This paper provides the healthcare industry, in particular the pharmacy and inpatient facility sectors, with historical and background information on the patient risks associated with hidden sources of acetaminophen and recommendations for best practices to mitigate those risks through facility management and electronic medical record systems.
Acknowledgements

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Executive Summary

Since publication of Version 1.0 of NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen in May of 2011, collaborative efforts among all key stakeholders have resulted in significantly improved pharmacy container labeling of acetaminophen-containing prescription medicines. Publication of Version 1.1 provided additional guidance to facilitate their efforts for ensuring full implementation of the NCPDP recommendations, necessary to improve safe and appropriate use of acetaminophen by the public. Tremendous strides have been made in the adoption of these best practice recommendations.

With this white paper, focus is shifted to mitigating the risk of acetaminophen overdose in the inpatient setting through use of available functionality inherent in hospital and nursing facility patient management and electronic medication systems. The principles described for mitigating the risk of inadvertent overdosage are expected to apply to other drugs with narrow therapeutic ranges in the inpatient setting.

Based on the background and studies cited in this white paper, it is apparent that patient safety in the inpatient setting associated with the administration of acetaminophen carries many of the same risks as experiences observed with acetaminophen use in the outpatient setting. Importantly, lack of knowledge about maximum recommended daily dosages and failure to recognize duplicate therapy contribute to inadvertent acetaminophen overdose in the inpatient setting just as they do in the outpatient setting. While the inpatient hospital setting is a much better controlled environment for patient treatment than the outpatient environment, inadvertent overdoses still occur.

Studies presented, indicate evidence of supratherapeutic dosing of acetaminophen among patients in hospitals and long-term care (LTC) facilities. This prompted a review of the inpatient medication-use process, clinical decision support (CDS) and information systems available, and technology capability for monitoring dosage accumulation in order to:

- Further understand the risks associated with inpatient transitions of care
- Identify the hospital, skilled nursing, and other LTC discharge processes for education
- Develop guidance for prevention

and, in the end, identify recommendations to reduce or eliminate acetaminophen supratherapeutic dosing in the inpatient setting.

The medication-use system is defined as the provision of medication by the pharmacy to patient-care units and ultimately administration to the patient. The process includes various activities, including key ones where best practices should be applied to minimize the risk of inadvertent acetaminophen overdosage. Those activities include product selection, appropriate prescribing and pharmacist evaluation of the order, drug verification at dispensing and administration, and recording in the medication administration record (MAR). Monitoring for therapeutic duplication in the patient’s medication regimen (e.g., simultaneous use of multiple acetaminophen-containing products) and for appropriateness of the dose are key elements in the medication-use system.

Drug database publishers and pharmacy system vendors state that currently available technology supports drug dose alerts and accumulator calculation applications for drugs with narrow therapeutic margins, including acetaminophen. Technology barriers that could prevent or restrict hospital implementation include suboptimal integration of hospital and pharmacy systems, lack of or inadequate
CDS interfaces, insufficient data supporting the need and benefit for patient safety, and decision support alert fatigue that prompts over-ride and a lost opportunity to prevent medication errors.

Some of the technologic problems stem from regulatory mandates that impact budgetary decisions. Meaningful use (using certified electronic health record technology) and the Affordable Care Act (ACA) incentivized the adoption of technology by providing both funding for electronic health record (EHR) adoption and fiscal penalties for noncompliance. The tendency was to budget to meet minimum compliance requirements and once met to consider additional funding to implement optional functionality and upgrades as unnecessary, even though lack of this functionality might negatively affect patient safety and outcomes.

Inpatient transitions of care status include clinical handoffs and between different levels of care and settings within the hospital and also between the hospital, LTC, rehabilitation facilities, and discharge to ambulatory care. Medication reconciliation, the process overview of a patient’s medication orders, can prevent medication errors by capturing duplications, omissions, and discontinuations and serve as the basis for an optimized treatment plan based on the current patient status. This patient safety function is best provided by the clinical pharmacy staff. Upon admission, medication reconciliation is used to clarify and verify the patient’s medication list from family or outpatient pharmacy database. During each transition of care, documented medication updates per patient status should be routine. The discharge process should include comparison of admission medications and changes during the admission and discharge orders. Medication reconciliation within the transition of care provides an updated medication list to outpatient treatment providers, pharmacies, and caregivers and also provides an opportunity for safe use counseling.

