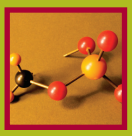

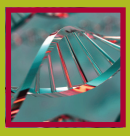

Urine Drug Monitoring: **Opioids**

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TABLE OF CONTENTS

Preface

The role of the healthcare system is to prevent, identify, and treat illness. Pharmacotherapy is, and continues to be, one of the most powerful methods we have to treat and/or cure disease. Recent advances in technology, molecular biology, pharmacology, chemistry, biophysics and analytical chemistry have made available to prescribers the same powerful diagnostic procedures used during drug discovery, development and the FDA clinical drug approval process. When used appropriately as part of the pharmacotherapeutic strategy, Urine Drug Monitoring (UDM) can augment pharmacotherapy by increasing patient safety, identifying patient variability, and objectifying clinical outcomes. The application of these scientific advances is forming the basis for diagnostic and prescription adherence monitoring procedures that can "predict rather than react, respond rather than deny and cure rather than fail."[1] A current and continually expanding complement of pertinent diagnostics (e.g., clinical drug testing, pharmacokinetic interpretation, biomarkers for pain, neurophysiological testing, pharmacogenomics) combined with clinical pharmacology and prescriber and patient education, represent the core of UDM. This strategy represents one possible solution for performing individualized medicine, reducing or eliminating adverse drug effects, thus improving patient safety, clinical efficacy, fiscal responsibility, treatment expediency and accuracy and ethicality.[1]

Introduction

Pain and its treatment pose significant concerns for society's health. Pain can be caused by a disease process, become the disease itself or lead to other comorbidities including depression and anxiety.[1] Approximately one-third of Americans suffer from chronic pain.[2] The annual financial impact of pain due to lost productivity by full-time workers was conservatively estimated at $55 billion.[3]

The treatment of pain is evolving and, in recent years, the use of opioid analgesics has increased. As a result, demand for opioids in the United States has risen 127% from 1997 to 2006.[4] In a healthcare environment where pain treatment standards and guidelines are not well established and educational curricula are not standardized,[5,6,7] clinicians have attempted to assemble policies, procedures and tools to accommodate patients' needs, build successful practices and adhere to government regulations. Despite these efforts, undertreatment or non-treatment of pain affects over 75 million people annually in the United States.[8]

Monitoring patient usage of Schedule II Controlled Substances is a major concern and the responsibility of prescribing clinicians. Opioids, as the most commonly prescribed Schedule II medications, are addictive substances known to be abused, misused and overprescribed. As a result, clinicians have utilized opioid monitoring to verify proper medication use, decrease misuse, identify and minimize addiction and prevent diversion. While these concerns are well founded, overemphasizing misuse and addiction limits the scope of monitoring to a subgroup of patients. It is estimated that addictive disorders occur in 10% of the general population.[9] A clinical study concerning long-term opioid therapy for non-cancer pain in patients who had been selected based on low risk of addiction found that a very small number of these patients developed addiction.[10] For patients outside the addiction subgroup, adherence is a significant issue. With approximately 45% nonadherence in pain patients, frequent and standardized clinical monitoring is imperative.[11] The annual financial impact on healthcare from medication nonadherence was estimated at $300 billion.[12] Adverse Drug Reactions (ADRs) contribute to nonadherence and may be prevented or lessened by early intervention using appropriate clinical drug monitoring and diagnostic tools.[1,13] In 1994, it was estimated that ADRs recorded in hospitalized patients were the 4th-6th leading cause of death in the United States affecting up to 137,000 people.[14] By utilizing tools capable of monitoring medi-

cation adherence and efficacy along with misuse and addiction, clinicians can improve outcomes for many of their patients.

The science of drug discovery and development provide an effective model for pharmacotherapeutic monitoring. The purpose of the FDA clinical drug trial approval process is to statistically demonstrate drug efficacy and safety prior to its release to the general public. The same diagnostic tools and procedures utilized to prove efficacy during a trial should also be applied post-trial to maximize drug efficacy in clinical use and are part of an FDA initiative known as co-development.

The most effective techniques available for monitoring pharmacotherapy are presented here as a practical, objective and comprehensive monitoring strategy called **Urine Drug Monitoring (UDM)**. This handbook places emphasis on utilizing UDM with opioid prescribing. This method merges current patient prescription information with the identification or lack of corresponding pertinent analytes within the patient, in addition to identifying pertinent nonprescribed, illicit or other drug substance(s) with the appropriate level of sensitivity, accuracy and precision. The overall goal is to objectify pharmacotherapy, identify patient prescription adherence/nonadherence and stratify these patients based upon biochemical, genetic, clinical and psychosocial parameters.

The suggestions are practical in that they are currently being utilized in clinical practice, all data collected is obtained using objective tools and the strategy is comprehensive utilizing a multidisciplinary monitoring approach. The authors have set up a companion blog for this handbook to encourage discussion about UDM concepts and components. We welcome you to join the discussion at **www.udmsolutions.com**.

Connections Between Clinical Drug Trials and Patient Pharmacotherapy

Pharmaceutical companies are required to conduct clinical drug trials in order to release a new drug to market. The trial validates and maximizes drug efficacy and safety and establishes effective therapeutic dosages. Though some access to diagnostics utilized in clinical trials is available in the post marketing phase, clinicians have not traditionally incorporated these diagnostics when structuring patient treatment. This is most likely due to real and perceived differences between the structure of clinical drug trials and individual patient pharmacotherapy. These differences include population sampling with many participants, candidate selection for optimal research outcomes,[15] limitations in the candidate selection process,[16] simplified trial parameters focused on demonstrating drug benefits[17] and statistical data analysis of results from multiple participants.[18] Despite these differences, there are practices, procedures and concepts from clinical drug trials that can be directly applied to or modified for individual patient pharmacotherapy to maximize efficacy and efficiency.

Individualization - Both clinical drug trials and patient pharmacotherapy rely on a process of selection/individualization to produce optimal outcomes. Prior to and during the trial, patients are selected who will have the greatest chance of demonstrating a therapeutic benefit from the medication. During post approval utilization, a medication(s) is selected that will demonstrate maximal efficacy and minimal toxicity. While subject and medication selection may be divergent, both individualizing processes must evaluate drug and patient to determine a complementary relationship and, ultimately, optimal outcomes.

Diagnostics - Reproducible data obtained using scientific methods and relevant diagnostics are required by the FDA for clinical drug trial reporting. These diagnostics are deemed the most appropriate for determining drug efficacy and efficiency and therefore, can continue to be utilized for the same purpose in routine patient pharmacotherapy.

Specialists - Clinical drug trials recruit specialists appropriate for the type of evaluation required for the research drug.[19] One example is employing specialists in both basic and clinical pharmacology to determine drug pharmacokinetics and pharmacodynamics. These specialists continue to be best suited for assessing clinical pharmacological data in the post marketing phase.

Informatics - Today, statistical data analyses, data mining/merging, interpretation and comprehensible, functional reporting performed in clinical drug trials rely heavily on computational power and appropriate biological data models.[20] These tools add efficiency to data intensive processes and are necessary at each patient encounter and in establishing and adjusting pharmacotherapy regimens.

Components of Urine Drug Monitoring (UDM)

Current methods used to monitor opioid efficacy in patient pharmacotherapy primarily rely on subjective feedback, objective clinical findings, limited diagnostic data and trial-and-error adjustments to the therapeutic regimen. Clinical drug trials have largely been referenced only for safe use of a drug based on generic population data rather than for monitoring techniques utilized in drug development research.

Urine Drug Monitoring (UDM) is an objective patient-specific pharmacotherapeutic monitoring strategy which logically combines practices and procedures employed in clinical drug trials with current prescribing practices. UDM is a single solution comprised of many complementary parts. Each component scientifically addresses a necessary piece of the drug monitoring equation.

The components of UDM are:

- Laboratory Diagnostics
- Clinical Pharmacology
- Pharmacogenomics and Pharmacogenetics
- Patient Assessment
- Medical Informatics

When appropriately utilized, UDM provides a scientifically sound drug monitoring strategy that allows:

- Enhanced clinician/patient relationship, trust and dialogue
- Optimization of patient pharmacotherapeutic regimens and treatment outcomes
- Improved prescription and overall treatment adherence
- Early identification of abuse, misuse, diversion and addiction
- Support for specialist referrals
- Medico-legal compliance to minimize regulatory scrutiny

The rationale for implementing UDM presented in the above list is expanded in Appendix A.

Laboratory Diagnostics in UDM

Scientific measurements obtained using appropriate diagnostics are fundamental data elements in UDM. Appropriate diagnostics are analytical drug testing procedures capable of identifying[9,21] and quantifying a parent compound and relevant metabolites.[1,8,13] Pharmacokinetic analysis by clinical pharmacologists depends on the sensitivity, specificity, precision and accuracy of these measurements.[1,13] This relationship between laboratory diagnostic data and clinical pharmacological analysis form the foundation of UDM.

Urine drug testing (UDT) is primarily used in clinical settings (e.g., patient pharmacotherapy, clinical drug trials) and workplace/non-clinical settings. The testing methodologies for each of these uses have differing focuses. Diagnostics for workplace/non-clinical settings are designed for rapid, large scale testing at low cost to qualitatively detect the existence of a drug class in urine. These tests were originally designed with high limits of detection to indicate use or abuse of illicit and/or prescription substances. In this setting, results are typically expected to be negative. In a clinical setting, results should indicate expected or unexpected drug use in accordance with medications a patient is currently prescribed. Clinical urine drug testing should provide parent drug(s) and/or relevant metabolite(s) identification[9,21] and quantification that are essential to clinical pharmacological analysis and the evaluation of drug efficacy and patient adherence to a therapeutic regimen.[1,13] Methodologies utilized by clinical drug trials (e.g., LC/MS/MS, GC/MS) are the most appropriate for obtaining clinically relevant data regarding the presence of urinary analytes (drug/metabolite).

Clinical Pharmacology in UDM

Clinical pharmacology is a complex discipline that draws on many different sciences pertaining to human pharmacokinetics and pharmacodynamics including chemistry, biochemistry, physics, genetics, physiology, pathology, nutrition, toxicology and forensics. Clinical drug trials rely on basic and clinical pharmacology for drug discovery and development. This process, when successful, maximizes drug safety and efficacy. This utilization of

basic and clinical pharmacology and new analytical technologies is integral to releasing a new drug to market.

To individualize pharmacotherapy, clinicians should integrate basic and clinical pharmacology with scientific analyses and laboratory data in relation to a patient's history and physical examination. These analyses consider how an individual patient's absorption, distribution, metabolism and elimination (ADME) of a drug or drugs, along with external factors including impurities, influence the collected data. ADME properties are studied and defined during drug development in a clinical drug trial by basic and clinical pharmacologists.[22] These specialists are trained and licensed to properly interpret, evaluate and validate individual patient pharmacotherapeutic drug usage data.

Pharmacogenomics and Pharmacogenetics in UDM

A primary process in achieving drug efficacy and efficiency is the personalization of patient pharmacotherapy. Variations in a patient's genetic profile influence a drug's pharmacokinetic and pharmacodynamic profile. This is inconsistent with current averaged or one-size-fits-all dosing paradigms. A patient's genetic profile should be considered when determining a pharmacotherapeutic regimen to accurately establish dosing.[23]

In UDM, individualizing patient pharmacotherapy is a primary goal. In clinical drug trials, genetic profiles are analyzed to identify patients who will increase the likelihood of successful research outcomes. These categories may be based upon pathobiological mechanisms providing predictive biomarkers that eliminate variability in drug responsiveness and optimize the selection of patient populations. In patient pharmacotherapy, the same selection process can be applied by changing the focus from patient selection to drug selection and dosing parameter customization. Metabolic genotyping and phenotyping identify patients with variable pharmacokinetics who most benefit from customized dosing thus optimizing drug safety and efficacy.[13,24]

Patient Assessment Tools in UDM

In clinical practice, adherence to prescription regimens is a prerequisite for clinical care.[25] Numerous factors influence patients' adherence. In UDM, the impact of pharmacokinetics, pharmacodynamics and pharmacogenetics[1,26] on adherence is measured by

laboratory diagnostics and analyzed based upon clinical pharmacological principles. Other factors that may contribute to adherence include patient personality and beliefs, socio-demographic and environmental issues, patient-clinician communication, severity and chronicity of health problems, complexity of treatment regimens (e.g., frequency of dosing), comorbid conditions, adverse effect profile and drug–drug interactions[25,27] Objective data concerning these additional factors can be collected and analyzed in UDM by utilizing validated assessment tools.

Patient adherence to prescription regimens is challenging for both clinical practice and clinical drug trials.[25] Results from clinical drug trials may be questioned or disregarded when adherence rates fall below acceptable levels. While there are no specific definitions and standards for these levels, scientific journals are reluctant to publish results from trials with less than 80% adherence.[25] To maximize adherence, clinical drug trials conduct pre-trial screening to select patients least at risk for adherence problems and in-trial adherence monitoring to detect problems and assign adherence-enhancing interventions.[25] Both assessment techniques utilized by clinical drug trials are relevant to improve adherence for individual patient pharmacotherapy. Initial patient assessments objectively identify psychological predispositions that may affect patient adherence. This allows clinicians to enlist specialists, efficiently provide adherence education and adjust pharmacotherapy regimens for their patients.[25] Adherence assessments, in combination with other UDM data and clinical pharmacological assessment, provide objective insight into the nature of developing adherence issues, allowing for timely treatment intervention.[25]

Medical Informatics in UDM

Data elements obtained by objective methods are at the core of the UDM strategy. UDM data is the starting point for clinical interpretation that assists in clinical decisions regarding patient pharmacotherapy. Proper clinical interpretation depends on the reliability, accuracy and completeness of these data, and clinical decisions, in turn, depend on appropriate clinical interpretation and contextual presentation of available data. In addition to direct evaluation of data elements, insight into aspects of patient pharmacotherapy status beyond the scope of individual data elements may be obtained through the careful analysis of multiple data elements, clinical models and evidence-based clinical knowledge. This broad relationship to patient pharmacotherapeutic data demonstrates

the need for the accessible, comprehensive and comprehensible presentation of monitoring information at each patient encounter. Medical informatics provide the most efficient solutions for the processing and comprehensible delivery of data.

A vast amount of data is collected during a clinical drug trial due to population sampling and trial duration. These data types collected vary widely to describe both the participants and the medication(s) and to measure response to treatment.[28] Clinical drug trials rely heavily on statistical analyses to evaluate these complex data to monitor research status and develop viable research conclusions.[29] Decisions made about how to perform statistical analyses are subjective and have the potential to produce different results and conclusions. The integrity of trial conclusions depends on careful a priori identification of the data type(s) and the appropriate selection of the most robust and unbiased statistical analyses. Clinical drug trials gain efficiency in this process through the computational power, organizational and archiving capabilities provided by medical informatics solutions. While data types and analyses may differ from those in clinical drug trials, patient pharmacotherapeutic data present similar challenges and can be analyzed more efficiently employing medical informatics. Large quantities of data can be collected during the course of long-term patient pharmacotherapy. Tasks that gain efficiency by incorporating medical informatics include the presentation of results and conclusions in a comprehensible, statistically significant format, the integration and analysis of heterogeneous data to provide insight for interpretation and clinical decisions and the organization and archiving of patient pharmacotherapy monitoring data for documenting treatment.

Opioid Pharmacotherapy Essentials

Key Note

All opiates are opioids, but not all opioids are opiates.

An accurate understanding of opioid classification, differences in chemical structures, pharmacokinetics, pharmacodynamics and pharmacogenetics is essential for effective patient pharmacotherapy. A common misconception is that the terms **"Opioid"** and **"Opiate"** are one and the same. According to scientific and molecular classification, however, this is not the case. Opioids are classified as either opiates or synthetic drug compounds. Opiates are natural alkaloids derived from poppy resin (opium) or semi-synthetics derived from natural alkaloids (see Table 1).

