmacologists randomly selected from government agencies and pharmaceutical companies. The goal of the survey was to understand the quality of communication among pharmacometricians and seek perspectives on their different styles. The survey questions are presented in **Table 2**.

Fifty-seven clinical pharmacologists/pharmacometricians completed the survey. The survey results are presented in **Figure 2**. Approximately 70% of the survey responders had more than 5 years of experience in the field of clinical pharmacology/pharmacometrics. Eighty-two percent of the survey-takers reported that, on average, pharmacometricians lack strategic/effective communication skills. This opinion is consistent with our motivation for this tutorial. Thirty-seven percent of the survey-takers ranked "Identifying the key decisions at the decision meeting" as the most important skill needed for effective communication followed by "Knowing the audience" (35%), "Credibility" (21%), and "Impactful presentation" (9%). Sixty-two percent of the survey-takers reported the use of a deductive approach when communicating to drug teams at the decision meeting. The survey results reemphasized the need for training pharmacometricians in terms of soft skills i.e., communicating decisions to interdisciplinary drug teams.

"Identifying the key decisions" and "Knowing the audience" were ranked as the top two skills for effective communication. These findings are in alignment with the tenets proposed for effective communication later in this tutorial. Additionally, the survey results indicate that establishing credibility with the interdisciplinary team over time is one of the most critical factors to influence the decision.

Lastly, on the topic of communication style, surveyors preferred the deductive approach over an inductive approach. The deductive style of communication begins with the decision followed by the rationale.

TENETS FOR EFFECTIVE COMMUNICATION

Good communication is grounded in several interrelated principles. In order to keep the communication goal at a manageable level, we propose four relatively important tenets for effective communication summarized as "CDSK," pronounced as "see disk." They are: Credibility, Decision, Style of communication, and Knowing the audience.

Credibility

Establishing credibility throughout the lifecycle of a pharmacometrics project is one of the most important skills for

Table 2 Survey questions for effective communication for pharmacometricians

Effective communication for pharmacometricians		
	Question	**Answer choices**
1	Please select your years of experience post-graduation in pharmacometrics/clinical pharmacology.	a. <1 year b. 1–5 years c. 5–10 years d. >10 years
2	On average, do pharmacometricians lack strategic/effective communication skills?	a. Yes b. No
3	Rank the importance of the following for effective communication to the drug teams (1 = highest; 4 = lowest).	a. Credibility b. Knowing the audience c. Identifying the key decision d. Impactful presentation
4	What presentation approach do you use for the decision meeting with the drug teams?	a. Deductive approach (decision first followed by the supporting results) b. Inductive approach (objective, methods, results, discussion, conclusion)