As this White Paper will elucidate, the key factors contributing to inadvertent acetaminophen overdosage in inpatient settings include:

- Simultaneous use of multiple acetaminophen-containing products,
- Lack of recognition of recommended maximum daily dosages of acetaminophen,
- Lack of recognition that acetaminophen is the principal cause of acute liver failure in the US,
- Failure to optimally communicate medication information at transitions of care,
- Failure to optimally implement medication safety technologies, particularly dose accumulator calculation features and associated alerts, and
- Alert fatigue and override

### Summary of Recommendations and Stakeholders Call to Action for Dose Accumulation Monitoring for Medications Containing Acetaminophen

<table>
<thead>
<tr>
<th>Recommendation: Minimize use of multiple-ingredient products containing acetaminophen.</th>
</tr>
</thead>
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Stakeholders: Directors of Pharmacy, Pharmacy & Therapeutics Committees

- Clearly identify all acetaminophen-containing products and their associated dose in computerized prescriber order entry (CPOE) and other clinical decision support (CDS) systems
| 2 | **Recommendation:** Implement prescriber and nurse education with emphasis on maximum daily dose for medications at risk for overdose.  
**Stakeholders:** Directors of Pharmacy, Clinical Staff Pharmacists, Pharmacy & Therapeutics Committees, Nursing Education  
- Renewed emphasis on maximum 4 g and/or weight-based (75 mg/kg for patients weighing less than 50 kg) daily dosage of acetaminophen  
- Awareness of multiple sources (e.g., single- and multiple-ingredient products) contributing to the accumulated dose  
- Awareness that maximum daily dose of acetaminophen is based on all routes of administration (IV, oral, and rectal)  
- Awareness of the risks involved with exceeding the maximum recommended daily dosage  
- Awareness that some patients (e.g., the elderly, patients with chronic liver diseases) may not tolerate the usual maximum recommended acetaminophen dosage of 4 g daily |
|---|---|
| 3 | **Recommendation:** Provide patient education on medication use and the risk for overdose.  
**Stakeholders:** Clinical Staff Pharmacists & Pharmacy Technicians (Medication Reconciliation), Nursing Staff, & Nurse Case Managers upon discharge  
- Validated discharge instruction sheet  
- Drug-specific maximum doses and warnings  
- For acetaminophen-containing medication  
  - Information on over-the-counter (OTC) drugs  
  - Warnings for example on  
    - Concomitant use of multiple products containing acetaminophen  
    - Co-morbidities  
    - Liver toxicity  
    - Alcohol intake  
  - Safe use education  
  - Possible acetaminophen icon use |
**Stakeholders:** Directors of Pharmacy and Clinical Informaticists, Chief Information Officers, EHR Vendors  
- Integrate with pharmacy management system  
  - Including management of robotic dispensing and automated dispensing cabinets (ADCs)  
- Dialogue with EHR vendors regarding availability of drug accumulator tools  
- Activate full alert functionality available in internal software or as part of the drug database in use  
- Revise protocols that potentially result in duplicate therapy

5. **Recommendation: Establish pharmacists as the primary actor in the Medication Reconciliation Process.**  
**Stakeholders:** Directors of Pharmacy, Pharmacists, Pharmacy Technicians, Pharmacy & Therapeutics Committees, Chief Nursing Officers, & Nursing staff  
- Comprehensive medication review on admission and discharge  
- Pharmacist oversight of all medication use activities during inpatient stay, emphasizing areas of greatest risk such as during clinical handoffs and transitions of care  
- Communication of reconciled drug regimen and recommendations to the patient’s outpatient pharmacy and caregivers

6. **Recommendation: Integration of health information technology solutions that minimize the risk of inadvertent overdosage for high-risk medications into all process flows and decision support.**  
**Stakeholders:** Directors of Pharmacy, Clinical Informaticists, Pharmacists, Pharmacy Technicians, Chief Information Officers & IT staff, EHR vendors, Medical staff via Pharmacy & Therapeutics Committees, Chief Nursing Officers & Nursing staff  
- Customize and monitor CPOE and CDS systems to optimize rate reductions in medication errors and adverse drug events (ADEs) associated with inadvertent overdosage of high-risk medications  
- Review policies for order entry that aim for increased safety (e.g., reviewing current medications before entering new orders)  
- Update existing medication databases as necessary to prevent duplicate order errors  
- Install and activate dose accumulator, alert, and monitoring tools  
  - Target all medications with a narrow therapeutic margin  
  - For acetaminophen, implement a “never event” strategy for daily dosages
exceeding 4 g, including for any combination of IV, oral, and rectal administration

