Commentary

Clinical Pharmacology Knowledge, Opportunities and Working Strengths (CPKNOWS): a competency model for pursuit of excellence in clinical pharmacology

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How does one define the discipline of clinical pharmacology? This has been a subject for much debate in recent literature [1–5]. The historical discipline of clinical pharmacology is one of integrating information across disciplines, requiring a broad knowledge base in several areas and the ability to synthesize and apply a ‘full picture’ from the parts. Can a discipline whose strength comes from cross-discipline knowledge survive when the complexity of disciplines over which one must integrate information is rapidly expanding?

While such debate is critical to ensuring the continued growth and differentiation of clinical pharmacology as a discipline, a lack of clarity within an organization with regard to the scope of expertise and resulting responsibilities for a functional department can be problematic. Without a universally accepted definition of what a clinical pharmacologist (CP) is/does, how does an industry clinical pharmacology department ensure that staff are engaging in development activities that will contribute to the future success of both the individual and the department as a whole? Honig [2] suggests that a prevailing definition of clinical pharmacology is the ‘reductionist definition that distills clinical pharmacology to being whatever is done by those who declare themselves to be clinical pharmacologists’. From a departmental perspective, the importance of projecting an unambiguous definition of the role of clinical pharmacology as well as the expectations for an individual who fills this role to both departmental staff and key development partners within a company is paramount to the department’s success within the organization. Failure to do so can dilute the overall role of the department, and potentially lead to key decisions being taken without full utilization of company expertise.

Most companies invest in staff development to build company expertise and maintain a competitive advantage. In the past at Roche, this typically consisted of an annual training plan that was the result of a one-to-one dialogue between manager and staff. Both external training programmes and on-the-job opportunities would be discussed in the context of the individual’s current position and responsibilities and personal career interests. The employee would then prepare and execute an ‘Education and Development’ plan over the course of the annual cycle, and the process would then repeat itself. The drawbacks to such a system are severalfold. Gaps between individual skill sets and required skill sets for a given departmental role were difficult to quantify, assessment of an individual’s professional growth at the end of a review cycle was largely subjective and not referenced against any set baseline, and the alignment of the collection of individual development plans with long-term departmental growth goals designed strategically to address organizational models and/or changing paradigms for drug development were difficult to assess. Perhaps one of the biggest drawbacks is that the approach above can lead to a lack of continuity in development plans for an individual because of the lack of means to track long-term progress along a development pathway objectively. Effective development plans should be considered over the course of several years rather than in isolation, a year at a time.

We present a competency model-based staff development method that defines the core expertise areas for clinical pharmacology as practised at Roche, and provides a mechanism for staff to assess and plan their personal development in the context of what is required for the role, both currently and in the future. Key emphasis is placed on

meshing the career interests and needs of the individual to those of the department. Realized benefits, as well as challenges in the development and implementation of the method, are presented with feedback from management and staff after 1 year of use.

Competency models have a rich history in the education literature [6, 7]. A competency model refers to the collection of skills, knowledge and behaviours required to perform a specific role in an organization effectively. The Clinical Pharmacology Knowledge, Opportunities and Working Strengths (CPKNOWS) method is a competency model with the added feature of a clear graphical means to communicate where individuals stand with respect to organizational expectations and vision. The methodology consists of the following three basic components: (i) defined core knowledge areas for CPs with subtopics that can be assessed and rated; (ii) a rating scale that allows scoring of individual expertise on a given topic; and (iii) a graphical means to represent the data on an individual as well as a departmental level.

In Roche, clinical pharmacologists are members of the project team from before candidate selection to the end of the product life-cycle, contributing to many development activities and decisions. The department of clinical pharmacology's lead team convened over the course of several meetings to define a set of 'core' knowledge areas where CPs were expected to have some level of expertise to meet the requirements of the CP role. Of key importance is the concept that what is being developed with this step is a comprehensive list of knowledge areas that define the role of the clinical pharmacologist specifically as practised at Roche, both now and in the future. The question of 'What expertise must we have now, and what expertise must we develop to remain successful in the future?' was iteratively discussed during this step. It is recognized that clinical pharmacology is a broad and diverse discipline and that it is unlikely and unnecessary to have individuals considered as experts in all areas. Rather, this exercise defines the area of minimal core competency, with the understanding that depth of expertise will vary between individuals.

