



July 14, 2010

David Challoner, MD
Chair, Committee on the Public Health Effectiveness
of the FDA 510(k) Clearance Process
Institute of Medicine
500 Fifth Street, NW,
Washington, DC 20001

Dear Dr. Challoner:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to provide input to the Institute of Medicine (IOM) Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process regarding the FDA's current medical device review process. We support the FDA's decision to seek an outside examination of this widely used process. AACC urges the panel to address the 510(k) De Novo process in its final report.

Congress authorized the De Novo process in the FDA Modernization Act of 1997. This mechanism permits the agency to reclassify low risk devices that would automatically be designated as Class III devices, solely because there is no predicate device, as Class I or II. This means that manufacturers, in certain instances, are able to seek clearance through the less burdensome 510(k) process, rather than the more costly and onerous pre-market approval (PMA). AACC supports this approach.

The use of the De Novo process is particularly important for devices, such as tests for Therapeutic Drug Monitoring (TDM), where consumer demand is often limited, but the potential for improved patient care is significant. Shifting the review of a low volume, low risk test from a PMA to a 510(k) review may make development of a previously unprofitable test, now cost-effective. This change benefits the manufacturer, which now has an incentive to develop and market the test, as well as the patient, who now has access to a valuable test for managing their drug therapy.

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We are concerned, however, that the use of the FDA De Novo process for low risk much needed TDM tests has dropped precipitously in recent years. In the past, AACC worked with industry and laboratory professional societies to draft special guidance documents for TDM applications to assist the FDA in this process. Internal differences within the agency, however, prevented many new assays from moving forward, thus bringing our involvement to an end. We would gladly spearhead such efforts again if the agency could resolve this internal dispute.

AACC recently completed a white paper on the value of TDM assays and the regulatory problems manufacturers are encountering getting them to market. We are including a copy of that paper, which goes into further details on the issues we have raised in this letter. Please let us know if we can provide you with any other information that could assist you as you develop your recommendations.

By way of background, AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and its application to health care. If you have any questions, please call me at (919) 966-3724, or Vince Stine, PhD, Director, Government Affairs, at (202) 835-8721.

Sincerely,

A handwritten signature in cursive script that reads "Catherine Hammett-Stabler".

Catherine A. Hammett-Stabler, Ph.D., DABCC, FACB
President, AACC

Challenges in Therapeutic Drug Monitoring AACC TDM Renaissance Working Group

Introduction

Therapeutic drug monitoring (TDM) in the United States is an under-appreciated clinical discipline, championed by American thought leaders such as Drs. Charles Pippenger and Harvey Kupferburg in the early 1970's, and international counterparts such as Drs. Folke Sjoqvist and Alan Richens. Among other things, these clinical scientists demonstrated that a patient's response to anti-epileptic drugs, such as phenytoin, more closely correlated with the blood concentration of the drug, than with the prescribed dose of the drug (1-4). The concept of optimizing the dose of a therapeutic drug to achieve a therapeutic concentration (or "target") in the blood, while simultaneously avoiding concentrations (or "thresholds") shown to be unsafe or toxic, is an excellent example of personalized medicine. TDM is known to improve patient outcomes in the areas of neurology, solid organ transplant, cardiology, and infectious diseases (5-10). In truth, many pharmacogenetic tests that have been introduced over the past decade have evolved from the phenotypic relationships originally defined by TDM (11, 12).

The basis of TDM is the measurement of drug concentrations in blood specimens that are collected at specific time intervals after dosing. The measured concentrations, in turn, facilitate the understanding of how individual patients absorb, distribute, metabolize (break down), and eliminate drugs. These processes grouped together are commonly referred to as "pharmacokinetics." When concentrations and total drug exposure (e.g. defined by the area under the concentration (AUC) time profile) are correlated with therapeutic response and/or toxicity, drug dosing can be personalized for an individual patient, and as a result, improve the likelihood that the patient will respond as desired to that drug, while at the same time, minimize likelihood of dose-related toxicity. It is important to remember that TDM is an objective tool, used along with other clinical biomarkers and a physician's experience and clinical judgment, to optimize treatment and minimize risk of adverse events – one of the primary principles of TDM is to "treat the patient, not the number".