- Customize alerts to target users in order to avoid “alert fatigue”
- Whenever possible, evaluate CPOE systems for their ability to reduce the rates of preventable overdosage errors using systematic, standardized tools

In addition to the recommendations for stakeholder action:

**Recommendation to NCPDP:**

- Identify a “model hospital” that
  - has adopted most of this White Paper's recommendations and
  - is willing to participate in an acetaminophen safety study
- Conduct a safety study
1. Audience

The audience includes all stakeholders involved in the generation of orders for and dispensing and administration of prescription medicines in inpatient/long-term care (LTC) settings including prescribers (e.g., physicians, nurse practitioners, physician’s assistants), nurses, pharmacists, and pharmacy technicians; drug database publishers; commercial and proprietary hospital and pharmacy management system vendors, including computerized prescriber order entry (CPOE) and clinical decision support (CDS) system vendors; chief information officers and clinical informaticists; and electronic medical record (EMR), electronic health record (EHR), and barcode-assisted electronic medication administration system (BCMA) companies.

2. Purpose and Problem

The purpose of this white paper is to provide best practices and guidance for improved detection and alerting of cumulative daily doses of acetaminophen and other medications with narrow therapeutic margins that approach or exceed recommended maximum levels in inpatient and skilled nursing and other LTC facility settings using electronic systems. In addition, this white paper provides best practices and guidance aimed at reducing the risk of inadvertent acetaminophen overdosage that could occur during clinical handoffs such as between units or departments and care transitions such as from the inpatient to ambulatory care setting, in particular, as a result of duplicate or additive acetaminophen-containing therapy (e.g., analgesic combinations). While the focus of this paper is prevention of acetaminophen overdose, the recommendations are meant to be applied to any medication where strict monitoring of dosage limits is critical for the patient’s wellbeing.

2.1 Inpatient Overdosage

Several recent studies have documented the problem of supratherapeutic acetaminophen dosing within hospitalized patients, despite policies and procedures to monitor and control acetaminophen exposure, and the failure of existing systems, including computerized prescriber order entry (CPOE), to adequately prevent them.\(^1\)\(^-\)\(^7\) In fact, such overdosage can occur despite the presence of robust decision support alerts to detect inappropriately-high ordered dosages and duplicate therapies.\(^1\)\(^,\)\(^3\) Regularly scheduled (standing-order rather than as needed [“prn”]) administration, use of multiple acetaminophen-containing medication formulations, and use of multiple- or single-ingredient products with 500 mg or more of acetaminophen were associated with the highest risk of inadvertent overdosage.\(^1\)\(^,\)\(^4\) Surgical units and intensive care units (ICUs) also were associated with increased risk.\(^1\)\(^,\)\(^4\)\(^,\)\(^8\)

The vast majority of inpatients do not appear to be at risk of acetaminophen overdosage despite such potential failures, at least in teaching hospitals;\(^1\)\(^,\)\(^4\)\(^,\)\(^9\) however, the consequences of hepatotoxicity associated with acetaminophen overdosage, should it occur, are serious and potentially life-threatening.\(^1\)\(^0\)\(^,\)\(^1\)\(^1\) Therefore, steps should be taken to minimize the risk of inadvertent overdosage in inpatient settings. In addition, despite apparent individual variations in maximum tolerated acetaminophen dosages and the inability to establish a specific threshold dose for toxicity,\(^1\)\(^0\) the current standard recommended maximum dosage of 4 g daily should be applied for inpatients just as it is for ambulatory patients.\(^9\)\(^,\)\(^1\)\(^1\)\(^,\)\(^1\)\(^2\) In some cases (e.g., the elderly, patients with chronic liver diseases), even lower maximum dosages (e.g., 3 g daily) may be warranted.\(^1\)

