

## Improving Heparin Safety: A Multidisciplinary Invited Conference

Carl Peterson, PharmD,\* Charles W. Ham, PharmD, MBA,<sup>†</sup> and Tim Vanderveen, PharmD,MS<sup>‡</sup>

### Abstract

Heparin is widely used in a variety of settings for prevention and treatment of thromboembolic events. Data from a number of sources indicate that it is also one of the drugs most frequently associated with adverse events and medication errors, many of which are serious. National media attention has focused on recent events involving heparin and The Joint Commission has included heparin in its 2009 National Patient Safety Goal to reduce patient harm from anticoagulants. Heparin safety is on the national agenda and health care organizations are struggling to improve it. Health care providers in clinical, management, and executive roles must work together to improve heparin safety.

Over 40 anticoagulation experts and practitioners came together in San Diego on March 13 through 14, 2008 to share information, offer perspectives, and address issues on the topic improving heparin safety. These individuals represented The Joint Commission, United States Pharmacopoeia, the Institute for Safe Medical Practices, academic institutions, large health care systems, and small hospitals who participated in a day and a half of presentations and round-table discussions. This article summarizes 21 presentations with a primary focus on types and frequency of heparin errors as well as identified opportunities to improve heparin safety. The conference was sponsored by Cardinal Health's Center for Safety and Clinical Excellence.

The complex nature of heparin administration creates many situations where medication errors and patient mismanagement can occur. The national media has recently reported incidents as diverse as look-alike vial errors at the bedside and potential contamination during the manufacturing process. If health care professionals can better understand this complexity and then apply the necessary steps to manage the involved processes, we can move closer to the ultimate

goal of “do no harm.”

### HEPARIN ERRORS – FREQUENCY AND DISTRIBUTION

Heparin is the anticoagulant most frequently involved in medication errors. More than 50,000 anticoagulant-related medication errors were reported to the United States Pharmacopoeia (USP) MED-MARX during a 5-year period from 2003 to 2007 and more than 17,000 involved heparin. Of these, 556 errors (3.1%) resulted in harm to patients—including 7 deaths.

The Joint Commission's (TJC's) Sentinel Event Database reveals that medication errors accounted for 9.3% of sentinel events. Of sentinel events associated with anticoagulants, two-thirds involved heparin and 82% were associated with patient deaths. Almost half of all errors (47.6%) occurred during drug administration followed by transcribing and documenting (18.8%), prescribing (14.1%), dispensing (13.9%), and monitoring (5.4%). The most common type of error, which is also most likely to be associated with harm to the patient, was administration of an improper dose or quantity; 4.8% of these errors resulted in harm. Next most common were omission and prescribing errors. The majority of heparin errors were due to “performance deficit” (43.1%) and failure to follow procedures or protocols (28.4%). Most errors (60.4%) occurred in the patient care unit and nurses were the staff members most likely to be involved (60%). Pooled data from 54 hospitals using smart intravenous (IV) pumps revealed that heparin was the number one drug associated with smart pump alerts that resulted in reprogramming or averted errors. Some of the doses averted were 50 to 100 times the limits, including both doses that were below as well as above the pre-established limits.

### HEPARIN FAILURE MODE EFFECTS ANALYSIS

Analysis of failure-mode

\*Clinical Director, Cardiovascular Diseases; <sup>†</sup>Vice President, Clinical Affairs; <sup>‡</sup>Vice President, Center for Safety and Clinical Excellence, Cardinal Health Center for Safety and Clinical Excellence, San Diego, California 92130.

