Why has model-informed precision dosing not yet become common clinical reality?

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Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future

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ABSTRACT

Patient groups prone to polypharmacy and special subpopulations are susceptible to suboptimal treatment. Refined dosing in special populations is imperative to improve therapeutic response and/or lowering the risk of toxicity. Model-informed precision dosing (MIPD) may improve treatment outcomes by achieving the optimal dose for an individual patient. There is however relatively little published evidence of large-scale utility and impact of MIPD, where it is often implemented as local collaborative efforts between academia and healthcare.

This manuscript highlights some successful applications of bringing MIPD to clinical care and proposes strategies for wider integration of MIPD in healthcare.

Considerations are brought up herein that will need addressing to see MIPD become 'widespread clinical practice': amongst those, wider interdisciplinary collaborations and the necessity for further evidence-based efficacy and cost-benefit analysis of MIPD in healthcare. The implications of MIPD on regulatory policies and pharmaceutical development are also discussed as part of the roadmap.

PRELUDE

This article appears in the so called 'State of the Art' section of the journal. 'State of the Art' is often considered to be cutting edge and the highest level of development in a given area. However, coining something as 'State of the Art' is a subliminal admission to the fact that the subject area has not yet become 'popular'. This article is a culmination of discussions and debates between many key opinion leaders, beyond the authorship, on the issue of model-informed precision dosing (MIPD), and why it has remained and is treated as 'State of the Art' rather than being used as 'widespread' clinical practice. It is hoped that the report provides a roadmap to advance the position of MIPD to a common clinical practice under the umbrella of precision medicine.

BACKGROUND TO MODEL-INFORMED PRECISION DOSING

The goal of MIPD is to improve drug treatment outcomes in patients by achieving the optimal balance between efficacy and toxicity for the individual patient. The approach is based on the available information about the patient and the disease that they are treated for, comorbid diseases afflicting the patient, and the medication(s) they are receiving. The concept is inclusive of various modelling approaches, *e.g.*, pharmacometrics (mathematical models of biology, pharmacology and physiology) as well as other modelling approaches (regression models, decision trees and other algorithms). The most suitable approach is likely to be determined by the goal, amount of available information about the patient and the drug, and performance of the model. Current dosing recommendations are determined by analysis of late stage (phases 2-4) clinical trial data which often include limited permutations of dosage regimens amongst vast number of possibilities. For certain drugs, the treatment effect can be improved by assigning the dose to be the function of a single covariate in the drug label, *e.g.*, body weight (*e.g.*, heparins) (1) or renal function (*e.g.*, oseltamivir) (2). It is however less common to see dosing guidance for special patient populations (*e.g.*, paediatrics, obesity or pregnancy) or dose regimens where more than one factor determines dose selection, *e.g.*, vancomycin dosed in paediatrics based on age, weight and renal function (3, 4), or ganciclovir dosed adjusted by

bodyweight and renal function (5). The absence of dosing recommendations translates to highly variable practices in clinical care particularly amongst the so called 'complex patients', leading to an increased risk of toxicity or suboptimal therapy, *e.g.,* the reported high variability in local guidance and practices on dosing antibiotics in neonates in the UK and France (6, 7). Similarly, it is almost two decades since it was shown that in hospitalised patients adverse drug reactions (ADRs) may rank as high as the fourth leading cause of death in the United States (8). Management of dosing in special populations, polypharmacy and drug-drug interactions (DDIs) in the elderly may be aided by integrating MIPD into healthcare.

In May 2016 a Healthcare Summit was held in Cheshire, UK, to discuss for the first time the opportunities and challenges in "Model-informed precision dosing" (MIPD). During the meeting, many of the experts in the field exchanged views from clinical, academic, industrial and legal/regulatory perspectives on the subject matter. The meeting was a timely follow on to recent initiatives on precision medicine (9). The current and future role of MIPD in healthcare as a necessary element in the wider context of precision medicine was debated. Case examples of MIPD were highlighted in several areas, including but was not limited to:

- DDIs and HIV (human immunodeficiency virus) drug treatment:
    - Predictability of metabolic DDIs – Experience from Geneva Hospital (10).
- Oncology:
    - Paediatric oncology – Exposure of actinomycin D (11),
    - Dose optimisation of monoclonal antibodies (12),
    - Dose personalisation in haematopoietic cell transplant patients (13).
- Paediatric dose adjustments:
    - Warfarin dosing in children,
    - Modelling and simulation (M&S) to develop practical guide in neonatal dosing (14-16),
    - Predicting the dose of antiepileptic drugs or chemotherapy in paediatrics (17),
    - Optimising drug delivery to critically ill children (18),

- The Dutch/Flemish approach to paediatric drug dosing – Modelling to bedside (3, 19-21).