An extensive list of subtopics was then prepared for each core knowledge area and, for each subtopic, a description of the specific topic with examples of 'on-the-job' application was prepared. The examples of applied knowledge were helpful both in further characterizing the description of the specific topic and in guiding the rating of expertise for a given individual. Core knowledge areas are summarized in Table 1.

A five-point competency scale, adapted from Dreyfus and Dreyfus [8] was used to rate individual staff on each subtopic within a given knowledge area. The possible scores assigned were as follows: 1, beginner; 2, experienced beginner; 3, practitioner; 4, experienced practitioner; and 5, expert (Table 1). The basic premise of this rating scale is that knowledge of a topic alone does not make an indi-

vidual competent to perform a given role. The ability to perform in a given role (e.g. a project team CP) requires a combination of knowledge, skills and behaviours, the latter two of which are primarily gained through practice and experience. Progressing from beginner to expert, the individual moves from a very rule-based, inflexible manner of approaching a situation, to one of full situational awareness where appropriate actions are taken intuitively. At the highest level, the individual is able to react to a situation without paying conscious attention to the situational components, rather focusing all thought on producing an instantaneous appropriate action [8]. Implicit in the use of this rating scale was that the rating of 5 would be granted only if an individual is a widely recognized authority on a particular topic. Examples of common situations with the expected behaviour for each rating, were prepared for use as a guideline in assignment of scores to individuals.

Scoring of an individual for a given knowledge area subtopic was left to the discretion of the manager and included a two-way dialogue with the staff member being scored. In practice, employees first completed a self-assessment and then discussed their scores with their manager, who would lead the career development dialogue, discuss alignment of personal goals with departmental vision, and adjust scoring as necessary to help ensure that scores were being applied consistently across the group.

A custom spreadsheet was designed in Microsoft Excel (Microsoft Excel 2010 v14, Redmond, Washington, USA) for collection of assigned scores during one-to-one staff development meetings. Knowledge area subtopic scores were averaged to obtain a single score for a given knowledge area. These composite knowledge area scores were then plotted on a matrix or 'star' plot containing one 'spoke' or 'vector' for each knowledge area. This plot was referred to as the 'competency matrix'. Individuals were therefore able to see the 'shape' of their competency matrix and immediately identify weak and strong areas in the context of departmental expectations.

Scores for the entire department were then summarized in an Excel spreadsheet, from which different views of the data could be created to assess individual and group progress by year, progress along vectors identified as critical development areas for the department, group-to-group comparison, etc.

The method was rolled out to the department through a series of presentations that described the method, the anticipated benefits to both individuals and the department, and the reassurance that the tool was developed purely to facilitate personal and professional development of staff. While gains in personal development would be expected to correlate with performance measures, department leadership agreed that the approach was not intended to replace or compete with the existing standardized performance management process in use by the global organization.