Table 1. Opioid Classification: Natural, Semi-synthetic, and Synthetic Opioids

Opioids	
Opiates	**Synthetics**
Natural alkaloids derived from poppy resin (opium) • Codeine • Morphine • Thebaine Semi-synthetics derived from natural alkaloids • Diacetylmorphine • Dihydrocodeine • Hydrocodone • Hydromorphone • Oxycodone • Oxymorphone	• Alfentanil • Buprenorphine • Butorphanol • Fentanyl • Levomethadyl • Levorphanol • Meperidine • Methadone • Pentazocine • Propoxyphene • Remifentanil • Sufentanil • Tapentadol[a] • Tramadol

[a]FDA approved but not commercially available in the United States at the time of this publication

Opioid Metabolic Pathways

When employing UDM in patient pharmacotherapy, clinicians must approach each patient individually. Patients are not generic, thus, individualized treatment is essential. Subjective patient feedback and objective clinical findings often determine clinical decisions regarding the initiation of or changes to drug regimens. Without objectively obtained monitoring data, this may not lead to effective and efficient treatment. The patient may fail to achieve the desired effect from the medication(s) and/or may experience unpleasant side effects. This scenario may lead to clinician concerns and questions regarding patient prescription adherence. Objective patient assessments and scientifically obtained and interpreted diagnostic data may increase the accuracy of clinical decisions. Customized drug selection, dosing, frequency and adjunctive therapy will maximize efficacy, efficiency and adherence.[1,13]

Pharmacogenomics and pharmacogenetics provide a platform to study how each patient's complex genetic makeup can affect his/her responsiveness to opioid medications (see Pharmacogenomics and Pharmacogenetic Testing for UDM section). Additionally, clinical pharmacology applies drug and patient specific pharmacokinetics and pharmacodynamics to maximize drug efficacy and safety (see Clinical Pharmacology for UDM section).

Opioid Pharmacokinetics

Pharmacokinetics (what the body does to the drug) is the science of the kinetics of drug absorption, distribution, metabolism and elimination (ADME). **Clinical pharmacokinetics** applies pharmacokinetic methods to drug therapy.[30] To optimize opioid pharmacotherapy, clinicians must understand the complexity of pharmacokinetics as it relates to metabolism, genetic and/or biological variations affecting metabolism, the role of both parent drug and relevant metabolite(s) and drug-drug interactions when optimizing opioid pharmacotherapy (see Clinical Pharmacology for UDM section).

To approach each patient individually, clinicians cannot rely on a mere "positive" or "negative" diagnostic test result for the opioid class. Accurate quantitative diagnostic data that is more useful in clinical decision-making is available from laboratories that utilize industry-leading analytical methodologies to quantify both parent analytes and pertinent metabolites in urine. This information provides the clinician with useful prescription adherence information.

Until recently, the importance and details of opioid metabolism as they pertain to clinical medication monitoring were not readily available to prescribers. An understanding of the various metabolic pathways and associated end products of commonly prescribed opioids assists in the accurate identification of a patient's regimen adherence. In addition, studies have revealed that a greater understanding of drug metabolism will enhance a clinician's interpretation of urine drug testing results.[2,31] There are a number of metabolic pathways to consider for patients taking opiate-based medications such as codeine, morphine, hydrocodone, hydromorphone, oxycodone and oxymorphone (see Clinical Pharmacology section). Table 2 displays the urinary analytes that are detectable in patients taking opiate-based medications. Table 3 displays additional excretion information for fentanyl and propoxyphene. For more detail including additional routes of metabolism and metabolites, see the Clinical Pharmacology for UDM section. For a list of generic/brand names of some common Opioid medications, see Table 4.

Table 2. Opiate Urinary Analytes That Are Also Prescribed Drugs[a]

Drug	Urinary Analytes
Codeine[b]	Codeine Morphine Hydrocodone
• Codeine: Prodrug metabolized via cytochrome P450 (CYP, P450, CYP450) 2D6 (CYP2D6) (*O*-demethylation) to morphine; analgesia dependent on CYP2D6 activity/morphine production • Morphine: metabolite, only morphine may be present in urine 30 hrs post administration[32] • Hydrocodone: minor metabolite (excreted in urine at concentrations of up to 11% of parent codeine)[33,34] • Minor amounts of 6-α–hydrocodol (dihydrocodeine) have been detected in urine[35]	
Morphine[c]	Morphine[33] Hydromorphone Codeine
• Hydromorphone: minor metabolite[36,37] • Codeine[d]: commercially manufactured morphine impurity (suggested to the extent of 0.04%)	

(continued)

Table 2. Opiate Urinary Analytes That Are Also Prescribed Drugs (continued)

Drug	Urinary Analytes
Hydrocodone[b]	Hydrocodone Hydromorphone 6-hydrocodol
• Hydrocodone and hydromorphone are expected urinary analytes after hydrocodone consumption • Hydromorphone: metabolite, metabolized from hydrocodone via CYP2D6, more conjugated hydromorphone excreted by rapid metabolizers (5.9%) than poor metabolizers (PM) (1%) from hydrocodone single dose in 48-hr urine[33] • Dihydrocodeine (6-α–hydrocodol): metabolite[32] *Note:* Hydrocodone is a minor metabolite of dihydrocodeine[a])[32]	
Hydromorphone	Hydromorphone
• The analyte detected in urine of patients administered hydromorphone is hydromorphone itself.[33]	
Oxycodone[b]	Oxycodone Oxymorphone Hydrocodone
• Oxymorphone: metabolite • Hydrocodone: commercially manufactured impurity ("allowable at a maximal limit of 1%")[38]	
Oxymorphone	Oxymorphone Oxycodone
• Oxycodone: commercially manufactured impurity ("no more than 0.30%")[39]	

[a] Detectable by liquid/gas chromatographic coupled mass spectrometry.
[b] Metabolized via CYP2D6.
[c] Excretion pH dependent.
[d] Certain investigators have suggested that codeine is also a minor metabolite of morphine, but most agree that codeine arises as an impurity in commercially manufactured morphine.

Clinically Significant Note to Table 2: Cytochrome P450 2D6 (CYP2D6) PM: approximately 5%-10% of Whites, 1% of Asians, up to 20% of Blacks, 3% of Mexican Americans, and 2% of Saudi Arabians.[40,41]

Table 3. Some Significant Urinary Excretion Percentages

Drug	Urinary Excretion Percentages[e]
Fentanyl	0.4%-6% fentanyl and 26%-55% norfentanyl (over 3-4–day period, intravenous dose)[32]
Propoxyphene	1.1% propoxyphene and 13.2% norpropoxyphene (20-hr urine, 130-mg single oral dose)[32]

[e] Expressed as a percentage of the dose.

Table 4. Some Common Generic and Brand Names of Opioids

Generic[42]	Brand[42]
Alfentanil	Alfenta®
Buprenorphine	Buprenex®, Subutex®
Buprenorphine/Naloxone[a]	Suboxone®
Butorphanol	Stadol®, Stadol NS®
Codeine/Acetaminophen (APAP)[a]	Capital® w/Codeine, Pyregesic-C, Tylenol® w/Codeine, Tylenol® w/Codeine #3, Tylenol® w/Codeine #4, Vopac™
Codeine/Aspirin (ASA)[a]	Empirin® w/Codeine
Codeine Phosphate/Guaifenesin[a]	Robitussin® AC, Guiatuss® AC, Tussi-Organidin-S NR®, Dex-Tuss Tussiden C®, Tusso-C®, Allfen® CD, Allfen® CDX
Codeine Phosphate/Promethazine Hydrochloride[a]	Phenergan® w/Codeine
Dihydrocodeine (DHC)	Paracodin
Dihydrocodeine/Aspirin/Caffeine[a]	Synalogos-DC
Dihydrocodeine/Acetaminophen/Caffeine[a]	Panlor® SS
Fentanyl	Actiq®, Sublimaze®, Fentora™, Duragesic®
Hydrocodone Bitartrate/Acetaminophen[a]	Lorcet®, Lortab®, Vicodin®, Anexsia®, Maxidone®, Norco®, Zydone®, Ceta Plus®
Hydrocodone/Bitartrate Homatropine Methylbromide[a]	Hycodan®, Hydromet®, Tussigon®
Hydrocodone Bitartrate/Ibuprofen[a]	Reprexain™, Vicoprofen®, Ibudone™
Hydromorphone	Dilaudid®
Levorphanol	Levo-Dromoran
Meperidine (Pethidine)	Demerol®, Meperitab®
Methadone	Dolophine®, Methadose®, Methadone HCl Intensol®

(continued)

Table 4. Some Common Generic and Brand Names of Opioids (continued)

Generic[42]	Brand[42]
Morphine	Avinza®, KADIAN®, MS Contin®, MSIR, Oramorph® SR, Roxanol™, Roxanol-T™, Rms
Morphine ER / Naltrexone	Embeda™
Nalbuphine	Nubain®
Oxycodone	OxyContin®, Roxicodone®, Oxydose®, Oxyfast®, Roxicodone Intensol®, Oxy® IR, Dazidox®, Eth-Oxydose™, Remoxy®™
Oxycodone Hydrochloride/ Acetaminophen[a]	Endocet®, Percocet®, Roxicet®, Roxilox®, Tylox®, Narvox, Magnacet™, Perloxx
Oxycodone Hydrochloride/ Aspirin[a]	Percodan®, Endodan®
Oxycodone Hydrochloride/ Ibuprofen[a]	Combunox™
Oxymorphone	Numorphan®, Opana®, Opana® ER
Pentazocine Lactate	Talwin®
Pentazocine Hydrochloride/ APAP[a]	Talacen®
Pentazocine Hydrochloride/ Naloxone Hydrochloride[a]	Talwin® NX
Propoxyphene	Pp-Cap, Darvon®, Darvon® N
Propoxyphene Napsylate/ Acetaminophen[a]	Darvocet-N® 50, Darvocet-N® 100, Darvocet® A500, Pronap-100®, Propoxacet-N®, Propoxacet-N® 100, Balacet® 325
Remifentanil	Ultiva®
Sufentanil	Sufenta®
Tapentadol	Brand Name Pending
Tramadol	Ultram®, Ultram® ER
Tramadol Hydrochloride/ Acetaminophen[a]	Ultracet®

[a] Drug order does not correlate with dosage order.

Implementing UDM for Opioid Pharmacotherapy

The components of UDM form a comprehensive objective monitoring strategy for patient pharmacotherapy in a clinical setting. To maximize medication efficacy and clinical efficiency when implementing a UDM strategy, it is important that clinicians closely evaluate how UDM components interrelate to affirm that the needs of their patients and their practice will be met.

UDM is a practical strategy for monitoring patient pharmacotherapy. While most of the tools required for UDM are currently available for use in opioid pharmacotherapy, some are in development and not currently available or standardized in a clinical setting.[43] The future standardization and acceptance of these tools will integrate easily in a UDM strategy to increase patient pharmacotherapy monitoring efficiency. UDM can be successfully applied with the tools that currently exist.

The following sections provide suggestions and resources to assist in the implementation of a UDM strategy. Guidance is provided throughout and collected in Appendix B.

Laboratory Testing Standards for UDM

Careful laboratory selection to perform reliable diagnostics within the UDM framework is essential. Scientific measurements obtained from laboratory diagnostics form fundamental data elements in UDM. This data is highly utilized by other UDM components and its accuracy will affect clinical interpretation of monitoring data and, ultimately, clinical decision-making. Laboratories should be evaluated by the clinician to determine laboratory quality and whether diagnostic solutions offered meet UDM implementation requirements for the practice.

Accreditations and Certifications

Accreditations and certifications are important to consider as they communicate organizational quality and demonstrate a commitment to continual improvement. There are many options available for laboratories to maintain licensure. When selecting a laboratory, clinicians should evaluate the significance of these governing structures as they pertain to their practice. A better understanding of what each accreditation may reveal about the laboratory's services and environment will help clinicians in the evaluation. To maintain leading industry accreditation (e.g., College of American Pathologists (CAP)) and required industry certification (i.e., Clinical Laboratory Improvement Amendments (CLIA)), a laboratory must sustain rigorous quality review and peer-based inspection of assay validity. In practice, clinicians should understand and consider a laboratory's accreditations and certifications when determining if a laboratory will provide scientifically accurate data applicable to patient treatment.

Specimen Selection

Urine has long been considered the preferred biological specimen for clinical drug analysis.[9] Diagnostic laboratories specializing in clinical applications regard urine as the biological specimen that provides the most appropriate data as it relates to drug elimination. See Appendix C for a comparison of biological matrices.

Urine specimens provide the following advantages in a clinical setting:

- Standard matrix for drug testing
- Extensively studied and documented pharmacokinetic elimination parameters
- Noninvasive collection procedures

- Large volume of specimen for multiple analyses
- Quantitative detection of parent drug and metabolite(s)

Additionally, urine provides an effective window of detection for current and recent use of most opioid-based preparations. Some factors that must be considered in the interpretation of detection time in urine include individual differences in hepatic and renal function, urine pH, dosage intervals, dosage strength and chronic use versus a single dose. Table 5 shows the typical opioid detection times in urine based on normal body excretion.

Table 5: Typical Opioid Detection Times in Urine[32,44-49]

Buprenorphine	Up to 11 days
Codeine	2 to 4 days
Fentanyl	2 to 3 days
Hydrocodone	2 to 4 days
Hydromorphone	2 to 4 days
Meperidine	2 to 4 days
Methadone	Up to 14 days
Morphine	2 to 4 days
Oxycodone	2 to 4 days
Oxymorphone	2 to 4 days
Propoxyphene	Up to 7 days
Tramadol	2 to 4 days
6-acetylmorphine	Less than 8 hours

Based on Enzyme Immunoassay (EIA) methodology

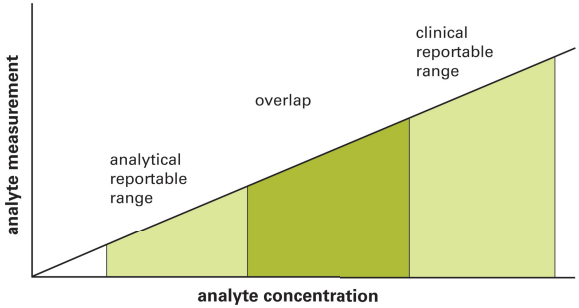
Usable quantitative data can be derived from the optimization of testing methodologies in a clinical laboratory. When monitoring medications, it is essential that these quantitative assays are sensitive and specific enough to detect the presence of parent drugs and metabolites. Before a laboratory method can be used for clinical testing, its analytical performance must be evaluated to demonstrate clinical significance. The scope of method evaluation varies, but should include the following key points:

- Linearity
- Precision
- Accuracy
- Sensitivity
- Specificity

Linearity

In its simplest form, linearity is a one to one relationship between an analytical measurement and the analyte of interest. Optimally, a linear relationship should form a straight line and represent the maximal overlap with an Analytical Reportable Range (ARR) and Clinical Reportable Range (CRR) (see Figure 1). If the overlap exists, an assay will detect the analyte present in a specimen.

Figure 1. Analytical Reportable Range vs. Clinical Reportable Range with Overlap



Limit of Quantification (LOQ) and Limit of Detection (LOD)

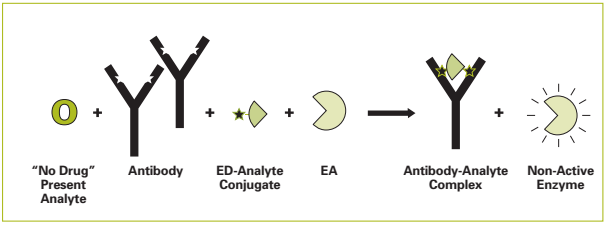
The laboratory usually establishes a Limit of Detection (LOD) and Limit of Quantification (LOQ) for each assay under development. In clinical testing, the LOD is the lowest quantity of a substance that can be distinguished from the absence of that substance within a stated confidence limit that has been established statistically. The LOQ is the specific and precise value determined by the laboratory where there is minimal chance of a false value and is the quantifiable lower limit at which a laboratory can determine the difference between two measurable values with confidence. Laboratory methods associated with increased assay sensitivity (lower LOQs) provide a greater opportunity to detect low parent drug levels, minor metabolites and potential contaminants associated with opioid pharmacotherapy.