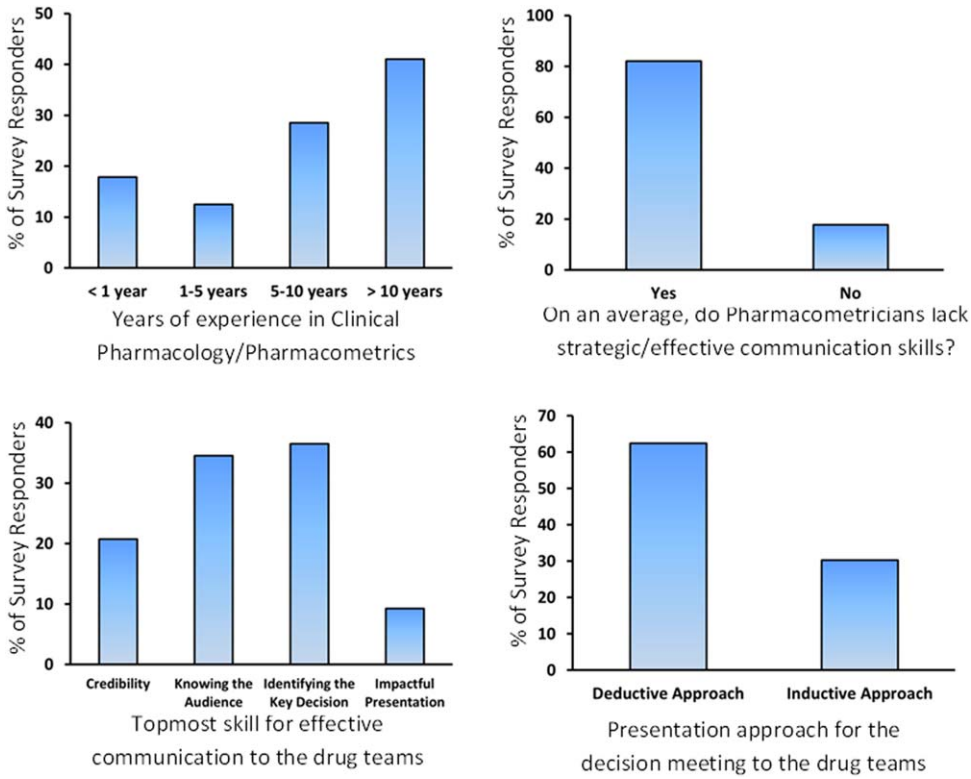

Figure 2 Results of the survey of the current state of effective communication in pharmacometrics.

strategic communication. Credibility can be divided into initial credibility and acquired credibility. The former is the initial perception of the audience even before the communicator starts the presentation, whereas the latter is earned after the communicator has presented. Initial credibility is associated with hierarchical rank, personal rapport with the audience (goodwill), and the communicator's expertise. Acquired credibility is gained by associating with an expert in the field or establishing common ground by associating the decision with regulatory guidance, policy, or law. Acquired credibility is the most powerful asset to influence key decisions. Acquiring credibility is a dynamic process and is attained over time. Pharmacometricians will need to take long-term rapport into consideration over short-term wins.

Establishing common ground enables the team to appreciate the common objective of the team members. For example, when a new drug application is submitted to a regulatory agency, several teams work together to perform the regulatory review. The clinical review team assesses the efficacy and safety information from the registration trials. The statistical review team reviews the primary statistical analysis and conducts other sensitivity analysis, whereas the clinical pharmacology team reviews the clinical pharmacology aspects of the application, including dose selection, exposure-response, etc. The lead communicator should emphasize the common goal for all the teams (i.e., to determine if the drug is safe and effective at the proposed dose and whether it should be approved). Common ground can also be established by providing reference to regulatory guidances and the code of federal regulation that supports the basis of the analysis and recommendations. For example, if the objective is to support the approval of a drug in pediatrics through extrapolation of efficacy, one can quote the regulatory guidance and code of federal regulation related to pediatric approval and regulation to convey the common intention of accelerating the pediatric drug development. Establishing this common intention upfront in the presentation aids in aligning the entire project team towards the main objective and establishes credibility.

Decision

Decision is defined as a tangible outcome of a project. Decision should be clear and actionable and must be placed in the context of drug development, therapeutic, or regulatory perspective. Furthermore, the decision should be stated in simple terms so it is understood by the majority of the project team, in particular the stakeholders. For example, if a project is about conducting an exposure-response analysis with phase II data to select a dose for a phase III trial, the appropriate decision is "X and 2X doses should be taken forward to phase III." In contrast, "Significant exposure-response relationship for efficacy is observed" is a conclusion, not a decision.

"Key question(s)," as the name implies, are the pivotal components of a pharmacometric project and are framed in the context of drug development, therapeutic, or a regulatory decision. Framing the right key question(s) is the backbone of influencing the decision and effective communication. Effective key questions can only be framed by

seasoned drug developers and regulators. It not only helps to send the right message to the audience but is also important for achieving the desired outcome. The key questions should be framed before the start of any modeling exercise. We can certainly have methodological questions in the pharmacometric analysis, but those are not the key questions. In some cases when the goal is peer-to-peer communication, key questions that are quantitative or technical may be desired. When the goal is communicating to an interdisciplinary audience, an objective and/or quantitative approach should be used to frame the key questions. As illustrated later in the example, the key question "Is there a need for dose adjustment of drug X to manage neutropenia in prostate cancer patients with moderate renal impairment" is quantitative in nature. Although in other cases, a key question such as "Should drug X be taken forward to phase III?" is not quantitative in nature. As pharmacometricians, we tend to sometimes get trapped in the technical zone and lose sight of the broader objective. Here are some examples of the key questions. First, from a drug development perspective, if a dose-response trial is conducted, two of the probable key questions might be "Does the drug work?" and "Does exposure-response relationship provide supportive evidence of effectiveness?" In this case, "Is there a statistically significant dose-response or concentration-response relationship?" or "Are there any covariates for the exposure-response relationship?" are not the most appropriately framed key questions. Consider another example; if a drug is eliminated mainly through kidneys and the population pharmacokinetic (PK) analysis is conducted to evaluate the effect of renal function on the PK of the drug, the relevant key question is "Is there a need for dose adjustment in patients with impaired renal function, and if so, by how much?" rather than "Is creatinine clearance a significant covariate on clearance?"