TDM and pharmacogenetic analyses work synergistically. Pharmacogenetic testing is designed to pre-therapeutically identify patients who might have altered pharmacokinetics. Identification of such patients provides opportunity to minimize risk for adverse drug reactions, and increase the likelihood to respond to a particular therapy. While this type of testing is useful, it is important to note that genetic differences cannot explain all the variability in a patient's pharmacokinetics and response to a drug. For instance, pharmacogenetic testing cannot predict problems with absorption of the drug, drug-drug interactions, variance in pharmacokinetics due to transient disease states or physiologic abnormalities (e.g. pregnancy, morbidly obese patients), or issues with patient compliance. TDM is complimentary to pharmacogenetics because TDM illustrates the pharmacokinetic phenotype for a drug in an individual; access to both tools is vital for truly personalized medicine.

While the potential benefits of TDM are clear, the actual proportion of drugs for which TDM assays are commercially available relative to the number of drugs available clinically is currently less than 10%. Unfortunately, there is evidence that TDM would be beneficial for many of the remaining 90% or so of pharmaceutical preparations marketed today. The low prevalence of commercially available TDM assays in the United States is evidenced by the relatively low number of therapeutic drugs included in the College of American Pathologists (CAP, www.cap.org) proficiency testing program, the most widely utilized laboratory proficiency testing program in the United States today. In 2009, there were fewer than 75 medications represented in all CAP proficiency testing surveys for therapeutic drugs, an extremely low number when compared to the greater than 4000 prescription drugs currently approved by the U.S. Food and Drug Administration (FDA).

Healthcare in the United States is short-changed by the paucity of TDM assays. Availability of TDM assays and utilization of those tests on behalf of patients requires a sophisticated drug testing capability. Broad accessibility to drug testing requires availability of automated assays and participation of the *in vitro* diagnostic (IVD) industry. An effective means to accelerate access to methods for new, emerging drug analytes is needed. Availability of assays that can be automated for the central hospital laboratory would be one of the helpful paths for improving the management of patients receiving key therapies for which TDM could be beneficial. Medical use of drugs is an evolving process, and TDM may enable drug safety by providing medical information that can be interpreted in the context of other uniquely individual clinical history.

As stated above, the currently available menu of automated TDM tests in the United States today reflects the proficiency testing survey provided by the CAP, a small number of commercially available methods which does not reflect the extensive menu of prescription medications available today. In the following sections, several possible explanations for this disparity are discussed, including the uncertainty and the required burden of proof that has significantly increased over the last 3 – 5 years with various regulatory bodies, including the FDA.

Hurdles to widespread development and availability of TDM

Several possibilities exist for why TDM assays are not widely available. One reason is that most package labels for pharmaceutical products do not indicate, recommend or require dose adjustment through TDM. Typically, clinical validity of TDM is not well defined when a drug is brought to market; however, the lack of assertive labeling in pharmaceutical products should not imply that TDM is not clinically useful. Indeed, many drugs are used for multiple indications, for which different therapeutic targets could exist. For example, the therapeutic targets for the antiepileptic drug carbamazepine differ when the drug is used for managing seizures, versus mood stabilization, or trigeminal neuralgia; all approved indications of this drug. Carbamazepine is also used for other indications, such as alcohol and benzodiazepine withdrawal and dementia, which may be associated with therapeutic targets and toxic thresholds unique to those clinical indications (13). Another explanation for underutilization of TDM is that the drug prescribed may not be directly responsible for the pharmacological activity or

toxicity of the drug, and hence, the analytical target may be inappropriate. Continuing to use carbamazepine as an example, few commercial TDM assays available today detect carbamazepine 10,11-epoxide, an active metabolite of carbamazepine. Failure to consider this active metabolite when using TDM lessens the benefit for patients who metabolize carbamazepine different from the general population (14).