Laboratory Testing Methodologies

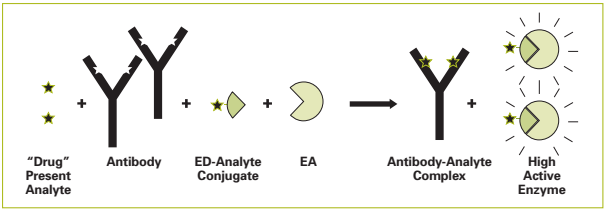
It is important to have an understanding of commonly employed testing methodologies when selecting a laboratory to perform routine urine drug testing. An optimal combination of quantitative testing methodologies provides many advantages related to the laboratory diagnostics component of UDM, including increased throughput, low LOQs and assay sensitivity.

One methodology commonly used in UDM is **Enzyme Immunoassay (EIA)**. An immunoassay is a biochemical test that measures the concentration of a substance in a biological liquid, using the reaction of an antibody or antibodies to its antigen. Various EIA methods can be used in the initial phase of testing to detect the presence of a drug(s) or drug class. In one example of an EIA method, free drug and enzyme-conjugated drug antigens compete for interaction with an analyte-specific antibody (see Figure 2). In the absence of free drug, the enzyme-conjugated drug binds to the antibody to preventing enzyme activity. If free drug is available in the specimen, the enzyme-conjugated drug antigen is displaced and an active enzyme forms. An output signal, directly proportional to the concentration of free drug, reflects this enzyme activity.

Figure 2. EIA Technology Principle



"No Drug" Present Analyte - Samples without analyte to compete for binding sites in the antibody result in reduced enzyme formation and subsequently lower absorbance values.



"Drug" Present Analyte - Analyte from the sample competes for binding to the antibody, making ED-analyte conjugate available for enzyme formation and subsequently higher absorbance values.
Figure courtesy of Thermo Fisher Scientific Inc., Fremont, CA.

EIA is an effective method used to detect the presence of a drug class and provides a number of different benefits to the UDM process. However, EIA will not definitively identify a specific analyte within the drug class detected and can present false results when: (a) the assay cross-reacts with the presence of structurally related compounds or non-specific interferences (e.g., turbidity); and (b) when drugs present are not detected below a certain LOQ. For example, an EIA assay is performed to detect the presence of morphine in a patient who has been prescribed morphine for chronic pain. This patient (if adhering to the prescription regimen) could produce a detected result for morphine (parent drug), hydromorphone (metabolite), and codeine (impurity). If there is drug present in the patient's urine at a quantity that can be detected by the EIA assay, the assay will provide an opiate/opioid positive result depending on the laboratory. EIA is unable to differentiate between the analytes present due to the fact that the similar chemical structures of morphine, hydromorphone and codeine will all engage the same analyte-specific antibody in the EIA assay. Cross-reactivities will vary depending on the methodology/reagent used by the laboratory. Therefore, EIA is limited in specificity and unable to differentiate between parent compound and metabolite (or potential impurity). For this reason, other analytical methods (to be discussed) are more clinically relevant in this scenario.

Table 6 illustrates analytes that have the potential for cross-reactivity in the opioid class utilizing EIA technology. If analytes listed in the right column "Analytes Present" are present in the specimen, there is potential that the analytes/classes listed in the left column "EIA Result" will be detected.

Table 6. EIA Cross Reactivity (Opioid Class)

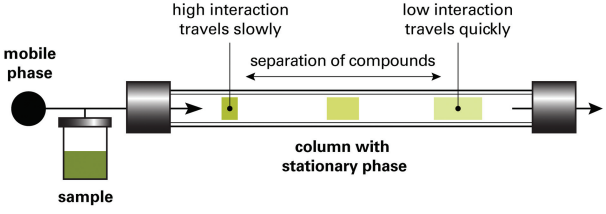
EIA Result[50]	Analytes Present[50]
EDDP	EDDP
Methadone	Methadone Alpha-Methadol LAAM Methadol Disopyramide

EIA Result[50]	Analytes Present[50]
Opiates	Morphine Codeine Poppy seeds[a] (morphine, codeine) Diacetylmorphine Dihydrocodeine Hydrocodone Hydromorphone Levofloxacin Ofloxacin *Low % cross-reactivity:* Naloxone Naltrexone Imipramine Oxycodone Oxymorphone
Oxycodone	Oxycodone Oxymorphone
Propoxyphene	Propoxyphene Norpropoxyphene

[a] May test positive up to 2,000 ng/mL (but occasionally higher).[51]

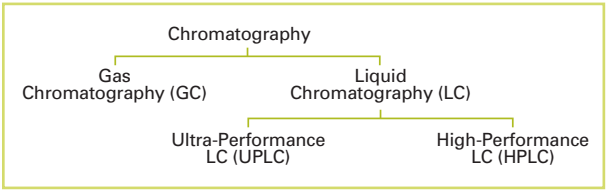
Chromatography is a more specific analytical method used to separate a mixture into its simpler components. Chromatography requires both mobile and stationary phases. In its mobile phase, this method carries the drug(s)/metabolite(s) of interest at a constant flow rate throughout the system when not interacting with the stationary phase. The stationary phase chosen is application-specific and determined by the chemical properties of the drug(s)/metabolite(s) to be detected (see Figure 3).

Figure 3. Column Chromatography



Unlike the enzyme-analyte interaction in EIA technology, the level of interaction of the analyte with the stationary phase in chromatography will differ depending on the analyte structure and stationary phase chemistry. Compounds that have little interaction with the stationary phase will quickly exit the system, spending most of their time traveling at the same flow rate as the mobile phase. Compounds that interact strongly with the stationary phase will be retained longer and therefore exit the system at a later time. This separation of compounds, resulting from the differential migration rates of analytes within the stationary phase column, allows for the highly specific quantitative detection of drug(s)/metabolite(s) by various chromatography methods (see Figure 4). Consider the morphine example described in the EIA section (where the detected result could be morphine, hydromorphone, or codeine). The main difference when using chromatography is the ability to quantify the levels of each individual analyte.

Figure 4. Types of chromatography.



In **Gas Chromatography (GC)**, the stationary phase employs a capillary column lined internally with a liquid coating. An inert gas (e.g., hydrogen, nitrogen, helium) carries specimen components into the capillary column where they undergo separation. Analysis times are often longer for laboratory results using GC because biological samples typically require more sample preparation time for this methodology. In urine, for example, water must be removed from the sample before injection into the GC system. Additionally, certain compounds must be chemically altered (derivatized) before analysis to increase their volatility. In GC, compound travel time (retention time) is largely dependent on column temperature. At higher temperatures, compounds exit the system more quickly thus reducing their retention times. It is often necessary to significantly increase the temperature of the GC column to allow compounds that have strong interactions with the stationary phase to exit the system.

In **Liquid Chromatography (LC)**, the stationary phase column is packed with solid particles while the mobile phase consists of liquid

solvents. A common LC mechanism for compound separation, the reversed-phase mode, exploits the polarity differences of the compounds of interest. This mode utilizes a hydrophobic (non-polar) stationary phase and a hydrophilic (polar) mobile phase. Due to the aqueous nature of the LC mobile phase, it is common to inject aqueous (water-based) samples directly, thus requiring minimal sample preparation time and minimizing result turnaround times when working with urine.

LC is used as a broad term that encompasses both **Ultra-Performance Liquid Chromatography (UPLC)** and **High-Performance Liquid Chromatography (HPLC)**. While GC had previously been the method of choice for chromatographers, UPLC has surpassed GC as the highest standard in biological analysis (see Table 7). With UPLC technology, first introduced in 2004, LC separations comparable to GC quality became possible. Today, UPLC often provides faster analysis times and improved sensitivity (limits of detection) over GC.

Table 7. Chromatography Technique Comparisons

Technique	Sample Size	Average Analysis Time	Laborious Sample Prep	Derivatization Required
GC	Large	10 min	Yes	Typically
HPLC	Small	10 min	No	No
UPLC	Small	3 min	No	No

Chromatographic methods are often coupled with **Mass Spectrometry (MS)** to analyze samples with improved levels of specificity and sensitivity. Mass spectrometry is an analytical technique that identifies the chemical composition of a compound based on its mass-to-charge ratio. MS is capable of analyzing nearly all pharmaceutical compounds and is configurable with both GC and LC systems. The MS system consists of three parts: (1) ionization source, (2) mass analyzer, and (3) detector. In the ionization source, compounds of interest are ionized as they enter the mass spectrometer. The ionization sources used for GC and LC differ because the compounds enter the respective ionization chambers in different phases. The compound is already in the gas phase when it exits the GC column, but is in the liquid phase when exiting the LC

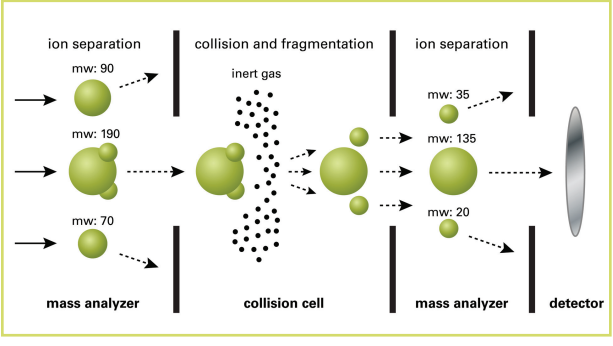
column. Analytes must be in the gas phase for analysis using MS. In the mass analyzer, ions are separated based on their masses (more specifically their mass-to-charge ratios). Finally, the number of ions that travel through the mass analyzer and reach the detector is proportional to the signal observed (used for quantification).

In **Gas Chromatography/Mass Spectrometry (GC/MS)**, electron impact (EI) ionization creates many small ions by bombarding the compound of interest with a beam of electrons. Drug(s)/metabolite(s) and similarly structured compounds from the same drug class typically have similar fragmentation patterns, thus producing identical ions and creating opportunities for interferences to occur in this stage.

Alternatively, **Liquid Chromatography/Mass Spectrometry (LC/MS)** and **Ultra-Performance Liquid Chromatography/Tandem Mass Spectrometry (UPLC/MS/MS)** use electrospray ionization (ESI). In ESI, the liquid mobile phase becomes charged and is subjected to high temperatures and high gas flows to facilitate solvent evaporation as it enters the MS. Charge is transferred to the compound of interest creating an ion that can be separated from other ions in the mass analyzer.

Laboratories may differ in their use of the mass analyzer portion of the MS system in which various ions are separated from each other. A single quadrupole mass spectrometer uses a single stage MS system to filter ions of interest from unwanted ions (i.e., GC/MS). A tandem mass spectrometer (see Figure 5) uses two MS systems in tandem to provide greater specificity. The combination of UPLC and tandem mass spectrometry (UPLC/MS/MS) is the optimal test methodology to use in the detection of opioids in clinical practice (see Appendix D).

Figure 5. Tandem Mass Spectrometry



UDM requires comprehensive knowledge of the analytical methods available for clinical use. When evaluating and selecting laboratory solutions that will best meet the needs of their patients and their practice, clinicians need to consider the advantages and disadvantages of each method. Table 8 is a general comparison of analytical methods currently available.

Urine Specimen Validity

Clinical laboratories have the ability to measure specimen validity to normalize laboratory results for the sake of comparison. Specimen validity refers to specific characteristics used in determining consistency with normal human urine. The following biological and validity markers are important to measure.

Biological Markers

Creatinine is a product of muscle contraction and is excreted at a relatively constant rate in urine. Its level in urine may be used as an indication of hydration. The normal range for creatinine in urine is 20 to 400 mg/dL. Levels below 20 mg/dL suggest overhydration by excessive fluid intake or intentional dilution of the specimen with an adulterant such as water. Creatinine-adjusted values can be used for drug elimination monitoring. Creatinine-adjusted values can only be calculated in conjunction with linear assays.

Urine **specific gravity** refers to the amount of dissolved substances in a specimen. Specific gravity measures the density of urine relative to the density of water, which is 1.000. The normal range is 1.003 to 1.030.

Urine **pH** measures acidity or alkalinity in a specimen. The average urinary pH is approximately 6.0 and the normal range can vary from 4.5 to 9.0. Values outside this range may be an indication of adulteration.

Validity Markers/Commercial Adulterants

An adulterant is any substance that is added to the urine for the purpose of interfering with the test analysis. Oxidants are a specific category of adulterants that work by altering the chemical structure of a drug. The most commonly used oxidants are nitrites, chromates, iodine, bleach and peroxidase. Laboratories may test for different combinations of these common oxidants to confirm specimen validity (see Appendix F).

Table 8. Methodology Rating Chart[a]

E=Excellent, G=Good, F=Fair, P=Poor, VP=Very Poor, U=Unattainable

	UPLC/MS/MS	UPLC/MS	GC/MS/MS	HPLC/MS/MS
Quantifiability[e]	E	E/G	E	E
Limit of detection	E	G	E/G	E/G
Sensitivity	E	E	G	G
Ease of sample preparation	G	G	P	F
Specificity (non-crossreactants)	E	G	E	G
Specific analyte identification (true-positive/true-negative)	E	G	E	E
Turnaround time	E/G	E/G	F/P	E/G
Minimal sample volume required	E	E	P	G
Linearity	E	E	E	E
Environmental friendliness	G/F	G/F	VP	F

[a] Ratings are based on Dominion Diagnostics' methodologies.
[b] CEDIA® Enzyme Immunoassay (EIA) assays performed and validated by Dominion Diagnostics as quantifiable using CAP standards
[c] Thin-layer chromatography (TLC)
[d] Point-of-care immunoassay (POC IA) based on lateral flow technology. Examples: cups, dipsticks (see Appendix E)
[e] Methodology must be validated as linear as the only way to be quantifiable.
[f] Some of the product may be recycled

GC/MS	HPLC/MS	GC	HPLC	EIA[b]	TLC[c]	POC IA[d]
E/G	E/G	F	P	G	U	U
G	G	G	F	F	VP	P
F	F	F	P	F	VP	VP
P	E	P	E	E	F	E
G	G	F	P	P	P	P
G	G/F	U	U	U	U	U
F/P	E/G	F/P	E/G	E	E	E
P	G	F/P	F	E	G	F
E	E	G	G	G	U	U
VP	F	VP	F	G	P	F/P[f]

Research and Development

One measure of laboratory quality is the capacity to recognize clinically relevant needs and to respond with scientifically accurate technologies. To accommodate future clinical testing requirements, laboratories must aggressively invest in research and development. It is important to evaluate and select laboratories whose test offerings and choice of testing methodologies are based on the latest clinical research and scientific technological developments.

Guidance

Specificity and Sensitivity

Clinicians should request assays which provide complete data sets for UDM components utilized in clinical decisions regarding patient pharmacotherapy.

Lack of detail or accuracy in data can produce misleading conclusions and limit clinical decision-making. Assays with limited specificity and sensitivity may not identify specific analytes, pertinent metabolites, impurities or low levels of drug presence

Guidance

Specimen Validity

Establish the integrity of the specimen.

Specimen validity is required for clinician confidence in laboratory results independent of the sensitivity and specificity of an assay. It is difficult to establish specimen validity without the use of laboratory diagnostics, even with closely observed specimen collection.

Clinical Pharmacology for UDM

The practical application of the science of pharmacology is the basis of clinical pharmacology and includes pharmacokinetics, pharmacodynamics and pharmacogenetics. Every drug has a pharmacodynamic, pharmacokinetic, therapeutic and toxic profile at each distinct dosage form, amount and frequency. In combination with other medications, phytopharmaceuticals (herbals), nutraceuticals (vitamins), illicit drugs and food products, pharmacological responses may be augmented, exacerbated, diminished and/or altogether altered. A critical component of clinical pharmacology in a UDM strategy is the optimization of patient care (e.g., maximizing therapeutic effect, minimizing side effects, preventing drug-drug interactions, enhancing medication safety, diminishing toxicologic events, improving efficacy). Therefore, a working understanding of pharmacokinetics and pharmacodynamics in clinical practice is imperative.

