White paper: Landscape on technical and conceptual requirements and competence framework in Drug/Disease Modeling & Simulation

Supplementary material

Results - Subgroup analyses

Domain I: Impact and benefit of DDM&S within organizations

A subgroup analysis for the two levels of M&S expertise, the Juniors and Seniors, reveals that in both organization (Academia and Pharma), throughout the entire drug development process and therapeutic usage Seniors see a higher impact of DDM&S. In particular, activities requiring a broader knowledge of the drug development process and strategic responsibilities in Pharma (e.g. approval of new drugs/decision-making/translational and line extension modeling) are related to a higher level of expertise (Figure 2 suppl.).

Domain III: Concepts, methodologies and tools utilized for DDM&S

There is a large variety in the nature of models developed and methodologies and data used for development (Figure 6 suppl.). Both in Academia and Pharma, a large number of models are developed for continuous single drug data with nonlinear mixed-effects modeling methodology using ordinary differential equations to characterize/predict the pharmacokinetics and efficacy in a clinical setting, but this is by no means exclusive.

Overall, within the DDM&S community the recognition and impact of concepts, methodology and software applications of systems biology seem low. However, it has to be considered that responders from systems biology might have been underrepresented in our survey, despite the questionnaire having been disseminated to a wide audience of the DDM&S community. Technical and conceptual knowledge as well as incorporation of systems biology into an overall drug development framework and the decision-making process seem of interest for the stakeholders.

Domain IV: Gaps for and personal challenges with DDM&S

After stratification for M&S level of expertisethe responses about gaps in DDM&S environment reveal remarkable differences between Juniors and Seniors as shown in Figure 4. While the need of better performance tools, education and training remains the primary gap for Juniors, Seniors identify the lack of common tools for DDM&S and the lack of resources as the most important gaps in the implementation of DDM&S. As the questionnaire did not further specify the 'lack of available resources', one might hypothesize that this term might cover different issues for Juniors and Seniors, the latter being more aware of a potential need for well-qualified personnel.

The overall personal challenges within DDM&S activities appear more prominent to Juniors (Figure 9 suppl.) although it is worth mentioning that Seniors also face personal challenges and they support the need for training and education.

Domain V: Willingness to share data for education & training purposes

Education and training highly benefit from implementing drug and disease models based on real-life data. Whereas the vast majority of responders is willing to share published models (85%) and data (79%), the majority is, however, unwilling to share unpublished ones (models: 55%, data: 65%), even for education and training purposes. Nevertheless, this implies that setting up a repository with real-life data is a viable goal within the DDMoRe project, and a goal which will help to develop applied competences in DDM&S.

Additional analyses of responses of the population of Reviewers and Appliers

Ten (n=10) responders defined themselves as primarily Reviewers, including one who also responded in a Modeller capacity, and all were from Pharma. Qualitatively their answers

were comparable to the Pharma group of Modellers/Multi, as can be seen from the Supplementary material Figures 12-15 suppl., to be compared with Figures 1, 3, 4 and 5.

A majority used DDM&S frequently for decision making, dose selection (n=8) and understanding of drug characteristics (n=6), and occasionally for methodological research, individualization of therapy and understanding of disease characteristics (n=6), a similar pattern to the one observed in Figure 1 for Pharma. The Reviewers were also heavily involved in population analysis (n=6 frequently), drug model development and clinical trial simulation (n=5 frequently). They identified lack of resources, training and education as major and minor gaps, and similar challenges in their reviewing of DDM&S activities. However, only 2 responders in this population stated they would attend training in other DDM&S activities, and their preferred way of dealing with challenges in reviewing was to ask for someone to help them (n=8). Taken together these two answers might indicate positions of management with little time to spare, but the population is too small for these results to be anything other than indicative.

The population of responders who defined themselves as pure Appliers was very small (n=6, with n=5 from Pharma). Many people who apply results from DDM&S are also involved in actual modeling activities, as shown by the fact that the two most important populations in our study were Modellers (n=84) and people who engaged in all three activities (n=35). All 6 Appliers were involved in the evaluation of safety and efficacy, with dose selection and clinical trial simulations performed each by 4 responders. This population responded more often by 'occasionally' on the different questions on DDM&S usage and methodology, suggesting less daily involvement in these activities compared to the other populatons, but due to the small size of this population no definite difference can be inferred.