Traditionally, the therapeutic targets for TDM assays, and apparent clinical validity, have been established based on statistical analysis of data obtained from discrete groups (populations) of patients – the lower boundary of the interval was selected to minimize the probability of treatment failure, the upper boundary of the interval was selected to minimize the risk of toxicity. These population-based therapeutic targets have invariably been established retrospectively, in small groups of patients. Thus, traditional therapeutic targets have not been established through highly powered prospective randomized concentration-controlled trials, and the value of such an approach has been well-accepted in the medical community. In practice, therapeutic targets are used only as guidelines, and the actual dose of a drug prescribed to an individual is modified based on TDM together with knowledge of specific characteristics of the patient, such as age, gender, concomitant medications, liver function, renal function, diet, etc., and subsequently tailored based on the patient's response. For example, therapeutic targets are different for the immunosuppressant mycophenolic acid when it is prescribed with cyclosporine compared to when it is prescribed alone (15). Use of TDM to guide dose optimization is particularly important when caring for special patient populations, such as neonates or the critically ill (16, 17). In addition, traditional therapeutic ranges for many drugs have changed as clinical practices have changed. For example, the clinically accepted target range for vancomycin has increased over time, whereas the clinically accepted range for digoxin has decreased over time (18-20). As such, inclusion of TDM in a pharmaceutical label should not be required, because doing so could restrict or jeopardize clinical validity of TDM testing for that drug as new information is gained or as needs change as we have seen with vancomycin and digoxin. TDM should simply be a widely available tool for dose optimization to promote and refine personalized medicine.

Regulatory uncertainty is also a deterrent for accessibility and development of commercially available TDM assays. Specifically, concerns exist among professional societies such as the American Association for Clinical Chemistry (AACC), IVD manufacturers, and patient advocacy groups that the FDA's expectations for clinical validity versus analytical validity of TDM assays are unclear or may be applied inconsistently in review of premarket notifications. Relationship between clinical validity and TDM should be demonstrated, but lack of clarity in expectations and lack of emphasis on analytical validity versus clinical validity discourages innovation and new method development. We believe the regulatory emphasis, when considering laboratory tests designed to support TDM, should be placed on analytical validity while still taking into consideration clinical validity, and that prospective clinical trials should not be required for TDM assays to enter the American marketplace. The use of randomized clinical trials applies to a specific application of the assay rather than a general application; these types of trials answer one question, not many. The implication is that many clinical trials would be necessary for each drug in each population; a wasteful and

counterproductive practice in that TDM is multi-factorial, evaluating compliance, pharmacokinetic variables, and pharmacological response. FDA-cleared TDM assays should provide standardized analytical target(s) and meet or exceed defined expectations for accuracy, specificity, reproducibility, and analytical measurement range. Utilization of TDM to clearly define clinical validity as clinical indications for a drug evolve should be encouraged by the FDA.

Wide availability of high quality TDM assays would not only increase patient access to TDM for a particular drug, but could also make larger clinical studies of drugs in large populations more economically feasible to promote personalized medicine and define clinical validity, particularly for clinical disciplines in which TDM is not currently routine, such as oncology.

Future Strategies

We believe that there are some basic, practical solutions to the above mentioned concerns that will promote patient safety and allow for innovative development of new tools for TDM, and in doing so, promote personalized medicine, while also ensuring regulatory oversight of new assay submissions to the FDA.

1) Promote increased utilization of the *de novo* 510(k) pathway for TDM assays. This pathway is particularly important for TDM assays, where initial market demand is often limited, but the potential for improved patient care is significant. It is important to note that the limitation of demand often stems from lack of access to the testing; test availability is limited to those few laboratories specially equipped to develop and perform testing that is not commercially available. Analytical tools for measuring drugs are low risk, because the analytical technologies commonly available, including automated immunoassays, have been used in clinical laboratory medicine for many years and have demonstrated reliability. Enabling expedited review of a low volume, low risk test by the 510(k) process may encourage development of TDM assays that may have previously been viewed as unprofitable. This approach benefits the manufacturer, which now has an incentive to develop and market the test, as well as the patient and clinician, who would have improved access to a valuable test for personalizing and managing therapy. We propose that the FDA collaborate with professional societies, IVD manufacturers, and patient advocacy groups to develop a working model that would allow consistent application of the *de novo* 510(k) pathway to TDM assay submissions. In the past, the AACC has drafted special guidance documents for TDM applications to assist the FDA in this process, and in our opinion continuation of this process could be a great asset for the FDA; it should be preserved and further utilized.