- Special patient populations:
  - Drug dosing in obesity and post-bariatric surgery (22-24),
  - Optimising drug exposure in pregnant women (25), M&S in psychiatric care (26),
  - Dosing following renal transplantation (27),
  - Drug exposure in heart failure patients (28).

Breakout sessions were hosted on the topic of how best to implement MIPD in healthcare with a view to answer the motion for the debate on "Why MIPD has not yet become common clinical reality?".

Against the background of the ongoing interest in precision medicine, and the utility for precision dosing under such a framework, we review here this meeting's outcomes to facilitate further discussion and help define the future direction on increased integration of MIPD into healthcare. This report also serves as an extension to previous discussions on the role of model-informed approaches to dosing in special populations from a regulatory and industry perspective during drug development (29, 30).

SETTING THE SCENE: CURRENT STATUS OF MODEL-INFORMED PRECISION DOSING

In contrast to a one-size-fits-all approach to drug treatment where a drug or set of drugs are given for a certain disease (treating the disease), personalised medicine is designed to treat the patient who has the disease and hence it provides a therapeutic recommendation for the individual patient based on their characteristics and specific needs (*e.g.,* finer diagnoses and sub-categorisation of the disease, age, body size, organ function, genetics of drug receptors and enzymes and transporters, drug interactions). Precision dosing lies within this broader concept and encompasses the process whereby the chosen drug therapy is modified to optimally treat an individual patient. The lack of specific

dosing recommendations for more complex scenarios necessitates clinicians to use their previous experience to personalise dosing before or after the start of treatment based on the patient response, in a process which can be called '*in cerebro*' modelling, as opposed computer-based '*in silico*' modelling. However, the process applied by an individual physician may not be uniformly defined and applied when new cases arise.

The concept of precision dosing has been reinvigorated recently with the emergence of more affordable technology for genetic testing, the increasing availability of 'big data' and awareness that special populations often require optimisation to attain the desirable treatment effect (9, 31). Clinical trials have traditionally aimed to answer the question whether a label-defined dose regimen offers a positive risk-benefit profile across a protocol-defined population sample. The therapeutic response surface, introduced by Sheiner (1991) (32), describes the balance between efficacy and toxicity to depend on both drug exposure and patient characteristics. Where current phase 3 clinical trials characterise the average treatment-effect relationship in a controlled sample, it is however well-recognised that the actual patient may differ because of the disease, underlying co-morbidities or DDIs (see 'randomised clinical trials', Figure 1).

Given the multiple levels of information that can influence an individual's dose response, common steps such as scaling by body weight, are unlikely to always address this question to a sufficient extent and in some instances (*e.g.,* obesity) may in fact worsen the situation. Statistical analysis and population pharmacokinetic and dynamic (pop-PK/PD) modelling enables, in principle, the interpolation of the observed treatment response in randomised clinical trials as a function of multiple covariates (see 'population PKPD', Figure 1). That being said, sometimes, in order to optimally identify a regimen in patients falling outside the tested response and patient characteristics space, extrapolation of exposure and/or response is required under the assumption that PK/PD is constant over time and between subsets of patients. The latest PDUFA (Prescription Drug User Fee Act) VI strategy document for 2018-2022 (33) has specified the use of such relationships as a potential area of further research for justifying approval of doses or dosage regimens which were not tested in the clinical trial setting but which can be derived from models built on other doses and regimens studied.