**Table 1. National Patient Safety Goal 3E  
Implementation Expectations**

- A1. The organization implements a defined anticoagulant management program to individualize the care provided to each patient receiving anticoagulant therapy.
- A2. To reduce compounding and labeling errors, the organization uses ONLY oral unit dose products and premixed infusions, when these products are available.
- C3. When pharmacy services are provided by the organization, warfarin is dispensed to each patient in accordance with established monitoring procedures.
- C4. The organization uses approved protocols for the initiation and maintenance of anticoagulation therapy appropriate to the medication used, to the condition being treated, and to the potential for drug interactions.
- C5. For patients being started on warfarin, a baseline international normalized ratio (INR) is available and for all patients receiving warfarin therapy, a current INR is available and is used to monitor and adjust therapy.
- C6. When dietary services are provided by the organization, the service is notified of all patients receiving warfarin and responds according to its established food/drug interaction program.
- A7. When heparin is administered intravenously and continuously, the organization uses programmable infusion pumps.
- C8. The organization has a policy that addresses baseline and ongoing laboratory tests that are required for heparin and low-molecular weight heparin therapies.
- C9. The organization provides education regarding anticoagulation therapy to staff, patients, and families.
- C10. Patient/family education includes the importance of follow-up monitoring, compliance issues, dietary restrictions, and potential for adverse drug reactions and interactions.
- A11. The organization evaluates anticoagulation safety practices.

effects reveals multiple causes of heparin errors. Look-alike vials and syringes have resulted in a number of tragic and highly-publicized fatal errors. Many infusion errors involve pump misprogramming, intentional warning overrides, calculation errors related to heparin concentrations or math mistakes, and use of incorrect patient weights. In some cases, the wrong dosing nomogram was used. Heparin may be accidentally stopped when the infusion is interrupted and not restarted or patients may unintentionally receive duplicate therapy with more than one anticoagulant. Transcription mistakes may occur,

especially when problem-prone abbreviations such as “u” for “unit” or trailing zeroes are used.

A frequent, potentially dangerous practice involves the administration of bolus doses from infusion bags rather than administering a loading dose or subsequent bolus dose via a separate syringe or minibag. This practice involves calculating the loading dose, programming the pump to quickly deliver the loading dose, and then reprogramming the pump to deliver the continuous dose. A related practice is to greatly increase the infusion rate to bolus the patient. In either case, a calculation error or failure to correctly reset the

infusion pump may result in dosage errors. An unexpected and perhaps poorly understood finding involves the use of mixed dosing units. For example, the initial loading and maintenance doses may be prescribed in units/kg and units/kg/hr but subsequent dose adjustments are made in units/hr increments. An example would be to reduce an 8 unit/kg/hr dose by 100 units/hr. Switching units is problematic in several ways: It requires nurses to recalculate the current dose from units/kg/hr to units/hr in order to reduce the dose. Or, they can convert 100 units/hr to the “per kg” dose. If dosing units are changed from weight-based to units/hr, the pumps must be completely reprogrammed, assuming both dosing units are available in the library. A variation of this error potential occurs when the loading dose is prescribed in units and administered by a pump. Since pumps are designed to administer medications in hour increments, programming a loading dose requires calculating the exact volume to be delivered. For example, to administer a 4,000 unit bolus, it is necessary to calculate both the volume required and the infusion rate.

**NATIONAL PATIENT SAFETY GOAL 3E – ANTICOAGULANT SAFETY**

TJC’s expert advisory panel recognized that: a) “anticoagulation is a high-risk treatment, which commonly leads to adverse drug events because of the complexity of dosing, monitoring, and patient compliance”; and b) “the use of standardized practices can reduce the risk of adverse drug events associated with heparin, low-molecular weight heparins and warfarin.” In response to panel recommendations, TJC established National Patient Safety Goal 3E

(NPSG 3E): Reduce the likelihood of patient harm associated with the use of anticoagulation therapy. NPSG 3E consists of 11 specific requirements or implementation expectations (see Table 1). There is a 1-year phase-in period with quarterly milestones during 2008. Hospitals that provide anticoagulation to patients will be required to be fully compliant with NPSG 3E implementation expectations by January 1, 2009.