Table 1

Competency matrix knowledge areas

Area	Knowledge
Biopharmaceutics and drug disposition	<p>Physicochemical characteristics of drug substance, e.g. solubility, acid–base balance, lipophilicity, permeability, particle size, crystal form, surface activity, chemical and physical stability, BCS categories, and their impact on ADME characteristics</p> <p>Deep knowledge of the various enzyme and transporter systems involved in drug disposition, along with the known genetic polymorphism in their expression</p> <p>Drug–drug and drug–disease interaction in all relevant ADME phases of drug disposition</p> <p>Understanding of preclinical ADME properties, toxicokinetics and allometric scaling and using that information to build the components of an early clinical pharmacology development programme</p> <p>Understand when low bioavailability is related to poor absorption, high first-pass elimination, or both, and address each situation</p> <p>Understand release characteristics of drug products and the potential use of IVVC to guide bioequivalence determination or waiver requests</p> <p>Familiarity with the relationship between chemical structure and activity, toxicity and biotransformation, including active metabolites, covalent binding and repercussions of disproportionate metabolites</p> <p>Understand issues specific to large-molecule development, e.g. impact of route of administration, target-mediated disposition, antidrug antibodies and target expression level on the pharmacokinetics and pharmacodynamics</p> <p>Understand issues and challenges associated with various large-molecule constructs, such as antibody fractions, antibody conjugates, multispecific and/or multivalent antibodies, oligonucleotides</p> <p>Familiarity with the <i>in vitro</i>, <i>in vivo</i> and <i>in silico</i> methods to predict metabolism and drug interactions in man</p> <p>Life-cycle strategy with improvement in biopharmaceutical properties and integrating with IP strategy</p>
Pharmacology and biomarkers	<p>Drug–target interaction</p> <p>Receptor affinity, reversibility, specificity, potency</p> <p>Relevance of mechanism of action to desired clinical outcome in the target indication</p> <p>Measures of pharmacological action and effect (on target and off target; desired and toxic)</p> <p>Understanding of drug- and disease-related biomarkers (molecular, cellular, genetic, histological and functional disease markers) and the spectrum of their application (predictive, diagnostic, prognostic, marker for response/toxicity)</p> <p>Understanding of the various methods for assessment of drug action and effect in humans</p> <p>Understanding of the learn–confirm paradigm in the context of the discovery, optimization, implementation and validation of biomarkers during nonclinical development, translational phase and early and late clinical development</p> <p>Understanding of the statistical, pharmacological and disease-related aspects of the ‘fit-for-purpose’ use of biomarker results for internal decision making vs. regulatory submission</p>
Quantitative concepts and methods in clinical pharmacology	<p>Knowledge of the various methodologies for M&S of the exposure–response relationship that can support development decisions, including the concepts behind them and how they may help to characterize the dose–response and exposure–response behaviour of the molecule (both desired and undesired effects)</p> <p>Knowledge of the limitations and potential pitfalls of the various methods and how they might lead to mischaracterization of the molecule is essential. Included in this would also be the ability to assess the probability of acceptance of a given approach by health authorities</p> <p>Ability to identify and concisely describe the issues that are of concern for the discussion of the exposure–response relationship, and critically evaluate the elements of the study design that are necessary to facilitate the quantitative analysis by M&S (single study vs. pooled data from multiple studies vs. other approach)</p> <p>Proficiency in techniques for data visualization for exploratory analysis, e.g. detection of patterns and correlations, identification of subpopulations</p> <p>Working knowledge of the various methods of data analysis, both individual and population based</p>
Nonclinical and clinical drug safety	<p>Knowledge of the preclinical toxicology and safety pharmacology (<i>in vivo</i> and <i>in vitro</i>) requirements for human dosing based on the relevant regulatory guidance and as driven by the nonclinical properties of the molecule</p> <p>Selection and justification of the formulation, dose/dosing regimen and species for <i>in vivo</i> preclinical toxicology and safety pharmacology</p> <p>Estimation of the relevant/required doses and exposures for toxicology studies and concentrations for <i>in vitro</i> screens</p> <p>Interpretation of the relevance of results of the preclinical toxicology and safety pharmacology (<i>in vivo</i> and <i>in vitro</i>) for the use of the IP in humans</p> <p>Understanding the safety margin and therapeutic index relative to the starting human dose/exposure, the target efficacious human dose/exposure and the potential effects at the expected human doses/exposures above the NOAEL</p> <p>Differentiation between the on-target and off-target effects; interpretation of the likely mechanism of toxicity, its causality and predictivity for occurrence in man</p> <p>Safety assessment in clinical studies, interpretation of results and their relevance for the risk–benefit ratio, regulatory expectations and the competitiveness in the marketplace</p>
Disease area and medical practice	<p>Disease definition, aetiology, pathophysiology, genetic variants (if any) and the spectrum of clinical phenotypes, incidence and prevalence, socio-economic and demographic risk factors</p> <p>Key parameters for diagnosis and monitoring of temporal changes (disease progression/oscillation)</p> <p>Main tools and techniques used for measurement of disease status, classification and subclassification</p> <p>Markers of disease activity or response to pharmacological intervention used in clinical studies, their variability and utility as biomarkers of drug response (validation status as surrogates of the clinical outcome)</p> <p>Main treatment options (pharmacological and nonpharmacological), indications, contraindications, mechanism of action, adverse effects and limitations</p> <p>Primary research areas for new treatment modalities, and justification (newly discovered disease pathways, new technologies, etc.)</p> <p>Ability to consider the impact of disease variability on drug action and of drug variability on disease, and how each could affect the risk–benefit for the chosen dose/dosing regimen. The clinical pharmacologist should be able to assess the relevance of the variability in drug response for its potential to have desired efficacy and acceptable safety in the associated variants of the disease state encompassed in the target indication for the drug</p>