Mechanistic modelling, such as physiologically-based pharmacokinetic (PBPK) M&S, enables extrapolation by using information about the physiology and the drug (see '*in silico* studies', Figure 1). Hence, model-informed approaches provide a rationale to precise dosing for an individual, as recognised by Dr Lewis B. Sheiner and Dr Roger W. Jelliffe as early as the 1960s (34, 35), and since then integrated into specific clinical decision tools (36-40). To mitigate off-label use, regulatory agencies have detailed label requirements which advise on dosing in relevant patient populations. Dosing recommendations in the label can be based on the full body of available scientific evidence, analysed by *in silico* models as applicable, and not necessarily via clinical trials dedicated to a unique target population of patients, where the performed trials may be considered narrow by necessity. There has been an increase in the use of modelling to inform drug labelling over the last decade, mainly for interpolation of the magnitude of metabolic DDIs, where 61% of applications of PBPK M&S were dedicated to the prediction of DDIs (29, 41, 42). Nonetheless, when dedicated studies are considered as the norm to provide dosing guidance it may lead to imprecise (and off-label) dosing in healthcare for special populations not explicitly addressed in the label, as indicated recently by Jadhav *et al*. (29), keeping in mind that it is practically impossible to conduct specific studies for all the permutation of possible combinations of co-morbidities. Dosing of special populations in clinical practice relies heavily on local guidance or is left to the discretion of the clinician (7). Dosing recommendations in special populations, *e.g.,* children or pregnant women, tend to err on the side of "caution" rather than being informed via evidence-based medicine (29). This caution often results in a label with either no mention of the specific population or a statement disclosing that the population was not studied, resulting in the prescriber making no dose adjustment, seeking alternative and possibly inferior therapy, or simply withholding the drug.

Model-informed approaches have been extensively used to optimise dosing in individual patients with significant success (10, 16, 19-21, 27, 43, 44). With the increasing level of patient information and advancements in computational tools for analysing omics data, such as the IBM Watson (45), MIPD appears an attractive option that may greatly improve efficacy and safety of clinical pharmacotherapy through efficient integration of patient data.

An MIPD approach is not an end in itself but rather a tool or guide towards optimal patient outcomes. It is associated with certain criteria that should be fulfilled. The first prerequisite is the existence of a scientific rationale for dose selection, such as the existence of a well-defined concentration target with acceptable error (the therapeutic window), which maximises the chance of therapeutic success and minimises concentration-related toxicity. The therapeutic target should be determined by best available measurement of efficacy/toxicity, whether directly or through a validated biomarker. Further, the lack of clinical data in a specific population, a narrow therapeutic window, inadequacy of allometric scaling methods (particularly in young children and obese patients) (46), impact of disease or treatment, the cost of relative overdosing of expensive compounds (*e.g.,* monoclonal antibodies) (47), and proportion of the specific subpopulation in the target population and their vulnerability are all indicators favouring a MIPD approach. Figure 2 highlights the patient, disease and drug characteristics that in unison indicate the space where model-informed approaches may prove a high impact case for dose optimisation.

A formal representation of MIPD is of benefit to highlight some of the important, but at times overlooked, milestones to implementing the approach in healthcare. For instance, the paradigm of 'predict, learn, confirm-implement' (Figure 3) is a requisite to the use of drug-independent (*i.e.,* systems data on patient physiology) and drug-dependent information, together with available clinical data to inform model structure and parameterisation (see 'Data', Figure 3). Dependency on data varies between MIPD modelling methods, as determined by the conceptual approach and its complexity (*i.e.*, decision trees, regression models, compartmental or mechanistic models). As a general guidance, models for precision dosing should undergo internal validation to diagnose any model misspecifications and external validation to test performance in a population sample different than the one used to develop the model. Prospective clinical evaluation is key to the process and should be carried out to evaluate the benefit of the MIPD approach over current best practice (see 'Validation', Figure 3). Therefore, monitoring and recording improvement in clinical efficacy, reduced incidence of toxicity, adherence and cost-benefit should be part of any such assessment. While costs are relatively easy to tabulate (purchase, maintain, use), some benefits are more nebulous, and can extend to

improved efficacy safety balance of pharmacotherapy, cost avoidance, improved patient satisfaction, and better quality of care. The MIPD model can be used clinically as either a clinical decision support tool, to develop a dose banding strategy (dosing methods based on predefined ranges in relation to a single or multiple covariates), or other alternative approaches. The MIPD model should be refined as needed in a 'predict, learn, confirm, apply, control' paradigm, but care must be taken to ensure that the quality of the data used to update the model remains high (Figure 3) (29, 48-50). Here, adaptive approaches, such as Bayesian methods, can be used for feedback control and to ensure continued refinement through updating prior available information based on data obtained in clinical practice (see 'Implementation', Figure 3).