Pharmacokinetics

Pharmacokinetics (what the body does to the drug) is the science of the kinetics of drug absorption, distribution, metabolism and elimination (ADME). A drug's ADME properties are influenced by countless chemical, biochemical and genetic processes. Some factors that may influence drug ADME properties are listed in Table 9.

Table 9. Some Factors Influencing Drug ADME[1]

Dosage form, route, dose
Route and rate of drug administration
Site of drug administration (local and systemic absorption)
Frequency of drug administration • Minimum effective drug concentration • Saturation of receptors and drug accumulation
Route and rate of distribution • Membrane permeability • Blood perfusion of organs and tissues
Extent and volume of distribution
One-compartment vs multi-compartment models

(continued)

Table 9. Some Factors Influencing Drug ADME (continued)

Drug–protein binding (e.g., albumin, alpha-1 acid glycoprotein) Concentration of protein available for drug–protein binding Quality of physicochemical nature of the protein synthesized Reduction in binding due to hepatic and renal insufficiency and other disease states
Drug–drug interactions, drug/food–herbal interactions
Cytochrome P450 inhibitors and inducers, enzyme deficiencies or upregulation, multiple genes, polymorphisms
Enterohepatic recycling
Renal and hepatic function
Disease states
Disease states and medications affecting absorption Intestinal blood flow, alterations in stomach emptying time, gastrointestinal (GI) motility, alterations in GI pH (degree of drug solubility in stomach and drug ionization in intestines), permeability of the gut wall, bile secretion, digestive enzyme secretion, alteration of normal GI flora
Sampling Time (e.g., post beta distribution phase, concentration at steady state (SS), trough level)
Altered GI tract
Pregnancy
Body weight, surface area, and muscle mass
Cardiac output
Age
Environmental factors
Sex

The role of pharmacists and PharmDs (Doctors of Pharmacy) is expanding in patient pharmacotherapy. These specialists are trained to consider each of the factors that are essential to UDM including the patient's history, medication profile, laboratory diagnostics data, physiology and patient feedback. Additionally, these specialists consider the ADME properties published in the drug manufacturer's package insert when assisting in pharmacological assessments. Clinicians should consider employing these specialists to improve patient safety and drug efficacy.

Metabolism (Biotransformation)

The main pathway for elimination of most drugs is through their biotransformation, also known as metabolism. Drugs are altered through metabolism facilitating excretion into urine and bile. Compounds undergo Phase I and Phase II metabolism to transform lipophilic and less polar drugs into hydrophilic and more polar metabolites. Active metabolites, toxic metabolites and metabolic interactions are some of the by-products of metabolism. It is imperative to completely comprehend drug metabolism and metabolite formation in determining and addressing the pharmacokinetic and pharmacodynamic profiles of medications.[27,52]

In phase I metabolism, compounds acquire hydrophilic functional groups through oxidation, reduction and hydrolysis reactions (see Table 10). See Table 12 for more information on the oxidation reaction in the Cytochrome P450 system.[27,52]

Table 10. Phase I Functionalization (Nonsynthetic) Reactions

Reactions	Some Enzymes Involved
Oxidation	Oxygenases and oxidases: cytochrome P450[a] (CYP, P450, or CYP450), flavin-containing monooxygenase (FMO), xanthine oxidase, others
Reduction	Reductase: quinone reductase and aldo-keto reductase
Hydrolysis	Hydrolytic enzymes: amidase, esterase, others

a Most important enzyme system

In phase II metabolism, conjugation transpires between metabolites, parent compounds and endogenous substrates. Glucuronidation is considered the most important of the conjugation reactions (see Table 11). The resulting polar molecule is water soluble and easily excreted. Aqueous (water) systems attracting polar compounds are urine (renal excretion) and bile (hepatic excretion). In both renal and hepatic excretion, high drug concentrations create competition between the drug transport systems allowing for drug accumulation.[27,52]

Table 11. Phase II Biosynthetic (Conjugation) Reactions

Most common: glucuronidation—glucuronic acid interacts with functional groups (e.g., OH, SH, NH2, CO2) to create a very polar (water soluble) molecule
Others: sulfation, acetylation, methylation, glutathione conjugation

Table 12. Typical Opioid-Specific Cytochrome P450 (CYP) Enzymes[35,53-59]

Drug	CYP Substrate	CYP Inhibitor
Alfentanil	**3A**	
Buprenorphine	**3A**	**1A2, 2A6, 2C19, 2D6**
Butorphanol		**2D6**
Codeine	**2D6, 3A**	**2D6**
Dihydrocodeine	**2D6**	
Fentanyl	**3A**	**3A**
Hydrocodone	**2D6**	
LAAM	**3A**	
Meperidine	**2B6, 2C19, 3A, 2D6, 2C18, 1A1, 1A2, 2C8, 3A5, 3A7, 4A11**	
Methadone	**3A, 2C9, 2C19, 2D6, 2B6, 1A2**	**2D6, 3A**
Morphine	**2D6**	
Oxycodone	**2D6**	
Propoxyphene	**2D6**	**2C9, 2D6, 3A**
Remifentanil	**Unknown**	**2D6**
Sufentanil	**3A**	
Tramadol	**2B6, 2D6, 3A, 2C19**	

KEY

For Substrate

Red Major (clinically significant role in drug's metabolism)
Blue Minor (clinically insignificant role in drug's metabolism)
Black Other (all others)

For Inhibitors

Red Strong inhibitor (drug strongly inhibits enzyme)
Green Moderate inhibitor (drug moderately inhibits enzyme)
Blue Weak inhibitor (drug weakly inhibits enzyme)
Black Other (all others)

Table 13 provides other routes of metabolism and metabolites in addition to the CYP450 enzymes.

Table 13. Some Routes of Metabolism and Metabolites[26,32,33,35,38,39]

Parent Drug	Routes of Metabolism	Metabolites
Alfentanil	*N*-dealkylation *O*-dealkylation Ring hydroxylation Amide hydrolysis Conjugation	*Inactive:* *O*-demethylnoralfentanil *N*-(4-hydroxyphenyl) propanamide *N*-(4-hydroxyphenyl) acetamide *Activity unknown:* Noralfentanil
Buprenorphine	*N*-dealkylation Conjugation	*Active:* Norbuprenorphine
Butorphanol	*N*-dealkylation Hydroxylation Glucoronidation *Extensive first-pass metabolism*	*Inactive:* Hydroxybutorphanol *Activity unknown:* Norbutorphanol
Codeine	*O*-demethylation *N*-demethylation Glucoronidation Sulfation	*Active:* Morphine Hydrocodone (minor) Morphine-6-glucuronide Norcodeine Normorphine Morphine-3-glucuronide *Inactive:* Codeine-6-glucuronide

(continued)

Table 13. Some Routes of Metabolism and Metabolites (continued)

Parent Drug	Routes of Metabolism	Metabolites
Diacetyl-morphine	Spontaneously Deacetylated in blood Blood esterases Hydrolysis	*Active:* Morphine Morphine-6-glucuronide Morphine-3-glucuronide 6-acetylmorphine (6-AM) Codeine (impurity) Normorphine *Inactive:* 6-acetylcodeine (by-product impurity)
Dihydrocodeine (6-α-hydrocodol)	*N*- and *O*-dealkylation *N*- and *O*-demethylation Glucuronide or sulfate conjugation at the 3- and 6-hydroxy positions 6-Keto reduction *Extensive first-pass metabolism*	*Active:* Dihydromorphine Hydrocodone *Activity unknown:* Nordihydromorphine Nordihydrocodeine
Fentanyl	*N*-dealkylation Hydrolysis	*Inactive:* Norfentanyl Despropionylfentanyl Hydroxyfentanyl Hydroxynorfentanyl 4-*N*-anilinopiperidine Propionic acid
Hydrocodone	*O*-demethylation *N*-demethylation Reduction of 6-keto group	*Active:* Hydromorphone Norhydrocodone Norcodeine 6-β-hydrocodol 6-α-hydrocodol (dihydrocodeine) 6-β-hydromorphol 6-α-hydromorphol

Parent Drug	Routes of Metabolism	Metabolites
Hydromorphone	Hydroxy reduction Glucuronidation Ketone reductase	Active: Hydromorphone-3-glucuronide (H-3-G) 6-α-hydromorphol 6-β-hydromorphol (dihydroisomorphine)
Levorphanol	Glucuronidation	*Inactive:* Norlevorphanol
Meperidine	De-esterification Hydrolysis *N*-demethylation Conjugation *Excretion pH dependent*	*Active:* Normeperidine (nonopioid) Meperidinic acid Normeperidinic acid
Methadone R-methadone (active) S-methadone (inactive)	Mono- and di-*N*-demethylation (primary) Spontaneous cyclization Hydroxylated Conjugation *Excretion pH dependent*	*Inactive:* 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP) *Activity unknown:* Methadol Normethadol
Morphine	*N*-demethylation Glucuronidation *Considerable first-pass metabolism*	*Active:* Codeine (impurity) Hydromorphone (minor) Morphine-6-glucuronide (M-6-G) Normorphine-3-glucuronide Normorphine-6-glucuronide Morphine-3-glucuronide (M-3-G): neurotoxicity, hyperglycemia, not analgesic

(continued)

Table 13. Some Routes of Metabolism and Metabolites (continued)

Parent Drug	Routes of Metabolism	Metabolites
Nalbuphine	*N*-dealkylation Conjugation *Considerable first-pass metabolism*	*Inactive:* Nornalbuphine
Oxycodone	*N*- and *O*-demethylation	*Active:* Oxymorphone Hydrocodone (minor impurity) *Inactive:* Noroxycodone (relatively inactive)
Oxymorphone	Reduction/ conjugation with glucuronic acid Extensive hepatic metabolism	*Active:* 6-OH (oxymorphone) Oxycodone (minor impurity) *Activity unknown:* Oxymorphone-3-glucuronide
Pentazocine	Oxidation Glucuronidation *Extensive first-pass metabolism; metabolism increased in smokers*	*Inactive:* Pentazocine glucuronide *Activity unknown:* *Cis*-hydroxypentazocine *Trans*-carboxypentazocine
Propoxyphene	*N*-demethylation Aromatic hydroxylation Ester hydrolysis Conjugation *Considerable first-pass metabolism*	*Active:* Norpropoxyphene (nonopioid) *Not reversed by naloxone—accumulates leads to pulmonary edema, QTC prolongation, and cardiac arrhythmias*

Parent Drug	Routes of Metabolism	Metabolites
Remifientanil	Ester hydrolysis *N*-dealkylation	*Inactive:* GI-90291 GI-94219
Sufentanil	Dealkylation Demethylation *Readily crosses blood–brain barrier*	*Active:* *O*-desmethylsufentanil *Activity unknown:* *N*-desalkylsufentanil
Tramadol	*N*-demethylation *O*-demethylation Glucuronidation Sulfation *Extensively metabolized*	*Active:* *O*-desmethylnortramadol *O*-desmethyltramadol (M1) *Activity unknown:* Nortramadol Dinortramadol *O*-desmethyldinortramadol

Pharmacodynamics

Pharmacodynamics (what the drug does to the body) is the relationship between a drug's concentration at the site of action and its pharmacologic response, including the biochemical and physiological effects that manipulate drug-receptor binding.[30] These interactions can create both pharmacologic and toxic outcomes. The pharmacological effect of a drug is affected by the dosage form, dosage amount, route of administration, site of administration (local absorption), the rate extent of systemic drug absorption, patient specific genetics, elimination pathways, organ functions and disease states.

Understanding Opioid Receptors

The pharmacological effects of opioid analgesics are derived from their complex interactions with the opioid receptors: mu (μ), delta (δ), kappa (κ) and Nociceptin/Orphanin (NOP). Tables 14 and 15 outline these opioid receptors and some of their primary characteristics. Table 16 illustrates exogenous ligands that act as agonists and antagonists to the three main receptors.

Table 14. Opioid Receptors and Some of Their Characteristics[27,57,60-62]

	μ Receptor	
Previous Names	OP_3, MOR, MOR-1	
Some Physiologic and Tissue Functions	Modulates response to pain, physical dependence and reward, stress responsivity, learning and memory, emotions, mood, feeling, thermoregulation (hypothermia), hormone secretion, GI motility; immune, neuroendocrine, respiratory, cardiovascular, sexual function; disinhibition of mesolimbic–mesocortical dopamine pathways that reinforce opioid properties; pupillary constriction; inhibition of neurotransmitter release	
Receptor Subtypes (Proposed Actions)	μ_1 (analgesia) μ_2 (sedation, physical dependence, delayed GI motility, vomiting, urinary retention, respiratory depression, euphoria, miosis, anorexia)	
Endogenous Ligands	β-endorphin +++ Endomorphin-1 (agonist) Enkephalins ++ Dynorphin A ++ Dynorphin B + α-neoendorphin +	
Transduction Mechanisms	*Gi/G0 family* Effector/response: Adenylate cyclase stimulation Adenylate cyclase inhibition Phospholipase C stimulation Potassium channel Calcium channel Phospholipase A_2 stimulation Phospholipase D stimulation	*Gq/G11 family* Phospholipase C stimulation

δ Receptor	κ Receptor	
DOR, DOR-1, delta, OP_1	KOR, KOR-1, OP_2	
Modulates the effects of μ-receptor directed compounds; analgesia, spinal analgesia, GI motility, mood regulation, behavior regulation, cardiovascular regulation; spinal anesthesia (mouse); GABAergic inhibition; thermal hyperalgesic reversal; seizure-promoting activity	Water diuresis (vasopression); stimulation of prolactin release; sedative and interoceptive effects in humans (psychotomimetic, dysphoric, potentially hallucinogenic); modulation of dopaminergic function; antinociception; immune changes; inhibits pruritis; enhancement of food intake; hypothermia induction; alleviates abdominal pain and bloating	
δ_1 and δ_2 (δ and μ receptors interact, augmenting antinociception)	(proposed) κ_1, κ_2, κ_3	
Enkephalins +++ β-endorphin +++ Dynorphin B + α-neoendorphin +	Dynorphins: A,B +++ β-endorphin α-neoendorphin +++	
Effector/response: Adenylate cyclase inhibition Phospholipase C stimulation Potassium channel Calcium channel	*Gi/G0 family* Effector/response: Adenylate cyclase inhibition Potassium channel Calcium channel	*G12/G13 family* Phospholipase C stimulation

(continued)

Table 14. Opioid Receptors and Some of Their Characteristics (continued)

	μ Receptor
Receptor Locations: Human	Immune cells (T/B lymphocytes, CD4+, monocytes/macrophages, neutrophils); dermal and epidermal nerve fibers
Some Proposed Receptor Locations	CNS and spinal cord: caudate putamen, nucleus accumbens, locus coeruleus, thalamus, globus pallidus, cerebral cortex, hippocampus, substantia gelatinosa, amygdaloid nuclei, hypothalamus, ventral tegmental area, central gray, dentate gyrus, substantia nigra; GI tract; optic tract; cochlea; pregnant uterus
Genes	*OPRM1* located on chromosome 6
Polymorphisms/ Phenotypes	A118 is the wild type. G118 *OPRM1* mutation increases sensitivity to opioids (require smaller doses) and therefore may be associated with addiction; decreases opioid-induced nausea and vomiting; increases response to naloxone. Allelic frequency: 10%-14% of Caucasians, Hispanics, and Native Americans; 35%-49% of Asians; 2.5% of African Americans; 17% of Ethiopians; 21% of Ashkenazi Jews.