NPSG 3E requires hospitals to standardize heparin concentrations. Review of concentrations used in drug libraries in 207 hospitals found 15 unique heparin concentrations, with 9 in pediatric libraries and 8 in adult libraries. There was also a wide variation in heparin nomenclature, with 191 different name descriptors in the same 207 hospitals.

NPSG 3E does not specifically mention standardization of dosing units. Data from a 54-hospital sample showed that 48% of hospitals have standardized on units/kg/hr, 22% use only units/hr, while 30% allow both. When both dosing units were available, there was up to a 4-fold increase in the number of smart pump alerts that resulted in reprogramming of heparin infusions.

#### **ADDRESSING PROGRAMMING ERRORS WITH SMART IV PUMPS**

While most inpatient administration of heparin infusions is regulated by infusion pumps, TJC is making the use of programmable infusion pumps a mandatory part of NPSG 3E. Presenters from TJC clarified that programmable pumps are not necessarily smart pumps, although there was a strong consensus from the conference participants that smart pumps should be used for all heparin infusions. Smart pumps, which are cur-

rently used in approximately 50% of all hospitals in the United States, have comprehensive drug libraries with standardized nomenclature, concentrations, and dosing units that are specific to individual hospitals and care areas (eg, pediatrics, adult intensive care units). These smart pumps also provide dose calculators and alerts if doses fall outside of pre-established parameters. In addition, the pumps can be connected to the hospital's wireless-communication system, allowing frequent downloads of averted programming errors as well as data on issues related to compliance. The use of bar-code label scanning was also introduced as a new smart pump feature, thus allowing the manufacturer's bar-code label on a premix heparin container to be scanned with automatic selection of the correct drug and concentration from the pump library.

The conference provided the opportunity for several hospitals to review specific initiatives implemented to improve heparin safety. At Brigham and Women's Hospital, 23% of adverse medication events in cardiac patients were associated with anticoagulants. Heparin was the most common anticoagulant associated with errors; infusion pump programming and parenteral delivery problems were the most frequent causes of error and drug administration was the stage at which over half the errors occurred. The hospital was experiencing an event every 10 days and 2 in every 133 events resulted in harm or prolonged hospitalization. Analysis of pump continuous quality improvement (CQI) programming alerts indicated that many mistakes were pump-programming errors involving 10-fold and even 100-fold keypad entry errors. Surprisingly, about a quarter of errors were repeated by

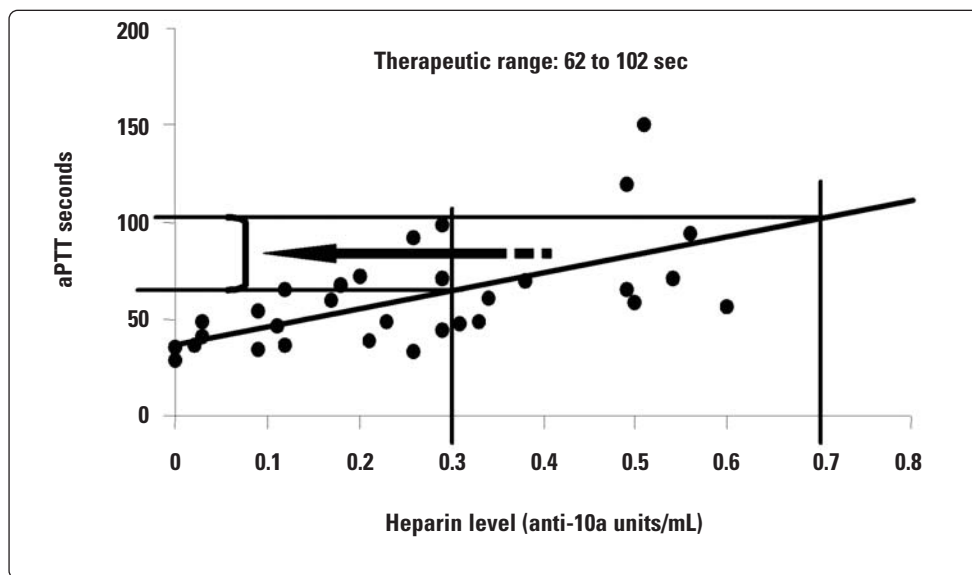
the user following the smart pump alert. The analysis also indicated that the highest incidence of alerts occurred around the afternoon nursing shift change and that alerts were more frequent on weekdays than weekends, suggesting that many programming errors occur when nurses are busiest.