There is ample of evidence to support the success of MIPD to address clinically relevant dosing issues (10, 16, 19-21, 24, 27, 36, 43, 51-55), whereas evidence of large-scale clinical utility and cost-benefit may be considered sparse if not lacking (51, 52, 56). Current MIPD implementation of modelling strategies can be divided into three categories:

- Real-time implementation of MIPD models aligned in healthcare,

- Mechanistic modelling and extrapolation based on prior information on patient characteristics, and

- Model-derived dose banding from covariate analysis of large population studies.

Real-time MIPD refers to the direct prospective implementation of M&S in a healthcare setting based on live read-outs from the patient, such as drug concentration samples (*e.g.,* digoxin and gentamicin) or measures of efficacy (*e.g.,* warfarin and statins). The approach may be considered particularly suitable for treatments dependent on continuous monitoring of efficacy/toxicity, *e.g.,* where therapeutic drug monitoring (TDM) is included in clinical practice or where measures of efficacy are easily attainable (*e.g.,* pain scores). The method lends itself well to Bayesian statistical methods to forecast individual patient response and control it via dose selection, as particularly applied in oncology, transplant medicine, and treatment of infectious diseases (13, 43, 48, 51-53, 57, 58). To fully capitalise on their potential advantages, the models must be implemented in a framework amenable to direct healthcare provider usage.

In many instances, precision dosing may be rephrased to what the right dose is for a given 'representative of a special subpopulation', once the target exposure in a reference population is known. Mechanistic models, such as PBPK, allow for extrapolation of exposure from patients represented in Phase 2-3 efficacy-safety studies to special populations through perturbation of model structure or parameters, as seen in cases such as: pregnancy, obesity, and for DDIs (10, 23, 25, 59, 60). Although currently PBPK M&S may be considered the best suited alternative for prediction/extrapolation of initial dosing in a drug-population combination that has not been previously studied, ability to incorporate all the patient information seamlessly from the patient records at the point of care is not in place. Moreover, this assumes that pharmacokinetics is the main determinant of inter-population differences (24). With increased ability to measure more individual patient covariates such as genotyping and metabolomics profiles, it is entirely possible for a PBPK model to serve as a Bayesian prior that can be updated to a Bayesian posterior model of the individual, suitable for dosing control (61). This is a marriage of "bottom-up" (PBPK) and "top-down" (population approaches) in a so called "middle-out" approach (62).

Model-informed dosage regimens reconcile internally validated models with dose banding based on the identified covariates which were recognised by statistical analysis and can be of value to guide dosing of special populations in clinical practice in the absence of other evidence. The approach has been successfully used for dosing of morphine, amikacin and vancomycin in paediatrics (19-21) and for wastage reduction of excess formulation for expensive monoclonal antibodies (*e.g.,* oncology) (12). The relative simplicity of this practical MIPD implementation makes it suitable for healthcare implementation, albeit care should be taken to prevent impractical dosing administration intervals and subsequent prescribing errors. An example of wide-spread implementation of model-derived dosage regimens is the Dutch Paediatric Formulary (3). This nation-wide web-based formulary presents dosing guidelines for over 650 drugs prescribed to children. The dosing guidelines are based on the summary of product characteristics or in case of off-label use, best evidence from the scientific literature and expert consensus. Published literature is monitored routinely, and papers including new pharmacokinetic and/or pharmacodynamic data are evaluated for additional evidence to update

guidelines. This has resulted in the implementation of model-derived dosing guidelines for *e.g.,* vancomycin, gentamycin, tobramycin and amikacin based on age and weight. In some cases, the dosing intervals and/or doses were slightly adjusted to comply with computer-based prescribing systems or to prevent calculation mistakes. The model-derived dosing guidelines for morphine have not been implemented to date, as no consensus has been reached on its general applicability given the potentially different doses for different types of surgery (cardiac vs. non-cardiac surgery) or different subgroups (preterm vs. term neonates). A recent example in this respect is necrotising enterocolitis in preterm neonates, an extremely painful clinical situation, for which substantially higher morphine target concentrations were found necessary (63).