Materials and Methods

To identify both technical and conceptual requirements for effective decision-making and knowledge integration management and develop of a competence framework, as first step a survey was performed.

Survey and Data analysis

The test-run was already performed using the online system SurveyMonkey®. If the first five compulsory questions were incomplete the responder was prevented from proceeding, whereas all following questions allowed responders to leave incomplete responses.

For analysis of free text responses (being graphically illustrated by using word cloud graphs) manual retransformation was performed in case of spelling or grammar differences, e.g. modelling/modeling; drug/drugs, understand/understanding.

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Supplementary material

Figure Legends

Figure 1 suppl.: Distribution of DDM&S activities in the targeted population; the figures represent the number of responses of the following categories:

◾Modellers in Academia, ◾Modellers inPharmInd, ◻ Modellers in SME;

◾ Multi in Academia, ◾Multi in PharmInd,◻Multi in SME;

◾Appliers in Academia,◻Appliers in PharmInd,◻Reviewers in PharmInd

Thecategories sticking out the pie chart were not included in the main analysis but in the additional analyses.

Figure 2 suppl.: Impact of DDM&S activities in the drug development process and therapeutic usage for (**a**) Juniors in Academia [n=35], (**b**) Seniors in Academia [n=38], (**c**) Juniors in Pharma [n=10] and (**d**) Seniors in Pharma [n=38]; ◉ frequent, ◎ occasional, ○ never

Figure 3 suppl.: World cloud: benefit of DDM&S in the organization/projects/collaborations of all responders (n=121)

Figure 4 suppl.: Methodological DDM&S concepts by (**a**) Juniors in Academia [n=35], (**b**) Seniors in Academia [n=38], (**c**) Juniors in Pharma [n=10] and (**d**) Seniors in Pharma [n=38];◉ frequent, ◎ occasional,○ never (multiple answers possible)

Figure 5 suppl.: Utilization of optimization methods within (**a**) Academia [n=78] and (**b**) Pharma [n=43]; ◕ frequent, ◐ occasional, ○ never(multiple answers possible)

Figure 6 suppl.: Nature of (**a**) models, (**b**) methodological concepts, (**c**) data, and (**d**) area/setting for □ Academia [n=43], ■Pharma [n=78](multiple answers possible)

Figure 7 suppl. : Utilization of DDM&S applications within (**a**) Academia [n=78] and (**b**) Pharma [n=43]; ◕ frequent, ◐ occasional, ○ never(multiple answers possible)

Figure 8 suppl.: Gaps by (**a**) Juniors in Academia [n=35], (**b**) Seniors in Academia [n=38], (**c**) Juniors in Pharma [n=10] and (**d**) Seniors in Pharma [n=38]; ■ major, □ minor, □ none(multiple answers possible)

Figure 9 suppl.: Challenges of (**a**) Juniors in Academia [n=35], (**b**) Seniors in Academia [n=38], (**c**) Juniors in Pharma [n=10] and (**d**) Seniors in Pharma [n=38]; ■ major, □ minor, □ none (multiple answers possible)

Figure 10 suppl.: Means/options to deal with challenges□Juniors [n=45], ■ Seniors [n=76](multiple answers possible)

Figure 11 suppl.: Domains of landscape of technical and conceptual requirements for effective decision making and knowledge integration management utilizing DDM&S

Figure 12 suppl.: Impact of DDM&S activities in the drug development process and therapeutic usage for Reviewers [n=10];◓ frequent, ◔ occasional, ○ never (multiple answers possible)

Figure 13 suppl.: Methodological DDM&S concepts by Reviewers [n=10]; ◓ frequent, ◔ occasional, ○ never (multiple answers possible)

Figure 14 suppl.: Gaps by Reviewers [n=10]; ◩ major, ◻ minor, ◻ none (multiple answers possible)

Figure 15 suppl.: Challenges of Reviewers [n=10] ;◩ major, ◻ minor, ◻ none (multiple answers possible)