Table 1

Continued

Area	Knowledge
Clinical trial methodology	Knowledge of all possible design options for clinical pharmacology studies in healthy volunteers and patients across all phases of clinical drug development, including their strengths and limitations Knowledge of the regulatory requirements and expectations for the above Familiarity with the investigators' and IRB/EC preferences regarding study design that would influence the feasibility of the study and/or the selection of the inclusion/exclusion criteria Knowledge of the Clinical Operations and Data Programming requirements for the design, set-up, conduct and reporting of clinical pharmacology studies Strong background in statistical concepts related to the design and interpretation of clinical pharmacology studies Mandatory knowledge of GCP for the Clinical Investigators and the Declaration of Helsinki
The drug development continuum	Familiarity with the format and content of the regulatory dossiers at different regulatory milestones for all phases of drug development, pre-IND/CTA to label Familiarity with internal and regulatory decision-making requirements to move a drug candidate from one developmental phase to the next Knowledge of ICH and GCP requirements Familiarity with agency (US and non-US) guidance relevant to clinical pharmacology Paediatric development (bridging strategies, special considerations for paediatric development, etc.) Ethnic/Asian bridging (ICH E5 and internal working practices) Cardiovascular safety assessment (ICH E14, ICH S7B and internal working practices)

Abbreviations are as follows: ADME, absorption, distribution, metabolism, excretion; BCS, biopharmaceutics classification system; CTA, clinical trial application; EC, ethics committee; GCP, good clinical practice; ICH, International Conference on Harmonization; IND, investigational new drug; IP, investigational product; IRB, institutional review board; IVIVC, in vitro in vivo correlation; M&S, modeling and simulation; NOAEL, no observed adverse event level.

Figure 1

Example competency matrix showing an individual staff member's development progression along knowledge area 'vectors' over a 1 year time frame. ■, 2010; ■, 2011

Figure 1 shows an example competency matrix plot of a mid-level scientist in the department over the evaluation periods of 2010 and 2011. One can immediately see that this staff member, whose education and development plan for 2010 focused on the area of 'quantitative concepts and methods in clinical pharmacology', showed noticeable progress in that area. Departmental development progress could be examined in a similar manner (data not shown).

Matrix representation provided an effective and flexible means for examination of different cuts of data (e.g. by year, by staff position), leading to more concrete discussions on how to drive staff development in critical areas more effectively.

Feedback on the method was collected in an informal manner through several discussions with junior staff, as well as managers who were not involved in the develop-

ment of the method. Upon initial implementation of the method, feedback from both staff and managers was mixed. There was anxiety among staff around the concept of being 'scored' in terms of their competency and that the information could be used for comparative or more formalized performance-management purposes involving promotion and pay decisions. There was also considerable criticism of the apparent subjective nature of the scores and the possibility for between-manager variability in scoring. The staff did, however, immediately appreciate the clarity with which potential development areas were identified, particularly in comparison to the previous education and development process. Planned development activities were always mutually agreed upon with major emphasis on the career interests of the individual staff member. Some managers shared the concerns described above, but appreciated how the method very clearly identified the expected skill sets of the individual and aligned them with the goals and vision of the department. Use of the standard spreadsheet for collection of scores allowed them to follow a guided and complete discussion on personal education and development with their reports. While not an intended use, one manager reported using the assessment spreadsheet during evaluation of applicants for positions within the department.

The CPKNOWS method has allowed us to align staff development better and more transparently with departmental needs both present and future, to represent individual strengths and weaknesses more clearly with respect to the expectations of the role of CP at Roche, to engage in more focused discussion around staff development activities, and to track progress on development activities more objectively at both an individual and a departmental level. We developed this methodology for application to the clinical pharmacologist role as practised at Roche. The method is easily adaptable to other roles/disciplines by modifying the knowledge area topics and subtopics accordingly.

The approach has also provided utility beyond individual and departmental staff development. Effectiveness of focused training initiatives can be assessed objectively on a continuous long-term basis, providing support for decisions to invest in more training vs. recruit new expertise into the department. In this manner, the method indirectly provides managers with the opportunity to measure their own effectiveness as 'staff developers', a perspective that we were not able to evaluate in the past.

A major limitation to the approach is that it does not attempt to capture the critical 'soft skills' required to be effective in a position where one's primary role is to influence rather than to direct others. Effective 'audience-specific' communication skills, negotiation and conflict-management skills, a mindset that embraces partnership and collaboration, and awareness and respect of cultural differences between individuals are only a few of the areas where an individual needs to excel in order to be effective

in such a leadership role. Based on the success we have had with the current implementation, we are in the process of developing an additional method to capture and develop these leadership/behavioural aspects of staff competency further.

Competing Interests

All authors were employees of Roche during the development of this methodology. There are no other competing interests to declare.

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