St. Joseph's/Candler Medical Center in Savannah, Georgia, has used smart infusion pumps for approximately 6 years. This health system applied a unique Harm Index to the smart pumps' CQI data. This index can be used to determine the potential harm for programming errors that were averted. The hospital determined that heparin administration in medical/surgical units posed the highest risk of harm for all IV infusions. To address heparin safety, the hospital system standardized IV heparin concentrations, streamlined the dose calculation process, eliminated the need for nurses and pharmacists to calculate infusion rates, standardized heparin dosing units, and educated providers on revised dosing protocols.

#### **CLINICAL ISSUES IN HEPARIN SAFETY**

The process of treating patients with anticoagulants involves a fine balance between achieving an antithrombotic effect sufficient to prevent new or further thrombosis while minimizing the risk of bleeding. Safe and effective use of heparin presents significant challenges.

The dose of heparin and the desired intensity of the anticoagulant effect vary depending on the disease state being treated. It appears that weight-based heparin dosing using nomograms designed to rapidly achieve a therapeutic effect is optimal but multiple treatment protocols with different tar-



**Figure 1. A typical heparin response curve.**

aPTT = activated partial thromboplastin time; anti-10a = anti-factor 10a activity assay. Both aPTT and anti-10a activity tests are run on blood samples from 30 or more patients who are receiving intravenous heparin. The results are plotted on a scatter graph and the best-fit linear regression line is calculated and plotted. Each point represents a patient sample. The lower limit of the aPTT therapeutic range is the aPTT that correlates with 0.3 units/mL anti-10a activity. The upper limit aPTT correlates with 0.7 units/mL anti-10a activity. In this example, the aPTT therapeutic range is about 60 to 100 seconds.

get intensities are needed to meet the needs of different patients. Because the response to heparin varies greatly between individuals, treatment must be monitored and adjusted using results from lab tests, the aPTT or anti-factor 10a activity assay (anti-10a), that have their own inherent variability and limitations. Appropriate timing of monitoring tests is critical to making correct dosing decisions. The effect of heparin is also dependent on the patient's endogenous levels of heparin cofactor antithrombin; heparin may be less effective if antithrombin levels are low.

The coagulation laboratory plays an important role in heparin therapy. The sensitivity of the thromboplastin reagent used in the aPTT test varies significantly between manufacturers and even between lot numbers from the

same manufacturer. Since the aPTT is useful only in so far as it correlates with serum heparin levels and because for a given serum heparin level the aPTT test result will vary depending on the test system being used by the lab, each laboratory will have different lower and upper limit aPTT therapeutic ranges. The therapeutic range for each laboratory is established by plotting a heparin response curve as illustrated in Figure 1. This process is repeated each time the laboratory receives a new reagent lot; if the sensitivity of the new reagent is substantially different from that of the previous one, it may be necessary to change the target therapeutic range.

A number of other factors can affect aPTT results. At the preanalytical stage, poor phlebotomy technique, use of incorrect sample

collection tubes, delays in sample transport, temperature, and inadequate sample centrifugation prior to testing can all lead to misleading test results. Some drugs and disease states can also affect the results.

Heparin protocols were developed to standardize the process of initiating and managing heparin therapy to rapidly achieve and maintain a therapeutic aPTT within the institution's established range. Comparing a weight-based dosing protocol with "standard" one-size-fits-all initial dosing followed by monitoring and dose adjustment, the weight-based protocol achieved a therapeutic aPTT more quickly and significantly reduced the

incidence of recurrent deep vein thrombosis. The incidence of bleeding complications was the same in both groups despite more aggressive dosing in the weight-based group. Improvements in the time required to reach a therapeutic aPTT were maintained over a 5-year period with a nearly 95% protocol implementation rate. Delays in, or failure to achieve, a therapeutic aPTT in medical patients were also associated with prolonged length of hospital stay in a preliminary analysis that used data linking laboratory, pharmacy, and outcomes information.