Table 15. Nociceptin/Orphanin (NOP) Receptor and Its Characteristics[27,57,60]

Previous Names	OP4, ORL1, LY322, N/OFQ receptor
Physiologic Functions	Motor and aggressive behaviors; reinforcement and reward; nociception; the stress response; control of the autonomic and immune functions; inhibition of glutamate, acetylcholine, serotonin, glutamate, noradrenaline; NOP agonist-induced anxiolytic, anxiogenic, cardiovascular depression, and water diuretic activity
Exogenous Ligands	Buprenorphine

(continued)

δ Receptor	κ Receptor
Skin; immune cells CNS (wide distribution) and spinal cord; GI tract; cochlea; pregnant uterus; placenta; embryo	Skin; immune cells CNS (wide distribution); GI tract; cochlea; pregnant uterus
OPRD1 located on chromosome 1	*OPRK1* located on chromosome 8
—	—

Table 15. Nociceptin/Orphanin (NOP) Receptor and Its Characteristics (continued)

Endogenous Ligands	Nociceptin/orphanin FQ (N/OFQ)
Transduction Mechanisms **Gi/G0 family**	Effector/response: Adenylate cyclase inhibition Potassium channel Calcium channel
Receptor Locations	CNS, cerebral: hippocampus, cerebellum, striatum; immune system cells; other peripheral tissues

Table 16. Exogenous Ligands of Opioid Receptors[27,57,60-62]

+ indicates agonistic affinity; – indicates antagonistic affinity

μ Receptor	δ Receptor	κ Receptor
Agonists:		
Buprenorphine (PA) +++ Butorphanol (PA) Codeine (very weak) Dihydromorphine +++ Fentanyl +++ Levorphanol +++ Methadone +++ Morphine +++ Normorphine +++ Pentazocine (PA) Sufentanil +++ Nalbuphine P Alfentanil Hydrocodone Dihydrocodeine Levorphanol Oxycodone Oxymorphone Meperidine Remifentanil Propoxyphene Tramadol	Buprenorphine Dihydromorphine Normorphine S-methadone S-pentacozine Sufentanil + Levorphanol Morphine Fentanyl Codeine (weak)	Butorphanol +++ Dihydromorphine Fentanyl Morphine + (weak) Nalbuphine ++ Nalorphine + Methadone Pentazocine ++ Sufentanil + Codeine Dihydrocodeine Propoxyphene Oxycodone Levorphanol
Antagonists:		
Nalbuphine – – Nalorphine – – – Naloxone – – – Naltrexone – – – Naltrindole – Pentazocine (partial antagonist) Buprenorphine	Naloxone – (weak) Naltrexone – (weak) Naltrindole – – – Buprenorphine	*Antagonists:* Buprenorphine[a] – – Diprenorphine – – – Naloxone – – Naltrexone – – – Naltrindole – Butorphanol

PA, partial agonist.

The pharmacokinetic and pharmacodynamic properties of a drug are characterized, quantified and modeled using laboratory diagnostic procedures developed and performed prior to and during the FDA approval process. Once a drug is approved, most of these diagnostic procedures are not performed in conjunction

with a patient receiving a prescription drug. Statistically about 50% of the drugs we consume do not demonstrate appropriate clinical efficacy.[63,64] As partly discussed in this section, the reasons for failure are numerous and may be ascertained using current laboratory technology.

In opioid pharmacotherapy, pharmacokinetic and pharmacodynamic parameters may vary depending on genetics, dosage, age, organ functions, or other factors listed in Table 9. As discussed in the Opioid Pharmacotherapy Essentials section, examining the molecular structure, chemistry, metabolism and elimination of opioids is important to understand side effects, drug-drug interactions and patient responses to opioid pharmacotherapy.

Guidance

Interpretation of Laboratory Diagnostics

Clinicians should apply clinical pharmacology when interpreting laboratory diagnostics.

Professionals trained in clinical pharmacology understand the complexity of individual patient pharmacotherapy (i.e., pharmacokinetics, pharmacodynamics and pharmacogenetics) and can assist in accurate interpretation of laboratory results. The most appropriate specialist to provide accurate and up-to-date interpretation of laboratory results is a clinical pharmacologist. Patient monitoring without applying clinical pharmacology could lead to inadequate patient care and/or have legal implications. Limited knowledge in common opioid pathways, as one example, may result in the misidentification of common metabolites/impurities and be misinterpreted as drug misuse. Scenarios such as this lead to suboptimal treatment or disposition decisions.

Pharmacogenomics and Pharmacogenetic Testing for UDM

"Pharmacogenomics and pharmacogenetics are both important disciplines involved in the study of genes that code for drug metabolizing enzymes, drug receptors, drug transporters, and ion channels or efflux systems."[30] Pharmacogenomics studies the role of genetic variation in the entire genome; pharmacogenetics studies genetic variation in specific genes of interest.

Essential to UDM is a clear understanding of the complex genetic polymorphisms that affect a patient's responsiveness to specific drugs. "It is impossible for prescribers to identify what the dose-response relationship will be in a given patient from a medical history and physical examination."[23] This genetic information may assist clinicians in personalizing and enhancing pharmacotherapeutic outcomes in the transition from subjective trial-and-error prescribing to objective drug regimen selection.

Traditionally, the interindividual variability in opioid response has been evaluated using standard subjective criteria such as patient perception. Prescribers now recognize the importance of genetic factors in influencing the pharmacokinetics and pharmacodynamics of opioid drugs. Among these genetic factors are polymorphisms in the receptors, transporters, metabolizing enzymes and intracellular signaling molecules involved in mediating opioid responsiveness.

Mu (μ) opioid receptor

The analgesic, as well as respiratory depression and euphoric actions of opioids are mediated in response to receptor activation and subsequent intracellular signaling. Pharmacological and molecular cloning studies have identified the opioid receptor types as mu (μ), delta (δ), kappa (κ) and Nociceptin/Orphanin (NOP). Most of the clinically used opioids are relatively selective for the μ-opioid receptor (OPRM1). Currently over 100 polymorphisms have been identified in the human OPRM1 gene, the most commonly identified polymorphism being the A118G SNP. Expressed at an allelic frequency of 2-48% depending on ethnicity, this missense mutation results in an amino acid exchange from arginine to aspartic acid (N40D) in the N-terminal region of the protein. The result is the loss of a putative N-glycosylation site in the extracellular receptor region of the protein.[65] Current data suggests that carriers of the 118G allele, as compared to their

non-carrier counterparts, may show a reduced effect to opioid agonists and an attendant increase in opioid dosing requirements (see Table 17). Available data linking additional OPRM1 genetic variations to changes in opioid efficacy and/or dosage requirements remains limited. While these studies support an association between genetic variability in the OPRM1 gene and altered opioid effects, further research is needed to determine if mutations in the μ-opioid receptor are important for opioid therapy.

Table 17. Clinical responses associated with A118G polymorphism

Requirement for higher doses of alfentanil for postoperative pain relief
Requirement for higher doses of morphine for cancer pain treatment
Decreased miotic potency of morphine and morphine-6-glucuronide
Decreased analgesic potency of morphine and morphine-6-glucuronide
Decreased nausea following morphine-6-glucuronide administration
No impact on methadone dosage requirements

Cytochrome P450 metabolism

The cytochrome P450 (CYP) family of enzymes serves as the primary system responsible for the oxidative biotransformation of a wide range of biologically and chemically distinct endogenous and exogenous substrates. DNA variations in the genes that encode these enzymes can quantitatively alter their ability to metabolize, and subsequently eliminate, specific drugs from the body. In many cases these DNA sequence variations are responsible for reduced or inactive forms of CYP enzymes that are unable to effectively metabolize drugs from the body, leading to a greater incidence of drug toxicity. Poor metabolic capacity can also be associated with a lack of drug response owing to the inability to convert a pro-drug to its therapeutically active metabolite. Other genetic events, such as gene duplications and amplifications, have been associated with an increased ability to metabolize drugs. Carriers of these show a greater propensity for therapeutic failure due to the rapid elimination of drugs from the body.

DNA sequence variations are associated with:

- Lack of enzymatic activity (poor metabolizer)
- Reduced enzymatic activity (intermediate metabolizer)
- Enhanced enzymatic activity (ultra-rapid metabolizer)

While studies have shown both the CYP3A family of isoenzymes and the CYP2B6 enzyme to be involved in the metabolism of many of the opioids, it is the role of the highly polymorphic CYP2D6 gene that is of the greatest clinical interest with respect to the observed interindividual variability in the opioid response. Specifically, CYP2D6 variation catalyzes the biotransformation of a number of opioid molecules including codeine, tramadol, dihydrocodeine, oxycodone, hydrocodone, dextropropoxyphene and ethylmorphine. To date over 60 allelic variants[66] of the CYP2D6 gene have been defined, with the majority of these polymorphisms resulting in the reduction or loss of CYP2D6 enzymatic activity (see Table 18). Interestingly, however, the majority of poor metabolizers can be detected with genetic testing for only a small subset of variant alleles.[67-71]

Table 18. CYP2D6 Allele Activity[66]

Allele	Identifying Mutation	Enzyme Activity
*1	Wildtype	Normal
*2	2850C>T	Normal
*3	2549delA	None
*4	1846 G>A	None
*5	CYP2D6 deleted	None
*6	1707delT	None
*7	2935A>C	None
*8	1758G>T	None
*9	2615 2617delAAG	Decreased
*10	100C>T	Decreased[a]
*17	1023C>T	Decreased[b]
*29	1659G>A	Decreased[b]
*41	2988G>A	Decreased
*NXN	duplication	Increased

[a] *10 associated with diminished enzyme activity in Asian populations.
[b] *17 and *29 associated with diminished enzyme activity in Black populations.

Identifying patients who have genetic variations cannot be accomplished through self-reported medical history and physical examination. With the rapid development of genetic testing platforms, genetic biomarkers of disease and discoveries of new genotype-phenotype associations, a shift from traditional to personalized medicine utilizing pharmacogenomics will be inevitable.[63] UDM will promote pharmacogenetic testing for a small subset of variant alleles to detect a patient's genotype before prescribing. In this way, pharmacogenetic testing provides a way to effectively optimize pharmacotherapy. Additionally, it helps clinicians distinguish between high metabolic capacity and nonadherence to prescription regimens.

While many factors can influence the large interindividual variability observed in the opioid response, increasing evidence suggests a role for genetic factors in mediating the clinical pharmacology of opioids. Such genetic targets include receptors, signaling molecules, metabolizing enzymes and transporters. Polymorphisms in these elements have been shown to alter the level of expression and/or function of the protein. Owing to the narrow therapeutic index of the opioid drugs, such variability can have a profound effect on drug efficacy and the overall clinical response. By combining the results of genetic analysis with the knowledge of drug efficacy and toxicity, clinicians will enhance their understanding of the mechanisms underlying the large interpatient differences in the response to opioid pharmacotherapy.

Current State of Pharmacogenomics in Clinical Practice

Currently, pharmacogenomics has not been well enough established clinically to be widely accepted or implemented in the field. Guidance addressing an approach to pharmacogenetic testing is still in development. This testing is currently being reimbursed by few payers. These key factors have hindered clinician adoption of pharmacogenetic testing as an objective diagnostic tool. Preliminary work in pharmacodiagnostics (Rx/Dx) co-development recognizes pharmacogenomics as an area of rapid growth and a way to approach therapeutic targeting. Advancing pharmacodiagnostics in UDM has the potential to provide many clinical benefits. Further developments in this area of study will allow clinicians to personalize pharmacotherapy by providing objective information to identify patient variability in drug response, detect

disorders earlier and understand risks for adverse drug reactions or drug-drug interactions.[23]

In 2005, the FDA issued a white paper on Rx/Dx co-development. Since then, the agency has discussed issuing formal guidance on the topic but has yet to do so. Industry observers have been eagerly awaiting the release of this guidance, particularly since agency officials have said that Rx/Dx companion products are the best way to encourage physicians and patients to adopt pharmacogenomics-guided personalized medicine. While progress has been slow, at a recent meeting on personalized medicine in Boston, Massachusetts, Lawrence Lesko, Director of FDA Office of Clinical Pharmacology, announced that the agency has convened a multi-center and multi-disciplinary working group to advance the stalled guidance.[23] Visit the companion blog for this handbook at **www.udmsolutions.com** for more information and discussion on this important issue.

Guidance

Pharmacogenetic Testing

Clinicians should utilize pharmacogenetic testing data to optimize patient pharmacotherapy and minimize trial-and-error prescribing.

As pharmacogenetic testing becomes further established in clinical practice, clinicians will be able to apply information about a patient's genotype to prescribing. Pharmacogenetic analysis provides an efficient starting point to help clinicians distinguish between variations in metabolism and pharmacotherapy nonadherence. Data resulting from this analysis should be applied to ongoing treatment goals and considered when making adjustments to pharmacotherapy. Once treatment goals are established, laboratory diagnostics and clinical pharmacology will assist clinicians in monitoring personalized pharmacotherapy over time.

Patient Assessment Tools for UDM

In patient prescribing, whether in clinical practice or for clinical drug trials, the ultimate challenge lies with prescription regimen adherence. Historically, patient assessment has been based upon subjective feedback and objective clinical findings. As such, barriers to prescription adherence have included adverse drug effects, limited dose quantities, frequent dosing and high costs. Additionally, factors such as insufficient access to the clinician, lack of trust between clinician and patient and in some cases, bias and inadequate knowledge on the part of the clinician have taken their toll on adherence.[72] Considering such and the fact that patient intervention is often labor intensive, adherence has been difficult to study.

UDM is a patient-specific approach, relying upon objective assessment of patient feedback as an integral component to optimize prescription adherence and improve pharmacotherapy. In conjunction with laboratory diagnostics, medical history and pharmacogenetic data, additional psychosocial parameters must be considered to individualize pharmacotherapeutic decisions and monitor adherence over time.

Adherence Surveys

Future intervention in the form of validated adherence surveys will improve patient correspondence and supplement the clinician/patient dialogue. Survey data is utilized upon the initial visit and at intervals throughout clinical drug trials to determine candidate eligibility, record side effects and assess progress. Similarly, in treatment, survey data should be used to appropriately monitor and adjust pharmacotherapy for individual patients. Validated adherence surveys should target the barriers to adherence listed above and assess the psychosocial factors that patients may consider when not adhering to prescription regimens (e.g., fears, beliefs, cultures). Ultimately, this assessment tool will give clinicians valuable insight into adherence and help to answer such questions as: (a) why is the patient not taking the medication as prescribed?; or, (b) what is the patient's potential for drug misuse? Currently, validated adherence surveys are in development and not yet recommended for clinical use.[42] To meet objective requirements in UDM, efforts in standardizing validated adherence surveys will be necessary.

Risk Assessment Tools

Risk assessment tools for clinical use are continuing to evolve. Many validated tools that currently exist (e.g., the Screener and Opioid Assessment for Patients in Pain (SOAPP)[73], Drug Abuse Screening Test (DAST)[74]) are designed to stratify patients based on risk for substance misuse and addiction. UDM will require improved patient education and support regarding these risk assessment tools and their clinical use. Clinicians may find these monitoring techniques useful in aligning appropriate treatment goals with patient pharmacotherapy. Much of the recent published literature suggests using a risk assessment tool to stratify patients into low, moderate and high risk categories. In UDM, both risk and appropriate next steps need to be defined by the clinician for each patient. Based upon the clinician's definition of risk in his/her practice, some patients will require more frequent assessment (e.g., diagnostic testing, adherence surveys) throughout treatment.

Guidance

Adherence Surveys and Risk Assessment Tools

Clinicians should use validated adherence surveys and risk assessment tools to stratify patients based on treatment needs rather than to support the discontinuation of care.

Risk assessment tools are not comprehensive enough to determine whether someone is truly at risk for addiction or to identify someone who intends to misuse or divert medications. As validated adherence surveys become further established in clinical practice, survey data can be evaluated in combination with risk assessment, laboratory diagnostics and clinical pharmacology to provide objective information that can support clinical decisions in treatment.

Documentation and Referrals

Selecting the appropriate patient assessment tools to use with individual patients is up to the practitioner. Even more important to the practitioner is the consistency of performing and documenting the assessments that he/she performs. In some cases, patient assessment may lead to the clinician consulting with specialists to offer treatment advice. Prescribers often include clinical pharmacists in prescription adherence assessment (i.e., misuse,

abuse, diversion and dosage/dosage form changes) to offer critical information about simplifying, improving or adjusting drug regimens.[72] Clinical pharmacists can also be helpful in direct patient counseling given their extensive training and knowledge of pharmacology. Clinicians may also choose to refer patients to pain management specialists, addictionologists or other medical professionals.