There are several reasons associated with data collection as to why MIPD has not yet delivered its full potential. MIPD is data driven, relying on the individual patient's current characteristics and clinical data, prior information on physiology to inform systems parameters, drug and formulation-specific properties. In many instances one or several elements of the necessary data to inform the modelling is missing. The lack of publicly available clinical data means that interpretation of data is based on trends in central tendency between healthy and special patient populations rather than the ability to base analysis on individual patient data. With a few exceptions, there is a general lack of routine genotypic testing or usage of metabolic markers to inform individualised dosing. Further, there is a need for fully validated drug databases with consistent data regarding drug-specific properties (*e.g.,* proportional importance of various elimination routes) and a more detailed and quantitative understanding of the physiology in special populations.

In the pharmaceutical industry, some progress has been made to enable sharing of clinical data (64). These models for data sharing provide gated access subject to the proposed analysis and mostly do not include historical data. This may be viewed as a problematic approach as it is prone to dissemination bias (65). Other efforts are underway to address this issue. Some efforts are also being made to collate patient data at a wider scale, the most prominent example being the Precision Medicine Initiative, aiming to collect data from over one million volunteers (9).

FUTURE LANDSCAPE: IMPLEMENTATION OF PRECISION DOSING IN HEALTHCARE

Although there are certainly cases of MIPD implementation in healthcare these mostly exist as isolated local efforts in collaboration between academia and clinical champions in individual hospitals or hospital departments (19, 21, 24, 36, 51-55). In order for MIPD to be more generally adopted in healthcare, locally and nationally, challenges must be addressed systematically. There are geographic and medical speciality cultural differences between healthcare professionals and the modelling community that hamper the exchange of knowledge and ideas on precision dosing. The decline in clinical pharmacology as a medical speciality, as seen in the United Kingdom, which could bridge the gap has not helped (66). However, the increasing clinical responsibilities given to clinical pharmacists would facilitate a natural link between pharmacokinetics, pharmacodynamics, systems pharmacology and clinical practice (67, 68). There is therefore a great need to educate and train healthcare professionals, both at a pre-graduate level and those working in practice, in the disciplines of quantitative clinical pharmacology and pharmacometrics, in order for model-informed approaches to gain traction in healthcare, whether employed independent of the modellers via smart systems (Apps on smartphones, tablets, or hospital systems) or in conjunction with modellers (particularly for more complex cases). Similarly, academic researchers should recognise wider impacts of their research at an early stage and plan towards monitoring and recording the necessary data to demonstrate such effects (for the purpose of assessing cost-benefit and beyond the mere treatment outcome). It is recognised that this may happen only through interactions and learning between science and practice otherwise presentations within academic groups may be seen as preaching to the choir, where academic research has produced many publications on dose individualisation that has yet to be translated into clinical dosing tools. To be able to target clinicians, clinical pharmacists, healthcare providers, patients and relatives it will also be necessary to provide additional evidence on the health economics of the specific context. Specifically, the questions and open issues that MIPD is required to

solve need to be unambiguously clarified for each treatment area. Further, advocates of MIPD in healthcare need to engage with patient groups, such as HIV and cancer patient groups to facilitate data collection, transfer of patient information as well as advocating the need for a MIPD paradigm through increasing the awareness amongst patients regarding the impact of individual characteristics on dose requirements. It is essential that both healthcare professionals and patients feel included and own the process rather than it being something that is imposed. Prospective clinical evaluation is one of the cornerstones to enable this, by showing concordance between predicted and observed exposure/efficacy/toxicity at both a population and individual level, in scenarios of relatively narrow therapeutic indices, where the risk of toxicity of sub-therapeutic treatment is relatively high and in vulnerable patient populations (Figure 2).