2) Support submission of TDM assays under general use claims. In the FDA public meeting on the premarket clearance process for medical devices on February 18, 2010, Arleen Pinkos discussed an example using a surgical robotic system for endoscopy. She stated that one option for indication of use would be for a general use claim. In this case, that would mean that the use of the device would be left up to the surgeon/medical practitioner because the surgical device could be used in many different medical scenarios. This description could also be applied to TDM tests, which can be used a

number of ways including evaluation of individual patient pharmacokinetics, to adjust dosing to achieve a targeted therapeutic blood concentration associated with clinical response, to detect changes in pharmacokinetics due to drug-drug interactions or changes in clinical status, for investigation of toxicity or lack of efficacy, and to monitor adherence. This wide range of utility is similar to other analytes in the clinical laboratory: for example, lactate testing can be used for patient evaluations in sepsis protocols, congestive heart failure, hypoxia, myocardial infarction, or shock; potassium testing can be used for patient evaluation in routine physicals, to monitor patients treated with diuretic drugs, evaluation of high blood pressure, evaluation of diabetic ketoacidosis, or monitoring patients that require renal dialysis. In this case, the primary focus in the TDM submission would be on the analytical validity (e.g. precision, bias versus a reference method, accuracy, analytical measurement range, etc.), and would be clarified as low risk because the testing represents a tool for patient evaluation rather than a diagnostic intervention.

3) Promote clarity in FDA cross-divisional and cross-organizational review activities. In 2004 the Critical Path Initiative was launched, with the goal of expediting movement of technologies from the research bench to patient bedsides – without sacrificing safety or quality in the process. As part of this initiative, it is possible that TDM assay submissions will be reviewed by those outside of the Office of *In Vitro* Diagnostics (OIVD). In these instances it is important to establish a clear, consistent framework for evaluation of risk classification. Review of premarket notifications should be based on criteria that are supported with a harmonized perspective between CDRH and CDER branches of the FDA. The scope of analytical studies and other studies should fit with the nature of IVD companies, who have expertise in the area of analytical tools and may not be structured as organizations for achieving population-based clinical studies that may be appropriate for a pharmaceutical company. This is especially true for small IVD companies where innovation may occur. In many cases, a clinical study involving human subjects may be excessive for an IVD company, and it may be inappropriate for an IVD company to establish medical practice on its own. Collegial discussion is needed between the clinical laboratory medical community, IVD manufacturers, CDRH and CDER, and perhaps medical practitioners so that a pragmatic, harmonized approach can be developed for premarket review of new TDM IVD devices.

Specifically, in the case of TDM, it is important to differentiate between the risk associated with specimen collection and running the test, versus risk associated with clinical treatment. Consider also the risks of clinical treatment when the medical information that TDM provides is not available. As previously discussed, TDM is one tool of several used for dose adjustment, and its validity should not be interpreted outside the context of other clinical parameters for a patient. TDM can be used to mitigate clinical risk.

4) Improve public accessibility to pharmacokinetic/pharmacodynamic (PK/PD) data collected regarding pharmaceutical products. The FDA currently requires PK/PD data to support dosing strategies, metabolic routes, and potential for drug-drug interactions. If made publically available (e.g. a public access database), this information could be useful

to those developing TDM testing assays and those that are involved in the interpretation of results, because it would provide extremes of concentrations expected with initial dosing recommendations, as well as definition of common metabolites and best specimens and specimen collection protocols for TDM. Such data would thereby support an IVD manufacturer's selection of analytical targets, specimen collection requirements, and help define design criteria for the analytical measurement range. Along with input from physicians with experience prescribing the drug, this data will also benefit the design of performance studies regarding proposed clinical reference ranges and/or other applicable medical decision criteria.

Conclusions

We feel that implementation of one or more of the previously discussed solutions will promote innovation in development of needed TDM assays, and improve patient access to testing that will enhance the current standards of care. Without development of new TDM assays, physicians will be denied objective data to optimize treatment of their patients. This will result in greater variability in treatment practice, lack of ability to assess drug-drug interactions and biological variation (e.g. in pregnancy, pediatrics, and aging), and loss of the ability to assess drug toxicity as a function of concentration and time. Over time, newer drugs will lack monitoring support, patient management will rely on less reliable assessment techniques, and adverse outcomes will not be placed in a quantitative or temporal framework. It is vital to achieve a balanced regulatory and technology environment that promotes both patient safety and innovation and new method development.

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