Even though the "key question" and "decision" are linked together, it is important to have clarity on the difference between the two. The right key question lays a strong foundation, whereas the decision is the end goal for a project. Needless to say, the right key question(s) can only be defined if there is clarity on the decision that needs to be reached. In some cases, there may be several key questions that lead to one common decision.

Let us now look at an example from a recent FDA advisory committee for edoxaban, an oral factor Xa inhibitor.[11] The reason the FDA material is used here is that the information is publicly available, unlike private sector company presentations. Edoxaban is approved for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It was observed in the registration trial that a subgroup of patients with creatinine clearance $\geq$80 mL/min had potentially unfavorable efficacy compared to warfarin. Based on the population PK and exposure-response analysis, the FDA clinical pharmacology review team concluded that lack of benefit in patients with normal renal function was due to lower exposures in this subgroup at the proposed dose of 60 mg once daily. Therefore, a dose of higher than 60 mg (which was not evaluated in clinical trials) may be needed to match the exposures in this subgroup of patients to those observed with mild renal function, thus potentially increasing efficacy. One of the key questions framed for the advisory committee panel members was the following: "If edoxaban was approved, would you recommend that a dose higher than 60 mg daily be marketed for patients with normal renal function, based on analyses of the relationships between edoxaban serum concentrations and the major efficacy and safety outcomes in ENGAGE AF?"[12] It is worth noting that exposure-response analysis and projecting efficacy and safety at higher doses using model-based simulations were pivotal to address this issue. However, the key question was clear and actionable and was related to the approval of a higher dose. In this case, the FDA decided that edoxaban should not be approved in patients with creatinine clearance $>$95 mL/min because the benefit/risk profile did not favor use of edoxaban in this patient population.[13]

Style

There are two common ways a message can be communicated, deductive and inductive. A deductive approach focuses on stating the conclusions upfront, whereas in the inductive approach, the thought process or the method is stated first followed by the conclusions. The deductive approach focuses on the decisions, whereas the inductive approach focuses more on the scientific methods. The inductive approach is what we teach during graduate training. In fact, most educational institutions have a rigid template that forces students to state the objective, methods, results, and then discussion. In addition, most scientific journals do not accept manuscripts if the authors do not follow this requirement. The insistence on an inductive approach is apt for communicating technical details, as the focus is "the model." This style is unfit for influencing key business decisions. In fact, it guarantees failure. It is possible that, in some business environments, the inductive approach may be preferred for communication. However, in general, we recommend that pharmacometricians use an inductive approach when the goal is to gain concurrence on the model and to use a deductive approach when the purpose is the decision. The latter approach makes sense from the point of view of the team member's psychology. The audience's attention span is greatest at the beginning and at the end of a presentation.[10] Therefore, following a deductive approach (i.e., stating the decisions upfront and reemphasizing at the end of the presentation), enables the audience to focus. This approach will aid the communicator to achieve the desired response.

The communicator can use different approaches in terms of style to deliver the key message. The four key communication styles are: (1) tell; (2) sell; (3) consult; and (4) join.[10] The first two communication styles are generally followed if the communicator has enough information regarding the project and wants to control the message. The latter two communication styles are more collaborative and are followed when the communicator needs input from other team members to make a decision. From a drug development and regulatory perspective, the "consult and join" approach is recommended as individual team members may not have sufficient information about the drug and, thus, the decision is made by an interdisciplinary team.