#### IMPROVING HEPARIN SAFETY WITHIN HEALTH CARE ORGANIZATIONS

Improving heparin safety may be a national health care goal but change is implemented at the local

level. At St. Mary's Medical Center (SMMC) in Duluth, Minnesota, a flurry of adverse warfarin events prompted the hospital to form a multidisciplinary anticoagulation safety team and to subsequently launch an inpatient anticoagulation program focused on warfarin. The program was successful at reducing warfarin-related adverse events so the team then directed its efforts toward low-molecular weight heparins and direct thrombin inhibitors. The team significantly reduced sentinel events in these areas as well and their attention has now turned to heparin. A medication use evaluation (MUE) identified a number of improvement opportunities, among them infusion errors, aPTTs not being drawn at appropriate times, misinterpreted dosing protocols, and inconsistently monitored platelets. These results prompted a major capital expenditure to purchase smart infusion pumps and the hospital is currently working to formally incorporate heparin management into the anticoagulation program.

Fairview Health Services (FHS), a fully integrated 7 hospital health system in the Minneapolis area, conducted a formal heparin failure mode effects analysis of the medication management core process—decide, order, transcribe, distribute, administer, monitor, evaluate—after a series of serious and potentially tragic heparin errors occurred. Many improvement opportunities covering every facet of the process were identified. The FHS team took a 3-pronged approach to improving heparin safety. To prevent errors, they took a number of steps including revised storage and distribution of heparin, use of pretyped protocols and a heparin dosing service, improved drug checking, and use

of smart pumps and bar coding. To detect errors, they used their anticoagulation management service, flow sheets, and error detection software. To mitigate the impact of errors they again used the anticoagulation management team and built anticoagulant reversal protocols into their dosing protocols. Their efforts reduced heparin errors by 42%.

Health care providers in the Indianapolis area took an innovative, community-based approach to improving heparin safety. The Indianapolis Patient Safety Coalition (IPSC) was formed in 2004 “to improve patient safety among the major health systems in Indianapolis.” The leadership, comprised of executives, safety officers, and pharmacy directors from participating institutions, meets bimonthly, CEO's meet semiannually, and work is accomplished by ad hoc taskforces and workgroups. To achieve one of its goals, “to make the use of anticoagulant medications in Indianapolis Health-Systems safer,” IPSC partnered with the Institute for Safe Medical Practices to conduct a failure mode effects analysis and develop best safe practices to be implemented throughout the coalition. The arduous task of building consensus and setting standards at multiple institutions resulted in successful completion of the group's targeted actions. A results analysis is in progress.

#### **PERSPECTIVES IN HEPARIN SAFETY** **Human Factors**

Heparin ordering, administration, and monitoring procedures have become more complex with the use of multiple protocols, varying target aPTT ranges, and use of programmable infusion pumps. This complexity adds to the potential that human factors can result

in errors during the heparin use process. A large Minnesota health care organization developed a Heparin Error Reduction Workgroup, including a human factors consultant, to examine heparin administration procedures, identify types and sources of errors, and develop solutions to reduce heparin errors. Using direct observation of nurses administering heparin, examination of the computer user interface, and individual and group interviews, the heparin administration process was evaluated for opportunities to improve “user friendliness” and reduce human mistakes. Among actions taken based on human factors analysis: revision of ambiguous protocols; created standardized and more self-explanatory terminology; improved access to computers and printers; and modified the computer interface to smoothly guide users through the ordering process. Subsequent evaluation of results showed a 37.8% reduction in heparin errors.