Although rare, few MIPD efforts to date have been associated with defined health-economic achievements (51, 52, 56). However, even when such information is available, communicating them to the management in healthcare is not an easy task. Engaging with healthcare management and healthcare providers (insurance companies/national healthcare organisations) to support the concept of MIPD necessitates not only the formal evaluation of the financial significance and added value in terms of patient benefit and satisfaction but also communicating in an effective and unambiguous manner. Investigators working in MIPD should strive for prospective assessment of improved patient outcomes and not limit themselves to optimising observed pharmacokinetics/dynamics alone, even though this will raise the costs of the studies. The modelling community, working together with clinicians, need to generate proof of concept for MIPD in a number of key clinical centres to generate critical mass of evidence that encourages wider adoption.

In order for MIPD models to be prospectively evaluated it is paramount that funding be available for collaboration between clinicians and the modelling community. The validation of previously published models in a larger scale may not be viewed as a sufficiently novel research activity for funding agencies. However, the increased attention given to rigor and reproducibility suggest that model validation is imperative. Further, the scene on ‘improvement science’ (exploring how to efficiently change methods to increase quality improvements) in healthcare is changing and most

providers now consider the topic extremely effective in defining their policies. Hence, identifying new funding sources away from traditional research councils is important (*e.g.,* the Patient-Centered Outcomes Research Institute in the US [http:/www.pcori.org/], Research for Patient Benefit [RfPB: http://www.nihr.ac.uk/funding/research-for-patient-benefit.htm] scheme in UK, the National Support Initiative in Switzerland [https://www.sbfi.admin.ch/sbfi/en/home/topics/research-and-innovation-in-switzerland/national-support-initiative--personalised-medicine-.html]). Perhaps patient and disease specific associations may play an important role in supporting these research activities involving practice improvement and implementation of MIPD, *e.g.,* ImproveCareNow (http://www.improvecarenow.org/), where patients, parents, clinicians and researchers are working together on database projects, including developing MIPD of infliximab in children with Crohn's disease.

There is no prescriptive measure of what the level of provided benefit need be against the standard of care in order for MIPD to succeed, as marginal gains depend on the size of the patient population. One should remember that the standard of care, depending on the speciality and the experience of the physician, has some degree of personalised dosing through the process we coined as '*in cerebro*' modelling and integration of prior knowledge, albeit not uniformly. In a large population, *e.g.,* patients treated with statins (69), a minor gain in benefit may translate into a significant improvement in drug therapy for a considerable number of patients and subsequent costs savings for healthcare providers and payers.

On a more practical aspect, the availability of drug-specific formulations and dose strengths will determine the short-term feasibility of implementing MIPD in healthcare. It is therefore thought that one of the natural starting points of implementing MIPD should be in therapeutic areas where multiple formulations and dosage strengths exist, such as in paediatrics and paediatric oncology. Both oncology and HIV would moreover be attractive areas for implementing MIPD as there is already some dose individualisation, *e.g.,* carboplatin, busulfan and abacavir (70-72). Predictions of DDIs may be considered the most mature field for MIPD, where poly-pharmacy is a cause of concern in many patient groups, including the elderly. Here MIPD can provide not only informative and

quantitative answers regarding dose optimisation, but could also be used to select the appropriate drugs to avoid DDIs. Further, there is a great need for guided dosing in special populations where little information is available on dosing or where current models are not suitable for clinical practice due to low predictive value, such as: renal impairment, renal replacement therapy, transplantation, obesity and pregnancy.

Implementation of MIPD in healthcare naturally begs the question as to who the end-user is. A realistic use of MIPD in healthcare would be to provide prescribing guidance to prescribers; here one could envision that the end-user would be clinicians. It is therefore important to consider a user-interface that is easily understandable to prevent dosing errors and at the same time give adequate transparency to build trust and confidence in its use amongst healthcare professionals and does not impose a time consuming activity during routine practice. Integration of MIPD tools into already existing electronic prescribing systems may help to streamline its usage.

REQUIREMENTS FOR MODEL-INFORMED PRECISION DOSING TOOLS

As discussed above, for any MIPD tool due attention needs to be given to the financial model under which they would be developed and implemented. This should consider issues such as liability were anything to go wrong. This process would have to ensure that the design, validation, and implementation are transparent and that the output strikes an appropriate balance between uses and the inherent risks associated with any extrapolative process. Several streams or scenarios for developing these tools would be possible, *e.g.,* through the pharmaceutical industry, research institutions, healthcare institutions, by clinicians themselves, patient advocacy groups or other for profit entities. Ideally a joint process across multiple partners would ensure that the above transparency, risk and use balances are appropriately struck.