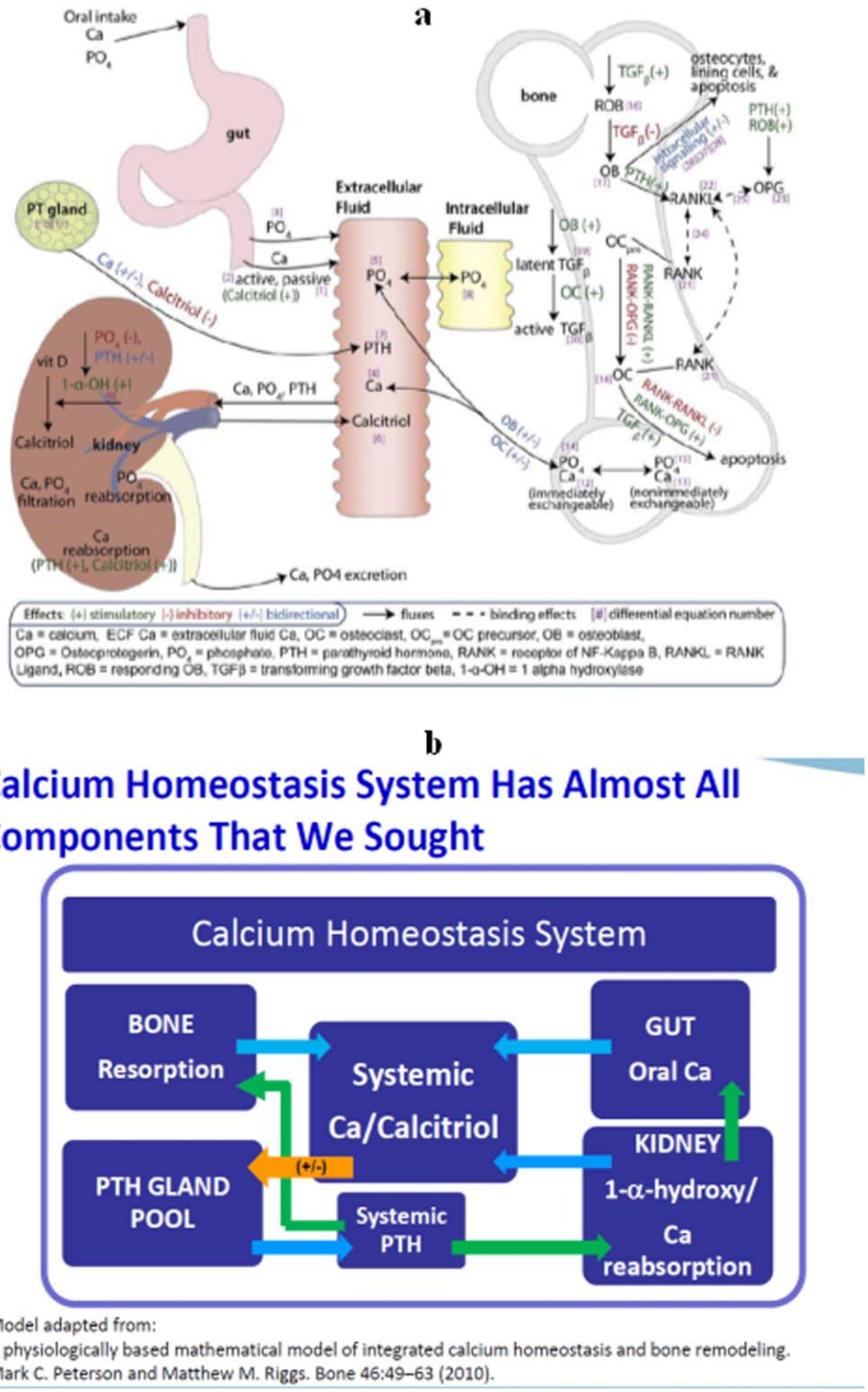

Figure 3 Description of the physiologic systems model (**a**) with details to describe calcium homeostasis and bone remodeling[15]; (**b**) simple schematic representation of the model[14] tailored for the audience.

Knowing the audience

Understanding the audience is also an important criterion that helps to frame pharmacometric reports and presentations. There are three key aspects of knowing the audience: (1) who are they; (2) what are their expectations; and (3) what will persuade them.