2.2 Cumulative Daily Dose Calculation

While robust algorithms for calculating cumulative daily acetaminophen doses from any product exposure and subsequently triggering associated alerts have been suggested as important safeguards
for preventing inadvertent overdosage in hospitalized patients, alert fatigue and override, as well as unfamiliarity with maximum recommended dosages may be contributing factors to failure of such safeguards. Healthcare providers often ignore alerts and decision support rules that are embedded in electronic systems. In addition, the American Society of Health-System Pharmacists (ASHP) 2013 national survey on informatics found that only about half of US hospitals employing clinical decision support (CDS)-enabled CPOE systems actually calculate cumulative daily doses. Importantly, about 90% of US hospitals employed barcode-assisted electronic medication administration systems (BCMA) in 2014. BCMA has been suggested as a more fail-safe intervention at preventing inadvertent acetaminophen overdosage because it is less prone to override.

Failure to appropriately customize and monitor computerized systems such as CPOE and CDS also contributes to non-achievement of desired safety benefits. The importance of such customization and monitoring for ensuring that safety outcomes are achieved is reinforced by recommendations from the National Quality Forum (NQF) and meaningful use requirements under the American Recovery and Reinvestment Act. The Leapfrog CPOE evaluation tool has been recommended as an independent, inexpensive, standardized tool for estimating the potential benefit of a hospital’s CPOE system by testing how it performs in addressing a variety of dangerous medication ordering scenarios.

In a recent application of the Leapfrog tool in hospitals, shortcomings of CPOE systems principally resulted from failures related to excessive dosing, either by therapeutic duplication or by exceeding dosing limits, and acetaminophen alone and in combination with other drugs were by far the most commonly responsible products. Unfortunately, the focus of recent EHR certification criteria and associated financial incentives on drug-drug interaction and drug-allergy alerts may have diverted attention away from drug dosing alerts as an important safety performance measure in CDS.

2.3 Transitions of Care

Effective transitions of care are important factors in reducing medication errors. Patients can experience medication errors any time they undergo a transition in care. Transitions of care include changes in patient location, provider, or both, such as:

- Between inpatient (e.g., hospital, LTC, rehabilitation) and ambulatory care locations,
- Between different levels of inpatient care and settings, and
- Between different care providers.

Complicating effective transitions of care is the trend of inpatient care increasingly being provided by hospitalists rather than primary care providers. Approximately 50–70% of hospital-related medication errors and 20% of all adverse drug events (ADEs) are attributed to poor communication at transitions and interfaces of care. In addition, the Joint Commission has reported that 22% of medication reconciliation failure occurs during patient admission and 12% occurs at the time of discharge. However, several studies have reported that medication discrepancies occur more commonly during discharge, with error rates in these studies ranging from about 40-60% of discharged patients.

The Joint Commission, Centers for Medicare & Medicaid Services (CMS), and others have published recommendations for optimizing medication reconciliation and avoiding medication errors at transitions of care, including when a patient changes service, setting, provider, or level of care within or outside an organization. Medication reconciliation is an integral part of clinical information reconciliation and a key objective in CMS’ stage 2 meaningful use objectives and EHR incentive programs for eligible
professionals, eligible hospitals, and critical access hospitals in 2015–2017, and were to continue with stage 3 meaningful use in 2018. Thus, medication reconciliation applies across the continuum of care, including inpatient, ambulatory, emergency and urgent care, long-term care, and homecare, and focuses on assisting providers in their direct patient care and on improving the accuracy of information provided to others through health information exchange (HIE).

Duplication of therapy, a common problem with inadvertent acetaminophen overdose, and prescribing the right drug but at high dosage can result in medication-related problems at care transitions. Opioid analgesics, which often contain acetaminophen, are among the most common classes of drugs requiring intervention at transitions of care to prevent medication errors.

2.4 Impact of IV Acetaminophen Therapy

The introduction of IV acetaminophen into the inpatient setting has raised new concerns about potential inadvertent overdosage of the drug. Although IV acetaminophen at recommended dosage is considered reasonably safe, particularly under close safety monitoring in the hospital setting, its potential concomitant use with opioids to treat postoperative pain could result in inadvertent overdosage if oral opioid combinations containing acetaminophen were also used. Acetaminophen alone is not effective for treating severe postoperative pain, making concomitant opioid therapy likely, and surgical units have been associated with an increased risk of acetaminophen overdosage. Therefore, the labeling for IV acetaminophen carries a warning about concomitant use with other acetaminophen-containing products to help reduce the risk of inadvertent overdosage. In determining accumulated daily dose of acetaminophen, all routes of administration (IV, oral, and rectal) must be included in the calculation.