It should be recognised that a MIPD approach would require adjustments and pose new challenges not only to patient care but also to the strategy of pharmaceutical research and development. There are several reasons as to why the pharmaceutical industry aims for a simplified dosing regimen with a

relatively limited number of alternatives. In order to minimise the need for individualised dosing, pharmaceutical drug discovery and development focuses on drugs that ideally have an intrinsically wide therapeutic index (via for example selecting pathways or mechanisms that are perceived to be of lower risk) and low DDI potential. On the downside drug selection based on the above criteria may not always be possible and may subsequently lead to abandonment of otherwise potentially successful drug candidates.

A MIPD 'companion tool' approach introduced in the early stage compound selection or drug development might help improve the feasibility of integrating precision dosing in patient care. The most likely drug candidates for this approach are those intended to act in areas with high unmet medical needs with highly motivated and informed patients, plus identified relevant biomarkers to drive dose selection (Figure 2). MIPD based dose selection may facilitate bringing forward valuable treatment options for patients where traditional drug development routes have been unable to produce successful candidate drugs. The ideal companion tool would be developed alongside the drug, refined and tested in early phase clinical trials and where later clinical trials are designed to validate the companion tool drug combination. Such a tool could also potentially facilitate enrolment in Phase 2 and Phase 3 clinical studies by relaxing exclusion criteria. If an exposure/PD control strategy, such as concentration controlled trial (73), is used during the trial rather than a homogenous dose, then an equally homogenous population would no longer be necessary. For example, subjects with DDIs or altered physiology who had not been previously studied and would have been excluded otherwise, could be enrolled with study doses adjusted via MIPD. This approach can be considered as 'dynamic label' via an App or similar device/program which provides the models capable of taking patient information and providing advice on how to adjust the dose in certain conditions as opposed to a textual or tabular information in the current 'static labels'.

The barriers to this approach include variability and quality of input data (such as variability in experimental *in vitro* data between laboratories to inform model parameters and out of date demographic data), increased development costs in terms of validation and more frequent monitoring, potential increases in the number of trial subjects, uncertainty over who would be the end-user of the

tool and who would be ultimately responsible for if something goes wrong. An overall schematic and summary of the considerations of this approach are given in Figure 4.

LEGAL/REGULATORY FRAMEWORK FOR MODEL-INFORMED PRECISION DOSING

The development and use of MIPD tools in healthcare requires consideration from a regulatory perspective too. There are a number of questions that need addressing. For example, to what extent would MIPD tools replace clinicians' judgement or guide the clinicians? The authors' opinion is that MIPD should guide – not replace – clinicians by summarising best current knowledge to inform dosing, drug selection or drug combination selection. Regarding liability, the clinician then would be responsible for ensuring responsible usage of the tool and the developer would be responsible to ensure that the tool is sufficiently reliable and accurate for its intended use. The acceptance criteria for a precision dosing tool would need to be judged on a case-to-case basis weighing its risk-benefit profile. A few unanswered questions remain around the implications of a device that proposes different dosing recommendations to what is established in the drug label, potentially being perceived to promote unapproved use of the drug. It is expected that these issues will be resolved once MIPD tools become available to the market and a regulatory practice is established. Certainly, regulators have been proactive in anticipation of the submission of applications for approval of *in silico* MIPD tools under the medical devices guidance (74, 75).

There may also be an opportunity to expand usage or extend patent protections and market exclusivities using an innovative drug/tool combination. These potential benefits could motivate not only research with new active moieties, but also research approved medications which could benefit from improved dosing regimens. For example there may be instances where initial approval on basic dosing and a subsequent approval include an MIPD based dosing strategy with an associated marketing authorisation for use of MIPD software. Also, as mentioned earlier, model-based approaches may likely prove most useful in patient groups where polypharmacy (and thus DDIs)

and/or multiple co-morbidities are present, such as the treatment of cardiovascular disease, cancers and infectious disease in the elderly, and for which disease-related outcomes and drug adverse effects are relatively frequent with large amount of data that can be made available. As data are gathered in the post-market setting after an initial drug or biological product approval, those data could inform development of software models that integrate what is discovered in the market, and ultimately lead to supplemental marketing authorisations that reflect reliance on an MIPD-based dosing strategy.