#### **Nurses**

Human factors may impact nurses more than most. Nurses work in a high traffic, highly congested, high-pressure environment and their work is marked by constant interruptions and distractions. In many areas there is a shortage of nurses, particularly in the medical/surgical and critical care areas, where heparin is often used. Patient acuity is increasing and therapies have become more complex at the point of care.

Busy nurses face a number of issues surrounding safe-heparin administration. Performing dosage calculations correctly can be challenging, particularly when weight-based dosing regimens are used; work pressures may lead to perfunctory or absent double checks.

Look-alike heparin vial and infusion bag labeling, particularly when multiple strengths and concentrations are available, can cause errors as well. When programming infusion pumps, a perceived “need for speed” can result in keypad entry errors and can tempt nurses to override pump alerts and develop work-arounds. Inconsistent protocols can cause confusion when dosing, titrating, and timing lab draws. In addition, nurses are the first line of defense in recognizing complications when they occur.

### **Pharmacists**

Pharmacists are expected to take the lead in drug storage and dispensing, which are 2 of the 6 steps—selection, storage, ordering, dispensing, administration, and monitoring—in the medication-use process. All purchasing should be done through the pharmacy to ensure consistency and compliance with institutional policy. Heparin should be dispensed in the final form for administration and only premixed infusions in hospital standard concentrations should be used. Access to multiple heparin vial sizes and concentrations should be carefully controlled. The pharmacy should be able to track every vial size and type in every patient care unit. Often overlooked areas that may require additional attention in some hospitals include IV push and subcutaneous doses, heparin use in procedural areas, heparin flush in neonatal areas where errors involving the 10,000 unit/mL vial have led to tragic outcomes, assuring training and competency in use of programmable pumps, and ensuring compliance with safety systems.

### **Physicians**

A physician presenter compared physicians to airline pilots.

Rather than rely on memory to ensure all necessary checks are made before a flight, pilots rely on checklists and protocols. Similarly, physicians benefit from a formal heparin “preflight checklist” to ensure that necessary baseline information is available before initiating treatment. Like pilots who rely on others to build and maintain their aircraft, physicians can rely on standardized treatment implemented by other professionals in accordance with medical-staff approved protocols. Just as pilots cannot read all the cockpit instruments all at once, the job of the physician can be simplified by “warning lights” notifying him/her of out of range lab values, signs of possible complications, and the like.

Physicians are generally self-reliant leaders who value autonomy. They are sometimes perceived as resistant to change when in fact they are more resistant to being changed. In developing and adopting standards and protocols to improve heparin safety, it is important that physicians be part of the planning and development process. The Deep Vein Thrombosis Prevention program at University of California San Diego serves as an example. Baseline measurement identified an opportunity to improve the rate of venous thromboembolism (VTE) prophylaxis. Next, a process of multidisciplinary consensus building resulted in development and implementation of a standardized, physician-friendly risk assessment process and VTE prevention order set. The result was that appropriate VTE prophylaxis rose from 55% of patients to over 95% and this was accompanied by a documented decrease in thromboembolic events.

### **Children**

Medication errors in children, including errors involving heparin, are at least as common in children as in adults. Many of the causes are the same; however, some are unique to children. Because children represent a relatively small and specialized population base, clinical information on optimal drug use may be scant and support systems such as computerized physician order entry may be problematic. Children vary greatly in size and weight and require different drug concentrations and dosage. Dosing in infants is particularly important, in part because there is little margin for error. Children can be more difficult to monitor and are often unable to provide the feedback that adults can. At the health care institution level, responsibility for medication safety in children is shared by all but additional commitment to children’s safety is needed at the executive, industry, and regulatory levels.

### **Heparin-Induced Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is an uncommon but potentially devastating complication of treatment with heparin and low-molecular weight heparins. HIT is characterized by a drop in the platelet count to less than 100,000/mm<sup>3</sup> and/or to less than 50% of baseline, usually after 4 to 14 days of treatment. The decrease in platelets is due to formation of antibodies that react with heparin bound to platelet factor 4 and cause platelet clumping. Despite low-platelet counts, HIT is associated with thrombosis associated with platelet activation but bleeding is uncommon.