Guidance

Consultation and Referrals

Clinicians should reference and document objective data resulting from patient monitoring when consulting with specialists or making referrals.

Maximizing the use of monitoring data will provide objective information to support the need to refer patients to appropriate specialists (e.g., addiction professionals, mental health professionals). Data collected through monitoring can be easily understood across multiple specialties and retained as medical record documentation to satisfy regulatory requirements.

Medical Informatics Assessment and Implementation

Medical informatics solutions are critical to UDM and information-driven patient-centered care. While there is consensus about the definition and vision of patient-centered care, specific solutions can be diverse, nonintegrated, nonstandard, insufficient or nonexistent. Careful evaluation of medical informatics solutions implemented in clinical practice and/or solutions offered by external providers is required when establishing patient pharmacotherapeutic processes and procedures. This evaluation should assess the appropriateness, reliability, efficiency and comprehensibility of medical informatics solutions as they relate to clinical practice and patient base.

Data Elements in UDM

A data element is defined as an atomic unit of data collection that is unambiguously defined in the controlled vocabulary of a project.[20] In UDM, data elements are obtained from laboratory diagnostics, patient medical records and patient assessment tools. Laboratory diagnostics provide biochemical, molecular and genetic data from a patient specimen. Patient medical records provide patient demographics, medical history and prescribing data. Patient assessment tools provide misuse and addiction risk data and adherence profile data.

Opportunities for Data Integration

Integration of data from multiple sources using medical informatics solutions adds efficiency and accuracy in processes involving clinical assessment and interpretation where multiple sources of data must be considered. For example, data integration can provide the ability to access date-specific prescription data that corresponds to date-specific laboratory diagnostics ordered.

For patient pharmacotherapy in a clinical setting, multiple medical informatics systems may be utilized by a variety of contributors. Laboratories use Laboratory Information Systems (LIS) for processing and reporting data. Clinicians may use Electronic Medical Records (EMR) to store patient medical records. When this data resides in separate systems that are not concurrently interfaced, retrospectively linking data (in the form of downloaded electronic files) is a possible solution.[75]

Data integration needs will vary based on pharmacotherapy policies and procedures implemented in a clinical setting. Examples of data integration in a UDM strategy that may be beneficial to monitoring opioid pharmacotherapy include:

- Laboratory diagnostics and prescribing data
- Laboratory diagnostics, prescribing data and adherence assessments
- Laboratory systems and pharmacy systems[75]
- Laboratory diagnostics and Prescription Monitoring Program (PMP) database

Guidance

Electronic Medical Records (EMR)

Patient information should be maintained in electronic format.

Where efficiency can be improved, systems should be interfaced. EMR systems should allow effective communication of UDM data analysis and subsequent clinical decisions to all clinicians contributing to individual patient pharmacotherapy.

Guidance

Prescription Monitoring Program (PMP) Database

When available, clinicians should use their state's searchable PMP database for controlled substance prescribing.

Obtaining prescription records for all patients initially, then periodically throughout the course of treatment, will assist in detecting patterns that could affect treatment outcomes, such as receiving concurrent prescriptions from multiple providers. Patient prescription records may also be useful when discrepancies occur between monitoring data and subjective and/or objective clinical findings.

Integrated Data Analysis

Insight into pharmacotherapy adherence beyond the scope of individual UDM data elements may be obtained through the integrated analyses of data, clinical models and evidence-based clinical knowledge. The process of determining appropriate data to include and the way it is integrated and analyzed involve several subjective decisions. These decisions must be made in the context

of current medical knowledge and current research[28] as they have the potential to produce different results and conclusions from a single set of data.[29] The relevance and accuracy of data generated through a process of integrated analysis depends on the appropriateness of these subjective decisions.

It is important when evaluating conclusions based on integrated data analysis that there is a clear understanding of established parameters for the analysis and comprehensive knowledge of subject matter relevant to the analysis.[20] Misleading conclusions from clinical trials and observational epidemiology demonstrate how improper data analyses can influence research outcomes.[29] Inconsistencies between population sampling and research conclusions are frequently cited as points of contention when trial results are called into question.[29] A recent example of misleading conclusions involved best quality observational studies which inferred a 50% reduction in coronary heart disease (CHD) for women receiving hormone replacement therapy (HRT). The currently accepted thought regarding CHD and HRT came from randomized trials that found a slightly increased risk of CHD for women receiving HRT. The reason for this discrepancy was found to have come from observational studies failing to adjust for socioeconomic position of patients despite the fact that use of HRT is strongly socially patterned and that socioeconomic status is associated with CHD.[76]

When utilized appropriately, integrated data analysis using medical informatics can provide an additional level of information regarding patient pharmacotherapy that would otherwise be problematical to obtain or difficult to comprehend. The possible iterations of analysis are limited only by the clinical requirements for monitoring patient pharmacotherapy. One example of integrated data analysis that may be beneficial to determining adherence is the analysis of laboratory diagnostics and prescribing data together with clinical pharmacological knowledge. By combining UDM data with evidence-based clinical knowledge, a more accurate assessment may be ascertained. These analyses and reports add efficiency and comprehensibility to clinical decision-making at each patient encounter.[20]

Benefits and Challenges of Implementation

The computational power and data storage capabilities of medical informatics solutions add speed and efficiency to data collection, organization, maintenance and archiving that is otherwise cumbersome to process and maintain. This efficient use of data

can have a broad, beneficial impact on practices and procedures in a clinical setting. An example of a process that benefits from medical informatics solutions is the documentation and record keeping required for patient pharmacotherapy. As detailed in the Compliance and Legal Considerations section of this handbook, maintaining comprehensible records concerning treatment is required in many state guidelines for pain medicine clinicians. UDM is a data-intensive strategy for monitoring patient pharmacotherapy and would be tedious to maintain without the utilization of medical informatics solutions.

The current trend in healthcare is toward information-driven care based on scientific evidence and supported by clinical information systems. The costs and demands on resources have overwhelmed many practitioners and slowed the implementation of medical informatics. In addition, assessing the usability of medical informatics as it relates to clinical staff and workflow present subjective challenges which can be unique to each clinical setting. As these systems develop and are implemented on a broad scale, the seamless transfer of non-redundant data and information between fixed or virtual healthcare providers will become more accessible and prevalent.[77] The evaluation and implementation of medical informatics solutions will benefit patient pharmacotherapy monitoring and improve UDM efficiency.

Guidance

External Solutions

Clinicians should carefully evaluate and utilize third-party medical informatics solutions.

Many medical informatics solutions offered by third-party providers may benefit the clinical evaluation and documentation of patient pharmacotherapy. Examples of these providers include laboratories, pharmacies and system interface vendors. Any external solution must be evaluated for clinical significance, scientific integrity, security and usability in practice.

Guidance

Clinical Decision Support Systems (CDSS)

Clinicians should utilize CDSS when evaluating potential drug-drug interactions.

The use of CDSS for determining drug-drug interaction is encouraged to add efficiency and decrease human error.[75] There are a number of software and online solutions available.

Compliance and Legal Considerations

Considering the dramatic rise in prescription drug abuse and the associated legal implications to controlled substances prescribers, it is important that clinicians have objective clinical tools available to them. A 2005 survey reported more people used prescription pain relievers for a nonmedical purpose than any other illicit drug except marijuana.[78] More recently, a 2007 Substance Abuse and Mental Health Services Administration (SAMHSA) report indicated that 5.2 million individuals aged 12 or older used prescription pain medication non-medically in the preceding month.[79] Additionally, 55.7% of those using a pain medication for nonmedical purposes reported that they obtained the medication from a friend or relative. Finally, a study of emergency department visits in the United States in 2004 through 2005 showed a 24% increase in visits involving the nonmedical use of opiates.[80] Between 1998 and 2005, serious adverse drug events increased by 260%, while fatal adverse drug events increased by 270%. Of the 15 medications most frequently related to these adverse events, seven were prescription medications, including oxycodone, fentanyl, morphine and methadone.[81]

The above is a small sampling of the information and studies that illustrate the significant increase in opioid misuse. As a result, pain practitioners are facing many significant legal challenges that include:

- Administrative and/or criminal liability relating to the prescribing of controlled substances for the treatment of chronic pain;
- Civil liability claims for the undertreatment of chronic pain; and
- Civil liability for the death or injury to a patient arising out of the prescribing of controlled substances to treat chronic pain.

As the prescription use of controlled substances continues to increase, clinicians will need to face these legal issues. To avoid liability and be protected from adverse consequences, the clinician must first be aware of and comply with the various Federal and State requirements surrounding the prescribing of controlled substances. The implementation of objective UDM practices can help minimize the potential for a clinician to be involved in a legal proceeding surrounding his or her practice. Also, by establishing patient-centered processes for laboratory diagnostics, utilizing

pharmacogenomic data and clinical pharmacological knowledge in decision-making, clinicians can help ensure that their medical records contain adequate documentation to demonstrate compliance with the various requirements.

Despite the fact that the UDM strategy provides an objective foundation for patient pharmacotherapy monitoring, it is important that clinicians are still legally prepared regarding the prescribing of Schedule II Controlled Substances. An awareness of governing laws and regulations allows clinicians to be proactive in establishing best practices in patient pharmacotherapy.

Clinicians need to be aware of the dual system of laws and regulations governing the issuance of prescriptions for controlled substances. Both the federal and state governments have their own requirements, all of which must be met by clinicians who issue these prescriptions (see Table 19). If requirements of the state law are different from those of the federal law, clinicians must comply with the more stringent requirement.

Table 19. Regulatory Schedule for Opioids

The following is a general non-comprehensive list. For more details, go to http://www.usdoj.gov/dea/pubs/scheduling.html.

Opioid	Regulatory Schedule
Alfentanil	C-II
Buprenorphine	C-III
Butorphanol	C-IV
Codeine	C-II
Codeine combination product 90 mg/du (Empirin, Fiorinal, Tylenol, ASA, or APAP with codeine)	C-III
Codeine preparations – 200 mg/100 mL (Cosanyl, Robitussin A-C, Cheracol, Cerose, Pediacof)	C-V
Diacetylmorphine (heroin)	C-I
Dihydrocodeine	C-II
Dihydrocodeine combination product 90 mg/du (Synalgos-DC, Compal)	C-III
Dihydrocodeine preparations 10 mg/100 mL (Cophene-S, various others)	C-V

(continued)

Table 19. Regulatory Schedule for Opioids (continued)

Opioid	Regulatory Schedule
Diphenoxylate preparations 2.5 mg/25 mcg AtSO4 (Lomotil, Logen)	C-V
Fentanyl	C-II
Hydrocodone	C-II
Hydrocodone combination product 15 mg/du (Tussionex, Lortab, Vicodin, Hycodan)	C-III
Hydromorphone	C-II
LAAM	C-II
Levorphanol	C-II
Meperidine	C-II
Methadone	C-II
Morphine	C-II
Opium extracts: Opium fluid extract Opium poppy (Papaver somniferum) Opium poppy capsules (poppy heads, poppy straw) Opium tincture (Laudanum) Opium, granulated Opium, powdered Opium, raw (gum opium)	C-II
Opium combination product 25 mg/du (Paregoric, other combination products)	C-III
Opium preparations – 100 mg/100 mL (Parepectolin, Kapectolin PG, Kaolin Pectin PG)	C-V
Oxycodone	C-II
Oxymorphone	C-II
Pentazocine	C-IV
Propoxyphene	C-IV
Remifentanil	C-II
Sufentanil	C-II

ASA, aspirin; **APAP,** acetaminophen; **LAAM,** levo-α-acetylmethadol

Federal Requirements

The Controlled Substances Act of 1970 (CSA) is the primary federal statute dealing with the prescription of controlled substances. It is administered by the Drug Enforcement Administration (DEA). Regulations implementing and related to the CSA can be found at Title 21 CFR Section 1300.

CSA Requirements for Valid Prescriptions[82]

According to CSA requirements, in order to be considered valid, controlled substance prescriptions "must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice." If a prescription is not issued in the usual course of professional treatment, the prescriber is subject to civil and/or criminal liability under the CSA. The prescribing clinician is responsible to ensure compliance with all requirements.

Controlled substance prescriptions must contain:[83]

- Patient's full name and address
- Practitioner's full name, address and DEA registration number
- Date and signature on the date issued
- Name of drug prescribed
- Strength of drug prescribed
- Dosage form of drug prescribed
- Quantity of drug prescribed
- Directions for use of drug prescribed
- Authorized number of refills (if any)

Additionally, CSA rules require that:

- The prescription must be either typewritten, written in ink, or indelible pencil
- The prescription must be signed manually by the practitioner on the date issued
- The prescription must be written by a practitioner authorized to prescribe controlled substances (e.g., physician, dentist, podiatrist, mid-level practitioner, other registered practitioner)
- The prescriber must be authorized by state of licensure to prescribe controlled substances
- The prescriber must be registered with the DEA or exempted from registration under the regulations

Factors Considered by the DEA to Determine Validity of Prescriptions

The DEA has considered some of the following factors as evidence that a prescription was not issued for a legitimate medical purpose. However, it is the DEA's official position that the ultimate determination is made on a case by case basis:[84]

- An inordinately large quantity of controlled substances prescribed
- Large numbers of prescriptions issued
- No physical examination given
- Prescriber warned patient to fill prescriptions at different drug stores
- Prescriber issued prescription(s) knowing that patient was delivering drug(s) to others
- Controlled drug(s) prescribed at intervals inconsistent with legitimate medical treatment
- Prescriber used street slang rather than medical terminology for drug(s) prescribed
- No logical relationship between prescribed drug(s) and treatment of condition allegedly existing
- Prescriber wrote more than one prescription on occasions in order to spread them out

Pharmacist Responsibility

The CSA and the implementing regulations also place responsibility on the pharmacists filing the prescriptions. Prescriptions for controlled substances may only be issued by registered pharmacists acting in the usual course of their professional practice. 21 CFR Section 1306.04 states in part as follows:

The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of Section 309 of the CSA. The person knowingly filling the prescription, as well as the person issuing it, shall be subject to penalties provided for violations of the provision of law relating to controlled substances.

Refilling of Controlled Substances

Schedule III and IV Controlled Substances:

May be refilled under these federal regulations if:[85]

- The original prescription authorizes the refill(s).
- A maximum of five refills are allowed within a six-month period after original date of issue

Schedule II Controlled Substances:

May not be refilled under the federal regulation:

On December 19, 2007, the DEA amended the Federal Regulations relating to the refilling of Schedule II Controlled Substances.[86] While prohibiting the refilling of Schedule II Controlled Substances, the new regulation permits the issuance of multiple prescriptions to provide a patient with up to a 90-day supply of a Schedule II Controlled Substance as long as the following conditions are met:

- Prescriber properly determines that there is a legitimate medical purpose
- Prescriber acts in the usual course of professional practice
- Written instructions are included on each prescription (except initial prescription) indicating the earliest fill date
- Prescriber concludes that multiple prescriptions do not create an undue risk of diversion and/or abuse
- The issuance of multiple prescriptions is permissible under state law
- Prescriber complies with all applicable state and federal requirements

Legal Note: Issuing multiple Schedule II Controlled Substance prescriptions on the same day is only permissible in states that allow the practice. Clinicians must check with their state medical board prior to prescribing multiple controlled substance prescriptions.

State Prescribing Requirements

Clinicians should be aware that laws and regulations of each state pertaining to controlled substance(s) prescription(s) vary.

Legal Note: Issuing controlled substance(s) prescription(s) is governed by both federal and state law. If one requirement is more stringent than the other, a practitioner must meet the more stringent requirement. The specific differences between state requirements are beyond the scope of this handbook.

Federation of State Medical Boards Model Policy

In 2004, the Federation of State Medical Boards ("Federation") revised its model policy for the use of controlled substances for pain treatment.[87] The model policy was an update of a document first issued in 1998: "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain."

The policy is an attempt to strike a balance between the need for adequate pain management through the use of controlled substances and the fear many physicians have that they will be disciplined simply because they have prescribed controlled substances for the treatment of chronic pain.