Attention should be paid to understanding the expertise and background knowledge that the audience possesses

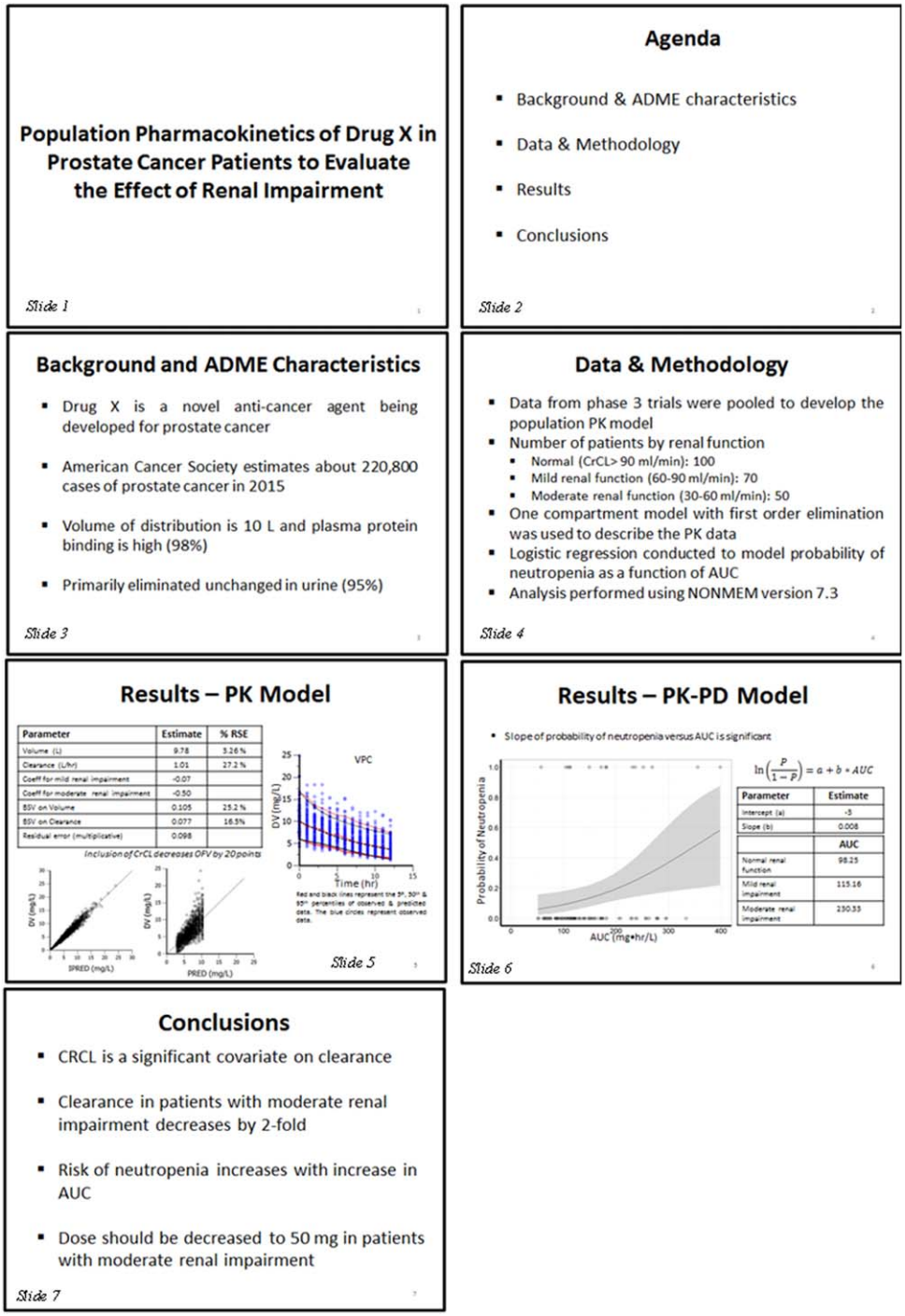

Figure 4 Presentation A, an example of ineffective presentation. ADME, absorption, distribution, metabolism, and excretion; AUC, area under the curve; CrCL, creatinine clearance; PD, pharmacodynamic; PK, pharmacokinetic.

regarding the topic. This information will help determine what necessary background material to include in the report or to mention while presenting. For example, if the intent is peer-to-peer communication, then including details pertaining to model building and methodology is critical for effective communication. However, when the goal is to present to an interdisciplinary audience, pharmacometricians in particular have to be cognizant of team members who do not have similar mathematical or quantitative expertise. Thus, it is in the interest of the presenter to include limited technical details in the presentation. In such cases, we should never communicate models but instead focus on responses to key questions to support the final decision. In addition, it is critical to know the decision-maker in the