It is essential that suspected HIT be identified early by monitoring platelet counts and being

attentive to changes in patient status suggesting new or recurrent thromboembolic events. HIT probability nomograms can be used to assess the likelihood that a patient has HIT. When HIT is suspected, all heparin, including line flushes, must be discontinued and anticoagulation with a direct thrombin inhibitor (argatroban, lepirudin, bivalirudin) must be initiated while awaiting results of confirmatory testing (which are often delayed). Failure to discontinue heparin and initiate alternative anticoagulation will result in thromboembolic complications in the majority of patients. For patients who will require extended anticoagulation for management of the underlying disease state, warfarin should not be initiated until the platelet count has recovered. Overlap between direct thrombin inhibitors (DTI) and warfarin is complicated by the fact that the DTIs, particularly argatroban, may have an effect on the international normalized ratio independent of warfarin.

#### **APPENDIX**

##### **Presenters**

Peter Angood, MD, The Joint Commission; Michael Cohen, RPh, MS, Institute for Safe Medical Practices; William E. Dager,

PharmD, FCSHP, UC Davis Medical Center; John Fanikos, RPh, MBA, Brigham and Women's Hospital; James Fuller, PharmD, Wishard Health Services; Samuel Goldhaber, MD, Brigham and Women's Hospital; Vicki Wilson Good, MSN, RN, CCRN, CCNS; Robert Gosselin, CLS, UC Davis Medical Center; Michael Gulseth, PharmD, Saint Mary's Medical Center; Vikas Gupta, PharmD, BCPS, Cardinal Health Clinical Research Group; Kathleen A. Harder, PhD, University of Minnesota; Charles Homer, MD, MPH, National Institute for Children's Healthcare Quality; Ian Jenkins, MD, UC San Diego; Patricia Kienle, RPh, MPA, FASHP, Cardinal Health Center for Safety and Clinical Excellence; Ray Maddox, PharmD, St. Joseph Candler; Steven Meisel, PharmD, Fairview Health System; Robert Raschke, MD, MS, Banner Good Samaritan Medical Center; Darryl S. Rich, PharmD, MBA, FASHP, The Joint Commission; John Santell, MS, FASHP, United States Pharmacopeia; Tim Vanderveen, PharmD, MS, Cardinal Health Center for Safety and Excellence

##### **Round Table Participants**

Bona E. Benjamin, BS Pharm,

American Society of Health-System Pharmacists; Cynthia L. Dakin, PhD, RN, Elms College; Darlene Elias, MD, Scripps Health; Joseph Dasta, MSc, University of Texas College of Pharmacy; Charles W. Ham, PharmD, Cardinal Health Center for Safety and Clinical Excellence; Amy Herrington, RN, MSN, CEN, University of Kentucky Healthcare; Doug Humber, PharmD, UC San Diego Medical Center; Marla Husch, RPh, Central DuPage Hospital; Julie Lear, RN, BSN, CCRN, Mary Immaculate Hospital; Stephen Lewis, MD, Cardinal Health Center for Safety and Clinical Excellence; Karla M. Miller, PharmD, BCPP, HCA; Carl Peterson, PharmD, Cardinal Health Center for Safety and Clinical Excellence; Sylvia Martin-Stone, PharmD, BCPS, Cedars Sinai Medical Center; Phil Schneider, The Ohio State University; Oxana Tcherniantchouk, MD, Cedars Sinai Medical Center; Misty Vo, PharmD, Banner Desert Hospital Pharmacy; LeAnn Warfel, RN, BSN, Doylestown Hospital; Gay Wayland, RN, Scripps Health; Jonathan Weisel, MD, Christus St. Frances Cabrini Hospital; Heather Wyma, RN, BSN, Sharp Memorial Emergency Department.