The policy was adopted to provide guidance to the various state regulatory authorities on the issue of appropriate use of controlled substances for the treatment of pain. Since its initial adoption, approximately 32 states have adopted the policy in some form into their regulations or guidance documents. Others have used the policy as a basis to update and modify their regulations dealing with the use of controlled substances for the treatment of pain.

The Federation recognizes that the undertreatment of pain is caused by a number of factors and that it poses a serious public health problem. Factors affecting the undertreatment of pain include:

- Lack of knowledge of medical standards, current research, or clinical guidelines for appropriate pain treatment
- Perception that prescribing adequate amounts of controlled substances will result in unnecessary scrutiny by regulatory authorities
- Misunderstanding of addiction and dependence
- Lack of understanding of regulatory policies and processes

The policy defines the term inappropriate treatment of pain to include:

- Nontreatment
- Undertreatment
- Overtreatment
- Continued use of ineffective treatments

Federation Guidelines To Evaluate a Clinician's Treatment of Pain

1. Evaluation of the patient—the clinician should conduct a thorough evaluation of the patient:

- Take a complete medical history
- Conduct a physical examination
- Document in the medical record
  - Everything that was performed including all current and past treatments for pain
  - The existence of diseases or conditions that may be causing or impacting the pain
  - A history of any substance abuse by the patient

Legal Note: Although not set forth in the model policy, it does make good sense for the practitioner to obtain and review copies of the patient's records from former physicians and practitioners who had treated the patient.

2. Treatment plan—should be in writing, be included in the medical records and contain the following:
   - Objectives that will be used to determine treatment success
   - Further diagnostic evaluations or treatments that are planned
   - Adjustments to drug therapy based on patient needs
3. Informed consent and treatment agreements

The clinician should discuss with the patient the risks and benefits of the use of controlled substances. The medical record should document the discussions. The clinician should consider a written treatment agreement for patients at high risk for medication abuse. Some of the typical terms of treatment agreements include the following:

- Requires the patient to take medication as prescribed
- Requires the patient to agree to use a single pharmacy
- Places restrictions on refills and replacement of lost/stolen prescription
- Patient agrees to submit to urine drug tests
- Discloses side effects and risks associated with the use of controlled substances
- Sets forth terms for termination from the program for violation of the agreement
- Prohibits the selling or sharing of medications
- Patient agrees to disclose medications prescribed by other doctors

4. Periodic review of treatment
   - Documentation showing periodic review should be contained in the medical records
   - A reviewer should be able to see that the practitioner has adequately reviewed the course of treatment

- If patient's progress is unsatisfactory, the practitioner should consider the use of other treatment methodologies and consider the appropriateness of the continued use of controlled substances

5. Consultation
   - Should be willing to refer patients as necessary, especially patients at high risk for substance abuse or diversion
   - Does not prohibit treatment of patients with a history of controlled substances abuse, but does indicate that extra care may be required and referral to appropriate treatment specialist may be necessary
6. Medical records
   - Must be accurate, detailed, complete, legible, etc.
   - Must be easily accessible for review by any appropriate regulatory body and should contain the following:
     1. The medical history and physical examination
     2. Diagnostic, therapeutic and laboratory results
     3. Evaluations and consultations
     4. Treatment objectives
     5. Discussion of risks and benefits
     6. Informed consent
     7. Treatments
     8. Medications (including date, type, dosage and quantity prescribed)
     9. Instructions and agreements
     10. Periodic reviews

Legal Note: As mentioned, a number of states have adopted the model policy or policies substantially similar to the model policy. Practitioners would be well advised to contact their state medical board to determine the exact policy in place in their state. Following the state policy and adequately documenting the medical records is perhaps one of the most effective ways to avoid an adverse decision in any type of licensing proceeding brought against a practitioner by the state regulatory body.

Legal Note: Many states have prescription monitoring programs that allow prescribers and pharmacists to access information regarding what prescriptions have been issued to a patient. This information can be invaluable in helping to identify potential diversion and to also identify potential ADRs. Failure to use this information, when accessible, may be used against the clinician in an administrative or civil proceeding.

Undertreatment of Pain

As noted in the model policy, the undertreatment of pain can be deemed to be inappropriate treatment for purposes of complying with state medical licensure board guidelines. The undertreatment of pain can likewise give rise to significant civil liability. There are a number of well-publicized cases that have occurred over the past years that recognize there is a cause of action for the undertreatment of pain.

1. In Estate of Henry James v. Hill Haven Corp. (North Carolina Superior Court, January 15, 1991), a health care provider was held liable for the failure to properly treat a patient's pain. The allegation in this case was that a nurse employed by the facility where the plaintiff was a patient withheld or reduced the pain medications that were ordered for the patient by a physician. The jury in this case awarded $15 million to the plaintiff.

2. In Bergman v. Chen (Alameda County Court, June 13, 2001), a jury awarded the plaintiff $1.5 million on claims of elder abuse and reckless negligence. This amount was later reduced by the court based on a damages cap in effect in California. In this case, the plaintiff (Mr. Bergman) was an 85-year-old man suffering from chronic lung disease. He spent the last few weeks of his life in acute pain. The allegation in this case was that he was not prescribed sufficient pain medications. The Medical Board of California reviewed the matter and indicated that, although the pain relief was inadequate, there was insufficient evidence to take further action against the doctor. As a result, the estate sued the doctor and the hospital. The hospital settled before trial and the jury held the doctor liable for damages.

3. In Tomlinson v. Bayberry Care Center et al (California, 2002), the state of California disciplined a skilled nursing facility and a physician on the basis that the patient's pain relief was not adequately addressed and that pain medications were not administered as prescribed. Civil litigation was also filed and all of the defendants settled prior to the trial.

Legal Note: These cases illustrate the fact that health care providers can and have been found liable for the undertreatment of pain. Given the increasing number of patients who are suffering from pain, it is expected that the number and instances of claims of inadequate treatment will increase over time.

Internal Policies and Procedures to Implement UDM

Implementing a UDM monitoring strategy presents benefits for both clinicians and patients. A balanced integration of UDM components will provide a comprehensive solution to broaden clinical knowledge, change treatment and improve drug therapy.

In practice, establishing internal policies and procedures to implement UDM will entail:

1. Incorporating scientifically-validated **laboratory diagnostics** (i.e., quantitative urine drug testing methods capable of detecting parent drug compounds and pertinent metabolites)
2. Utilizing **clinical pharmacology** knowledge/specialists to assist in proper clinical interpretation, patient education and adjustments to patient pharmacotherapy
3. Assessing **pharmacogenomics and pharmacogenetics** to identify genetic variances in patient pharmacokinetic and pharmacodynamic responses to medications
4. Integrating **patient assessment tools** to realize physiological and psychosocial factors affecting prescription adherence and refer when appropriate
5. Utilizing **medical informatics solutions** to collect, organize, integrate and analyze data to assist in clinical decision-making.

Laboratory Diagnostics

Multiple industry guidelines and state Departments of Health (DOH) recommend the use of laboratory diagnostics (urine drug testing) in patient treatment. The state of Utah DOH, for example, offers guidance on performing what they refer to as "drug screening" before initiating long-term opioid treatment for chronic pain. Utah recommends that this testing be considered for all patients. Under this program, a positive test indicates the need for caution but does not preclude opioid use for treatment of pain. Considering referral to substance abuse counseling and/or to a pain management specialist is recommended. If opioid medication is subsequently prescribed, the patient should be more carefully monitored.[88] The state of Louisiana has adopted regulations requiring the licensure of pain management clinics. The regulations require in part an initial "urine drug screen" and at least quarterly tests during the course of treatment.[89]

Additional literature recommends that clinicians develop an arrangement with a laboratory service provider for quantitative urine drug testing.[8,21] Although accepted standards have not yet been set, many sources support the following:

- A highly sensitive and specific laboratory assay to provide the most precise and accurate drug identifications
- The test should be capable of distinguishing between opioids (e.g., oxycodone vs. oxymorphone)
- The test should detect additional prescribed medications or illicit drugs (e.g., benzodiazepines, cocaine, alcohol)
- The testing laboratory should offer assistance with results interpretation using specialists qualified in laboratory science and clinical pharmacology

These laboratory diagnostics requirements are consistent with UDM's emphasis on utilizing standards applied in clinical drug trials.

Clinical Pharmacology

Knowledge of basic and clinical pharmacology is critical in the interpretation of laboratory results and application of such to individual treatment goals. Understanding pharmacokinetic, pharmacodynamic and pharmacogenetic parameters can assist clinicians in appropriately evaluating monitoring data in relation to a patient's demographics, medications, medical history and physiology (see Table 9). The application of this knowledge will help to maximize the efficacy of patient monitoring and pharmacotherapy.

Clinical pharmacology has an important role as the bridge that connects laboratory diagnostics with clinical practice and, ultimately, patient pharmacotherapy. The integration of these components has emerged from the discovery stages of clinical drug trials and is now driving solutions in patient treatment.[90] Specialists such as clinical pharmacologists, clinical pharmacists and PharmDs are available for additional support with treatment and monitoring.

Pharmacogenomics

In the near future, the study of pharmacogenomics will emerge as the ultimate personalized solution to optimize patient pharmacotherapy. The ability to prescribe medications, tailor dosage amounts and frequency, and avoid adverse drug effects based on knowledge of individual genetic polymorphisms will help to

minimize the trial-and-error method of drug treatment. Accurate prescribing will enhance patient care through improved safety and efficacy.

Several pharmacogenetic tests currently exist to determine whether a drug treatment will be safe for an individual patient. To encourage widespread acceptance by stakeholders (e.g., clinicians, laboratories, pharmaceutical manufacturers, biotechnology, regulatory agencies, insurance payers), pharmacogenetic testing must be established as a standard in patient pharmacotherapy. Additionally, FDA guidance will need to be issued for pharmacodiagnostics (Rx/Dx) where clinical drug development and diagnostic measures are pursued in tandem.[91,92]

Patient Assessment

The use of validated adherence surveys and risk screening tools is an important component of UDM. While laboratory urine drug testing, clinical examination and observation of patient behavior can offer clinicians information about prescription adherence and potential misuse or addiction, the challenge lies in recognizing underlying patient issues.

Validated patient adherence surveys, when approved for clinical use, will be useful in constructing psychosocial profiles for non-adherent patients. Additionally, surveys supplement patient histories by providing additional information about past prescription use, misuse, or addiction. Currently, validated adherence surveys are in development for opioid pharmacotherapy, but not available for clinical use.[43] To meet objective requirements in UDM, efforts in developing and validating adherence assessment will be necessary.

Several **validated risk assessment tools** are currently available to assist the clinician in determining whether opioid pharmacotherapy is appropriate and in determining the level of monitoring relevant to the patient's risk level (see Patient Assessment Tools for UDM section). Some states have presented guidelines that recommend the use of risk assessment tools to assess patients prior to prescribing an opioid for long-term chronic pain.[43] Similar state and federal guidelines have been designed to minimize diversion, misuse, abuse, addiction and overdose (see Compliance and Legal Considerations section).

Based on survey results, patient histories and other clinical factors, clinicians may choose to consult with or refer patients to

pain management specialists, certified addictionologists, or other professionals.

Similar to status surveys used in clinical drug trials, adherence surveys and risk assessments should be conducted prior to initiating drug treatment and at intervals deemed appropriate for each patient by the prescriber.

Medical Informatics

Clinical decision-making based on objective data obtained through multiple, integrated sources is crucial to UDM. When patient data resides in separate systems, appropriate clinical communication is limited and can result in inadequate care. Thus, UDM data elements comprised of laboratory diagnostic data, patient medical records, prescribing data, clinical pharmacology, pharmacogenetic profiling and patient assessment must be integrated into a comprehensible format for optimal application to patient pharmacotherapy. When multiple sources of information are not easily interpreted, integrated data analysis using medical informatics solutions can add efficiency to data collection and clinical interpretation in clinical patient monitoring.[75]

The current trend of information-based healthcare both drives and supports the need for medical informatics in patient pharmacotherapy.[77] The initial implementation of a system that works in clinical practice will present challenges of increased costs and demand for resources and expertise. In the long term, as medical informatics solutions become more prevalent, clinicians and patients will benefit from increased efficiency, improved documentation of treatment progress and higher quality patient prescribing.

Guidance

Initial Data Collection

As part of a patient's routine initial evaluation, clinicians may consider employing the following elements for UDM:

Urine Drug Testing

If considered appropriate by the clinician, request comprehensive identification and quantification of pertinent medications and illicit substances. This may assist in the identification of current or potential drug–drug interactions and provide additional insight into the potential for misuse.

Adherence Assessment

Adherence assessment tools need to be developed and standardized for routine clinical use. Adherence assessment may identify and stratify potential factors that affect adherence to a pharmacotherapy regimen. This may assist in selecting regimen parameters that suit the individual patient.

Addiction Assessment

Conduct an appropriate addiction risk assessment. Addiction risk assessment tools, such as the SOAPP, may assist in stratifying patients according to risk level.

Pharmacogenetic Testing

Pharmacogenetic testing needs to be standardized for routine clinical use. Evaluation of a patient's pharmacogenomic profile may provide detail on pharmacokinetic and pharmacodynamic parameters. These parameters should be used to determine a pharmacotherapy regimen for that patient.

Guidance

Ongoing Data Collection

Dynamic aspects of patient pharmacotherapy are measured using urine drug testing, adherence assessment and addiction assessment. As part of ongoing patient treatment, clinicians should continue to employ these elements to monitor changes in clinical status and adherence to pharmacotherapy.

Pharmacogenetic testing is most beneficial when performed at the onset of treatment to objectify individual responses to pharmacotherapy. Many of these genetic analyses only need to be performed once in a patient's lifetime and assist clinicians in structuring an initial and continual personalized treatment approach. In ongoing assessment, clinicians should reassess and order additional pharmacogenetic tests with the alteration/addition in a patient's medication regimen, treatment objectives, disorder, and/or disease state; when obtaining patient and/or other feedback of subtherapeutic, adverse, and/or toxic effects; with new allelic activity/functionality discovery; and as additional pertinent pharmacogenetic tests become commercially available.

Guidance

Ongoing Data Collection: Frequency

Clinicians should stratify frequency of UDM data element collection based upon individual patient assessment. In addition to changes in test frequency based upon risk assessment, frequency may increase or decrease based on the degree to which change is occurring in patient pharmacotherapy.

While patient behavior should not be overlooked when evaluating adherence, it should not be the primary factor considered when initiating the collection of UDM data or determining UDM data collection protocol.

Guidance

Ongoing Data Collection: Randomization

If any individual data element is not collected at every patient visit, the collection schedule of that element should be randomized.

Randomization increases objectivity in data collection over time, reduces the ability for patient or clinician to influence outcomes based on data and imposes a barrier for patients' intent on diverting controlled substances.

Conclusions

Monitoring patient usage of controlled substances is a major concern and responsibility of prescribing clinicians. Our legal system addresses these concerns through the strict prescribing regulations for these medications. Current methods used to monitor opioid efficacy in patient pharmacotherapy primarily rely on subjective feedback, objective clinical findings, limited diagnostic data and trial-and-error adjustments to the therapeutic regimen. Urine Drug Monitoring (UDM) is a practical, objective and comprehensive monitoring strategy that addresses the limitations of some monitoring methods currently in use and furthers the goal of patient-specific pharmacotherapy.

Basing clinical interpretation on heterogeneous monitoring data is the strength of the UDM strategy. Each UDM component may provide pertinent information regarding patient pharmacotherapeutic status. Based upon sound pharmacological and genetic principles, UDM can provide valuable clinical insight regarding each patient. Validated patient assessment tools can assist with adherence problems identified by UDM laboratory components. Efficient and comprehensible use of medical informatics makes real-time performance of UDM possible at each patient encounter. When its components are combined properly, a UDM strategy can objectify patient pharmacotherapeutic adherence and enhance treatment efficiency.