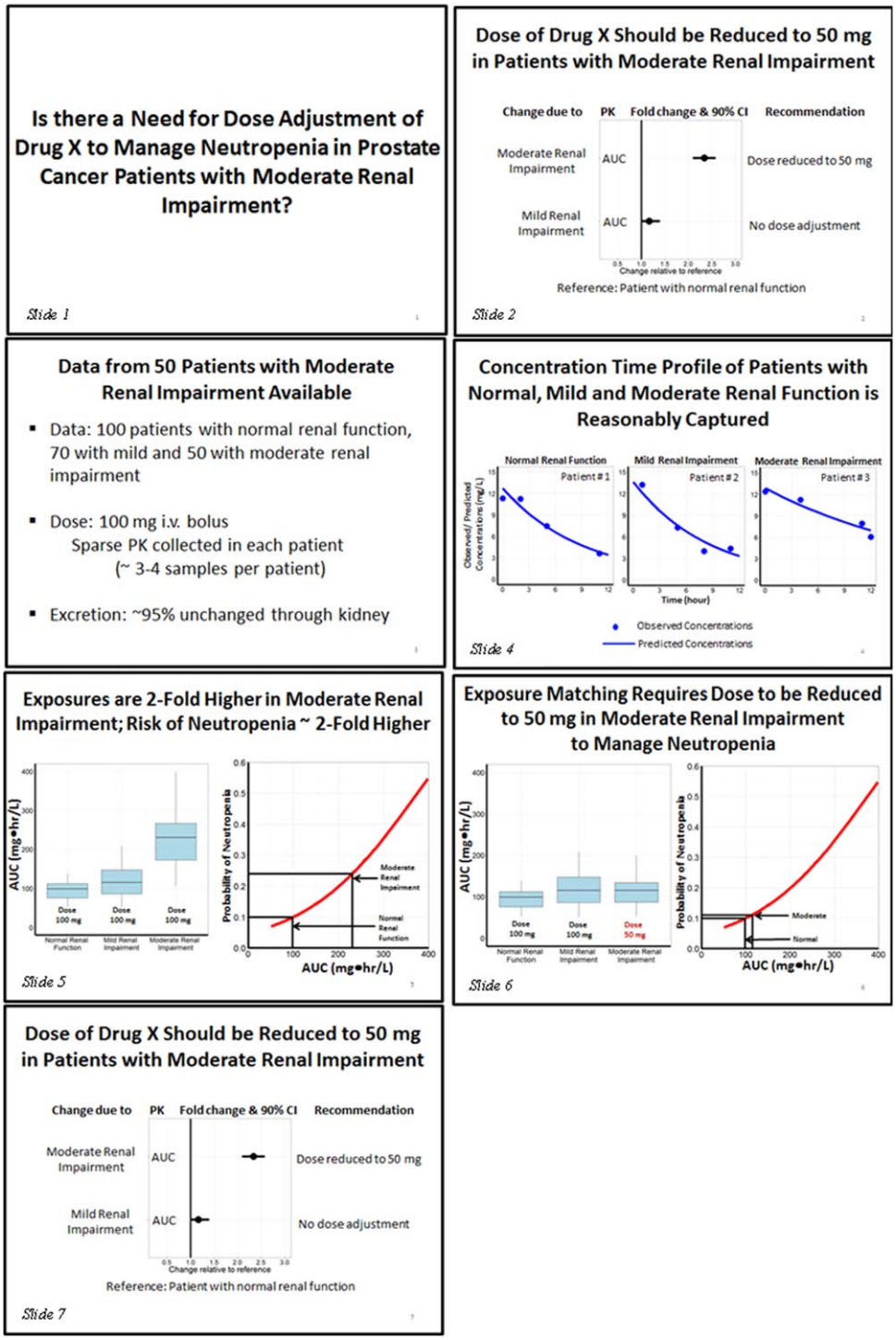

Figure 5 Presentation B illustrates principles of effective communication. AUC, area under the curve; CI, confidence interval; PK, pharmacokinetic.

audience, the person sometimes referred to as the highest paid person's opinion (HIPPO).[9] The audience can be persuaded by either highlighting the tangible audience benefits or establishing credibility.