Ultimately, these potential rewards for research could motivate further investment as MIPD research advances to the ultimate benefit of patients. However, engagement with regulatory authorities, both individually on product-specific application and as stakeholders more generally, will be essential because of the intricacies that can be involved in combination and complementary-use product regulation.

DISCUSSION

As highlighted herein, there is an abundance of published material detailing the benefit of model-informed precision dosing methods in answering clinically relevant questions, and given the increased acceptance towards model-informed approaches as evident in guidelines, formularies and drug labelling MIPD appears an attractive approach to tackling clinical dosing problems. However, to date there is little evidence of the use and impact of MIPD in large scale within clinical care. Here lies certainly an unfulfilled potential to improve patient care, as well as streamlining treatment costs. A number of considerations have been highlighted that will need addressing before MIPD becomes clinical practice. Evidence-based efficacy and cost-benefit analysis of MIPD in healthcare is pivotal to seeing its broader implementation. Advocates of modelling sciences need to engage healthcare professionals and patient groups to increase awareness and transfer knowledge regarding the approach; the most compelling argument would be proven clinical use. Special considerations are needed on the implications of MIPD tools on both regulatory policies and pharmaceutical development. The interdisciplinary nature of MIPD requires the collaboration across professions and interest groups, including: funding institutions, academic researchers, healthcare professionals, pharmaceutical industry, regulatory industries and patient groups.

There has been some progress on implementation of MIPD in healthcare over the last couple of decades (36-40), where advancements have been made possible through collaboration between academia and healthcare. Here, model-informed drug development is showing the way where advancements have been realised through close alignment between pharmaceutical industry, regulators and software providers.

Building fruitful collaborations and changing attitudes takes time. Meanwhile, provision of funding streams to support applied precision dosing and its clinical evaluation may help accelerate the development of MIPD tools. A wider continued commitment from regulators, pharmaceutical industry and other health entities on sharing of clinical data is warranted to support these research efforts. There is also a case for providing incentives to pharmaceutical industry to enable broader dose guidance at time of approval, including the MIPD companion tool approach highlighted here.

Educators in the health sciences need to ensure that future researchers and healthcare professionals are equipped with the tools to tackle these quantitatively complex clinical problems. The modelling community has a responsibility to ensure the application is not lost in the methodology by aligning with healthcare professionals, patient groups, industry and regulators. It is with great optimism and anticipation we look to the future of this field.

EPILOGUE

This article, for the first time, attempted to reflect over nearly half a century of using modelling as a mean of adjusting the dose for individual patients. It highlighted the achievements and the fact that advanced technologies (*e.g.,* computational power and analytical assays for genetics and chemical assays) should, in theory, move the MIPD from a scientific adventure to a common clinical practice. However, making MIPD an essential decision support tool in defining the dosage regimen faces several obstacles which were listed here. These explain why MIPD has remained in the 'State of the Art' level and has not moved to the 'State of Common Practice'. The current '*in cerebro*' modelling that most physicians will apply when diverting from one-size-fits-all dosage regimen, has its limitations in ability to integrate all pieces of information on patient and the drug quantitatively but until cost-benefit for MIPD is shown widely and unequivocally, it may remain 'State of the Art'.

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FIGURE LEGENDS

Figure 1. The three dimensional therapeutic utility surface (balance of efficacy and toxicity) as a function of drug related factors and patient characteristics. The red dots indicate the point estimates attained from randomised clinical trials, the yellow surface represents the area attainable through interpolation methods, such as compartmental population pharmacokinetic-pharmacodynamic (PKPD) analysis. The black arrow represents the surface available through extrapolation, *e.g.,* physiologically-based pharmacokinetic modelling. Extension of Sheiner (32).

Figure 2. Patient, disease and drug characteristics that together indicate a high impact case for model-informed precision dosing (MIPD).

Figure 3. Schematic of precision dosing model development, validation and implementation. PBPK: physiologically-based pharmacokinetics, PK/PD: pharmacokinetics/pharmacodynamics. Extension of **(29, 48-50)**.

Figure 4. Proposed scheme for bringing model-informed precision dosing through pharmaceutical development.