Patient-centered diagnostic healthcare moves the system away from generic solutions and permits the implementation of a customized UDM strategy. While the UDM strategy has specific requirements for appropriate use, the components of UDM can be integrated into clinical settings in a myriad of ways. Implementing this strategy in a way that maximizes usability in a clinical setting is critical to long-term efficiency and confidence.

The UDM strategy presents new concepts and new challenges to the way clinicians scrutinize patient pharmacotherapy. As clinicians begin to implement UDM, there will be new ideas and suggestions about specific ways to integrate its components. To encourage discussion about UDM, the authors have set up a companion blog for this handbook. We welcome you to continue the discussion at **www.udmsolutions.com**.

APPENDIX A. Rationale for Implementing Urine Drug Monitoring (UDM)[13]

The following are pertinent clinical reasons to consider incorporating UDM into a clinical practice. Not all of these may be applicable to every practice.

Enhanced Clinician/Patient Relationship, Trust and Dialogue

UDM may enhance the clinician/patient relationship, trust and dialogue by:

- Reinforcing trust that the patient is adherent with the prescribed medication
- Enhancing patient-clinician communication
- Integrating testing for drug substances as an essential part of a comprehensive pharmacotherapeutic treatment plan
- Providing the patient and clinician an opportunity for face-to-face interaction

Optimization of Pharmacotherapeutic Regimens and Treatment Outcomes

UDM may assist in the optimization of pharmacotherapeutic regimens and treatment outcomes by:

- Providing initial and comprehensive identification and quantification of many drug substances, including prescription and over-the-counter medications, illicit substances, etc.
- Identifying the use of drug substances from other sources and current or potential drug–drug interactions
- Identifying pertinent metabolic issues including medications that induce or inhibit the CYP450 enzymes, medications that compete for these enzymes and genetic polymorphic conditions that affect metabolism
- Identifying, where appropriate, the ratios of parent and drug metabolite(s) to phenotypically address possible and/or relevant pharmacokinetic issue(s)
- Monitoring of drug elimination rates
- Identifying other disease states (e.g. impaired renal function, diabetes) when accompanied by macroscopic urinalysis
- Providing objective clarification regarding changes in prescription dosages, frequencies, and/or medications related to changes in behavioral symptomatology (e.g., side effects, lack of efficacy, aberrant behavior)
- Minimizing and/or eliminating undertreatment, overtreatment and/or pharmacotherapeutic failure

Improved Prescription and Overall Treatment Adherence

UDM may improve patient treatment adherence by:

- Providing the clinician with objective tools that help document prescription drug adherence
- Allowing quantification and correlation of the amount of drug substance as it pertains to changes in pain measurement metrics and behavioral symptomatology
- Allowing the identification and quantification of potential approved drug contaminants in medications to prevent unnecessary confrontation and potential violation of the patient treatment agreement
- Identifying the use of medications from other sources that may complicate the treatment plan
- Providing the treatment team with objective evidence and knowledge to adjust pharmacotherapy
- Helping to identify patients who may divert controlled substances
- Assisting in the identification of misuse of prescription medications and potential addiction or relapse issues
- Reducing the risk of therapeutic failure by detecting patients who are nonadherent
- Enhancing appropriate prescribing to minimize the risk of doctor-shopping for additional doses of prescribed medications

Early Identification of Misuse, Abuse, Diversion and Addiction

UDM may assist in the early identification of misuse, abuse, potential for diversion and risk of addiction by:

- Providing the clinician with an objective test that documents prescription drug use, misuse/abuse and/or illicit drug usage
- Identifying patient inaccuracies with self-reported medication use
- Assisting in the clarification of patient historical data including suspicious stories, family reports of substance abuse, self-reporting of relapse, inability to self-administer medications, reports of cravings and urges, and poor relapse-prevention skills
- Clarifying behavioral observations including continued risky behavior, missed appointment(s), intoxicated appearance, pill-count discrepancies, premature refill requests, and pharmacy calls/concerns

- Objectifying clinical assessment/interpretation issues including confirmed use/presence of substance(s), behavior inconsistent with self-report, behavior inconsistent with laboratory report, abstinence/sobriety adherence, provide/support patient advocacy and relapse prevention
- Identifying intentional dilution, adulteration, substitution, or tampering with the urine specimen

Support for Specialist Referrals

UDM may provide support for referral to healthcare specialists by:

- Identifying the use of illicit substances throughout the treatment process
- Providing objective data to assist in making the appropriate decisions regarding discontinuation of medication/treatment and referral to the appropriate addiction and/or mental health professional

Medico-Legal Compliance to Minimize Regulatory Scrutiny

UDM may improve medico-legal compliance and reduce the risk of regulatory scrutiny and unwarranted investigation by:

- Improving documentation regarding patient monitoring and evaluating prescribed medications
- Preventing inappropriate dismissal or treatment bias when third-party information from family, friends or other entities becomes available

APPENDIX B. Guidance

The guidance in this handbook presents clinical suggestions that are relevant to the UDM strategy. Although guidance is presented individually for each component of UDM, clinicians should collectively evaluate data resulting from all components to support clinical decision-making. The use of UDM in clinical practice will be most effective and efficient when clinicians rely upon clinical interpretation derived from multiple, interrelated UDM components.

Laboratory Diagnostics

Specificity and Sensitivity - Clinicians should request assays which provide complete data sets for UDM components utilized in clinical decisions regarding patient pharmacotherapy.

Specimen Validity - Establish the integrity of the specimen.

Clinical Pharmacology

Interpretation of Laboratory Diagnostics - Clinicians should apply clinical pharmacology when interpreting laboratory diagnostics.

Pharmacogenomics and Pharmacogenetics

Pharmacogenetic Testing - Clinicians should utilize pharmacogenetic testing data to optimize patient pharmacotherapy and minimize trial-and-error prescribing.

Patient Assessment

Adherence Surveys and Risk Assessment Tools - Clinicians should use validated adherence surveys and risk assessment tools to stratify patients based on treatment needs rather than to support the discontinuation of care.

Consultation and Referrals - Clinicians should reference and document objective data resulting from patient monitoring when consulting with specialists or making referrals.

Medical Informatics

Clinical Decision Support Systems (CDSS) - Clinicians should utilize CDSS when evaluating potential drug-drug interactions.

Prescription Monitoring Program (PMP) Database - When available, clinicians should use their state's searchable PMP database for controlled substance prescribing.

Electronic Medical Records (EMR) - Patient information should be maintained in electronic format.

External Solutions - Clinicians should carefully evaluate and utilize third-party medical informatics solutions.

Internal Policies and Procedures

Initial Data Collection - As part of a patient's routine initial evaluation, clinicians may consider employing the following elements for UDM:

- Urine Drug Testing
- Adherence Assessment
- Addiction Assessment
- Pharmacogenetic Testing

Ongoing Data Collection - Dynamic aspects of patient pharmacotherapy are measured using urine drug testing, adherence assessment and addiction assessment. As part of ongoing patient treatment, clinicians should continue to employ these elements

to monitor changes in clinical status and adherence to pharmacotherapy.

Ongoing Data Collection: Frequency - Clinicians should stratify frequency of UDM data element collection based upon individual patient assessment. In addition to changes in test frequency based upon risk assessment, frequency may increase or decrease based upon the degree to which change is occurring in patient pharmacotherapy.

Ongoing Data Collection: Randomization - If any individual data element is not collected at every patient visit, the collection schedule of that element should be randomized.

APPENDIX C: Comparison of Various Biological Matrices Available for Laboratory Analyses[93-98]

Biological Matrix	Typical Opioid Detection Times	Advantages
Urine	2 to 4 days (some drugs have longer detection times—e.g., buprenorphine, methadone, propoxyphene)	• Standard matrix for drug testing • Noninvasive • Extensively studied and documented (pharmacokinetically relevant) • Large volume of specimen available for multiple analyses • Quantitatively detects parent drug and metabolite(s)
Saliva	< 24 hours	• Moderately invasive sample collection • Easily observable collection
Hair	1 week to 3 months (in some cases longer)	• May detect past chronic drug usage that may not be detected using other matrices
Blood	< 24 hours	• Difficult to adulterate • Assists with methadone dose titration

Disadvantages
• Adulteration is possible, although it can be minimized by: – monitoring urine biological markers (e.g., creatinine, pH, temperature, specific gravity) – testing for adulterants – direct observation of urine collection
• Limited window of detection • Length of collection time may range from 3-10 minutes • Results are not pharmacokinetically relevant • Error-prone collection procedure • Proper collecting techniques and time required or results may be uninterpretable • May be adulterated (e.g., oral cavity devices, pH alteration) • Standarized use of validity testing to detect adulteration has not been established • Collection methods influence pH and saliva/plasma ratio • Potential for contamination of oral cavity • Limited specimen volume for testing • Limited number of assays established
• Results are not pharmacokinetically relevant • May be contaminated by external sources • May be adulterated (e.g., bleaching, specialized hair treatments) • Not ideal for detecting recent or occasional drug use • Dark hair color and texture may bias results • Proper collection technique is necessary or results may be uninterpretable • Detection time dependent on hair length • Limited number of drug assays • Costly for donor/client • Sample collection requires 100 mg of sample retrieved close to scalp
• Limited window of detection • Invasive collection • Infectious matrix (universal precautions) • Limited number of pertinent drugs to examine

APPENDIX D. Typical Opioids and Metabolites Detected by LC/MS/MS

Drug Test	Analytes Detected
6-AM (heroin metabolite)	6-AM Morphine
Buprenorphine	Buprenorphine Norbuprenorphine
Butorphanol	Butorphanol
Dextromethorphan	Dextromethorphan Dextrorphan
Fentanyl	Fentanyl Norfentanyl
Levorphanol	Levorphanol
Meperidine	Meperidine Normeperidine
Methadone	Methadone EDDP (methadone metabolite)
Nalbuphine	Nalbuphine
Opiates	Morphine Codeine Hydrocodone Hydromorphone
Oxycodone	Oxycodone Oxymorphone
Pentazocine	Pentazocine
Propoxyphene	Norpropoxyphene
Tramadol	Tramadol *O*-desmethyltramadol

6-AM, 6-acetylmorphine

APPENDIX E: POC Relevance to Clinical Practice[9,99-104]

POC devices may not be clinically relevant to UDM due to:

- An inability to differentiate between analytes detected within a drug class[a]
- An inability to detect many commonly prescribed opioids
- An inability to detect low levels of an analyte in a specimen

When a clinician wishes to differentiate between the presence of specific opioids in a patient (e.g., morphine vs. hydromorphone),

a common POC device[a] offers little clinical relevance because it will only provide a positive or negative result for the Opioids class. High sensitivity and specificity are key factors in collecting laboratory diagnostics data relevant to UDM.

Laboratory Methodology	LOQ (ng/mL)	Opioids	POC cup LOD (ng/mL)[a,b]
UPLC/MS/MS	1	Fentanyl	n/a
	5	Norfentanyl	n/a
	25	Morphine	300
	25	Codeine	300
	25	Hydrocodone	50,000
	25	Hydromorphone	3,125
	25	Oxycodone	30,000
	25	Oxymorphone	100,000
	100	Propoxyphene (norpropoxyphene)	n/a
	100	Dextromethorphan	n/a
LC/MS/MS	1	Nalbuphine	n/a
	5	Butorphanol	n/a
	5	Buprenorphine	n/a
	10	Norbuprenorphine	n/a
GC/MS	10	6-AM	400
	20	Levorphanol	1,500
	20	Pentazocine	n/a
	25	Meperidine	n/a
	25	Normeperidine	n/a
	50	Methadone	n/a
	50	EDDP	n/a
	100	Tramadol	n/a
	100	O-desmethyltramadol	n/a

n/a, not applicable
LOD, Limit of Detection
LOQ, Limit of Quantification
[a] Source: Opiate 300 (MOP) package insert. Milwaukee, WI: Noble Medical, Inc.
[b] Any opioids detected will only trigger an "Opioid Positive" result. Source: Opiate 300 (MOP) package insert. Milwaukee, WI: Noble Medical, Inc.

POC Device Design

POC devices were originally designed for use in:

- Workplace testing (e.g., preemployment, reasonable cause, post-accident)
- Roadside testing where impairment is suspected

Compliance with POC Regulations

Compliance with regulatory standards for drug testing adds complexity to the implementation of POC testing in clinical practice. Clinicians may not be aware of some of the common POC testing requirements such as maintaining appropriate licensure, permitting inspections where applicable and establishing quality assurance and quality control for the device.

POC Limitations in Clinical Practice

Factors that may interfere with the test performance and/or result include but are not limited to:

- Limited specificity, especially for opioids and amphetamines
- Limited or variable test sensitivity that may deviate from the manufacturers' stated values
- Turbidity of the specimen due to particulate matter (centrifugation may be required)
- Limited time interval for interpretation (if not read within the strict time interval, results will become uninterpretable)
- Lot variability
- Contamination of the device
- Storage requirements (attention must be given to temperature, humidity, and light exposure)
- Urine temperature (requires strict attention to the manufacturer's recommendations regarding urine temperature)
- Controls and calibrators (they must be run, although they are imperfect, which casts doubt on the interpretability of the results and makes true method validation impossible)
- Operator vulnerability (limited or inadequate operator training can result in user error)
- Visual results interpretation (interpreting visual results can be highly subjective)
- Poor record keeping after testing (lack of an organized or proper method for recording actual test results)

Impact of Clinical Decisions based upon Results Misinterpretation

Misinterpretation of results may:

- Disrupt or destroy the clinician-patient relationship
- Contribute to an accusatory/confrontational environment
- Prevent proper pharmacotherapy
- Increase patient anxiety and clinician bias

The American Association of Clinical Chemistry has concluded that "Near-patient testing devices for drugs of abuse could be a potentially inaccurate means to monitor patient treatment and drug abuse status."

For all results (negative and positive) to be clinically relevant, they must be analyzed using more stringent and validated laboratory methods.

APPENDIX F. Adulterants[105-107]

Adulterants are substances ingested or added to the urine specimen to interfere with the ability to detect certain analytes. This may cause false-negative results on immunoassays, GC/MS, or UPLC/MS/MS. Household and chemical adulterants disable, interfere with, or lower the sensitivity of the immunoassay (IA) by:

- Changing pH
- Altering protein structure

Commercially Available Products

- Can act as oxidants to modify drug/metabolite molecule(s)
- Can interfere with detection by MS

Nitrite-containing Adulterants:

- Examples of products include "Klear" (potassium nitrite) and "Whizzies" (sodium nitrite)
- Oxidize the major cannabinoid metabolite detected by MS
- Designed to interfere with the mass spectrometric confirmation of tetrahydrocannabinol (THC), even though the initial IA may have been positive
- Urinary tract infections and/or some medications may cause an elevated nitrite level

Other Oxidizing Agents:

- Examples of products include "Stealth" (peroxide/peroxidase) and "Urine Luck" (chromate, pyridinium chromate)

- Designed to interfere with the mass spectrometric confirmation of THC and opiate(s), even though the initial IA may have been positive.

Note: Although oxidizing chemical reactions may change the molecules somewhat, the products of these reactions may still be recognized by IAs. The chart below illustrates laboratory methods used to detect common adulterants.

Laboratory Detection Methods for Common Adulterants

Adulterant	Laboratory Detection Method
Sodium chloride	Sodium or chloride (electrolyte) analyses
Detergents	Foaming, odor, pH
Acidic compounds	pH, odor, color
Basic compounds (e.g., ammonia, baking soda, bleach)	pH, odor, color
Other agents including Visine®, coloring agents, glutaraldehyde, drain cleaner	VAM
Chromates	VAM
Peroxide and peroxidases	VAM
Nitrites	VAM

VAM, various analytical methods

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Notes

ABOUT THE BOOK

Monitoring patient usage of scheduled controlled substances is a major concern and responsibility of prescribing clinicians. This handbook collects the most effective techniques for monitoring pharmacotherapy, with an emphasis on opioids, into a practical, objective and comprehensive strategy called **Urine Drug Monitoring (UDM)**. The UDM strategy presents new concepts and new benefits to the way clinicians use and view monitoring of patient pharmacotherapy.

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