At a recent Endocrinology and Metabolic Advisory Committee meeting for a recombinant human parathyroid hormone, the FDA's clinical pharmacology presentation seemed to be geared towards clinicians.[14] Although the FDA utilized a complex system pharmacology model[15] to address the key question pertaining to the dosing regimen, none of the details regarding modeling were presented at the advisory meeting. In fact, the complex mathematical

model (**Figure 3a**) with equations was modified to a simple conceptual figure (**Figure 3b**) that could convey the message to the clinicians.[14] The presentation instead focused on the available data, concept of modeling, results, and recommendations. This might have helped the clinicians at the meeting to appreciate and acknowledge the recommendations made by the review team. The FDA concluded that the dosing regimen of the human parathyroid hormone should be further optimized in a postmarketing trial to provide better control on hypercalciuria while maintaining normocalcemia.[16]

EXAMPLE OF EFFECTIVE COMMUNICATION

We have chosen a hypothetical example to illustrate the concept of effective communication through a presentation. Let us assume a pharmacometrics project is undertaken to assess the effect of renal impairment on the PK of drug X. The key decision is to determine if the dose should be adjusted in patients with moderate renal impairment and by how much. Shown below are two ways of presenting the results to an interdisciplinary audience. Presentation A is an example of the presentation not being tailored to the audience (**Figure 4**) and most likely being ineffective, whereas presentation B (**Figure 5**) is decision-oriented and follows the principles of good communication, as described in this tutorial. It is worth noting that, for the most part, all the pieces of information that are needed for the key decision are in both presentations, however, the organization of the content and the message delivery is substantially different between them.

1. The title of presentation A does not state the key question, whereas presentation B's title directly addresses the key question at hand.
2. Presentation B follows a deductive approach where the decision is communicated to the audience upfront followed by the supporting information and analysis. In presentation A, the audience has to wait until the end of the presentation to understand the implications of the analysis.
3. Presentation B uses graphics to convey the key messages regarding recommendations and results. For example, slide 2 uses a forest plot to display the change in exposure and dosing recommendations concisely on the same slide. However, presentation A states the recommendations as bullet points that the audience has to read and interpret in relation to the analysis performed.
4. Presentation B's slides have high skim value, whereas presentation A has text written on the slides that can be distracting to the audience. The information about the number of prostate cancer cases and the volume of distribution on slide 2 of presentation A is not relevant. Presentation A describes "methods" that include the information about the structural PK model, software, etc. This information may be important when we are communicating technical aspects of the project to peers, but is of little value to an interdisciplinary audience. Instead, slide 3 in presentation B shows three main aspects that are most relevant for the audience to understand the dosing recommendations: (1) availability of sufficient data across renal impairment categories; (2) type of data collected; and (3) the elimination mechanism of drug X.
5. Presentation A includes a table of the PK parameters and diagnostic plots to depict the validity of the model. Instead, the individual level predictions, illustrating that model captures the data reasonably well in patients with varying degrees of renal function, is more useful as shown on slide 4 of presentation B. Presentation A used modeling jargons, such as DV, PRED, and IPRED, which are difficult for an interdisciplinary audience to understand.
6. Presentation A shows a sophisticated logistic regression plot, displaying events/no events data as open circles and the probability of neutropenia as a solid line. It may be difficult for the audience to understand the relevance of individual data shown in the plot. Furthermore, the predicted area under the curves for each renal function group is shown in a table. Thus, the audience has to project the probability of neutropenia for each area under the curve value based on the graph and the table. In presentation B, the area under the curve for each renal function group is depicted as a box plot, and the corresponding probability of neutropenia is compared using a graph (slide 5). Such graphical representation is easier for an audience to understand. Immediately following slide 5, the implications of a dosage decrease on exposure and toxicity in patients with moderate renal impairment is depicted on slide 6. This helps the audience appreciate the need for dose reduction in patients with moderate renal impairment.
7. Another important feature of presentation B is that the take-home message appears on each slide as a title compared to conventional slide titles such as Background, Results, and Conclusions, as seen in presentation A.
8. Presentation B reinforces the decision again at the end of the presentation to remind the audience about the dosing recommendations in patients with moderate renal impairment.

CONCLUSION

In summary, apart from technical and drug development skills, effective communication is critical for a pharmacometrician to be influential. We propose four tenets for effective communication: "Credibility, Decision, Style of Communication, and Knowing the Audience" (CDSK) to influence drug development or regulatory decisions. Some real-world and hypothetical examples are presented to illustrate the concepts of effective communication. Usually, little emphasis is placed on the concept of communication to influence decisions. This tutorial highlights core principles of effective communication for a pharmacometrician.

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