The fact that interoperable communication between point-of-care activated devices (e.g., IV infusion pumps) and CPOE and EHR systems may not be optimal should be considered in developing procedures for ensuring global dosage calculation for all routes of acetaminophen administration. In 2014, about 90% of US hospitals used point-of-care activated small-volume parenteral products. In addition, procedures should be in place to ensure that IV acetaminophen is prescribed, prepared, and administered properly, that IV infusion pumps are properly programmed, and that mg and mL units are not inadvertently confused in calculating accumulated acetaminophen doses.

2.5 Education of Healthcare Professionals

Educating healthcare professionals about the risks of acetaminophen use, particularly those associated with exceeding maximum recommended daily doses, and changing hospital policies to reduce risk factors for excessive dosing are key elements in preventing inadvertent overdosage. Because the goal of preventing excessive acetaminophen dosing should be as a “never event,” one method that has been recommended for prevention is to engineer a process and embed it into electronic systems (e.g., CDS, CPOE, EHR, medication administration technology) such that it creates hard stops that prevent ordering and administration of daily doses exceeding 4 g or 75 mg/kg in patients weighing less than 50 kg. In doing so, the tendency of clinicians to ignore alerts and embedded decision support rules also should be addressed.

3. Research

Acetaminophen is widely and effectively used in both prescription and over-the-counter (OTC) medications to relieve pain and reduce fever. It is one of the most commonly used medicines in the United States (US). It is found in more than 500 different prescription and OTC medicines.
Although acetaminophen and hydrocodone combinations had been the most widely prescribed drug in the US for many years, it recently fell to second place behind levothyroxine mainly because of the US Food and Drug Administration (FDA) phased withdrawal of high-dose (greater than 325 mg) acetaminophen-containing combinations.

When used as directed, acetaminophen has a well-established record of safety and efficacy. Acetaminophen is often recommended for certain patient populations since it is considered to be a “safer” alternative as it lacks the adverse effects (e.g. gastrointestinal bleeding, opioid-induced respiratory depression, other bleeding) of other analgesic medications – namely the nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. Despite this, however, acetaminophen is the leading cause of acute liver failure. Exceeding the maximum daily dose (4 g daily) can place a patient at risk for severe liver injury. Recent analysis of the National Poison Data System of the American Association of Poison Control Centers suggests a disproportionate increase in acetaminophen-associated hepatic injury with the misuse and abuse of opioid combination products, likely secondary to increased self-dosage for the opioid effect without regard to concomitant acetaminophen dosage.

In a US based internet survey, 4.5% of acetaminophen users exceed 4 g daily for one or more days. Patients who exceeded 4 g daily were characterized by chronic pain, poor physical status, and heavy use of medical care.

3.1 Hospital Studies and Findings

Several studies found similar instances of supratherapeutic acetaminophen dosing in inpatient settings, despite policies and procedures aimed at monitoring and controlling acetaminophen exposure. Acetaminophen-containing products are some of the most widely prescribed drugs in inpatients, with more than 60% of adult patients receiving the analgesic in one study of two tertiary care hospitals. Risk factors associated with supratherapeutic acetaminophen dosing in hospital inpatients include:

- Orders for multiple acetaminophen-containing products
- Acetaminophen products containing 500 mg or more
- Regularly scheduled rather than “prn” dosing
- Higher number of doses per day
- Higher dose per administration
- Older age
- Chronic liver disease
- Diagnosis of osteoarthritis
- Surgical or ICU care
- Gaps in optimal implementation of medication safety technologies

In a retrospective review, acetaminophen use was examined in hospitalized patients in two academic tertiary care settings in an effort to identify factors that contributed to supratherapeutic acetaminophen doses. In this study, 23,750 patients who were at least 12 years of age were evaluated. Of these, 14,411 patients received acetaminophen and comprised the study population. Patient exposure to acetaminophen was obtained from the hospitals’ electronic MAR (eMAR) system. Each record included medication name, strength, dose, route, administration time, instructions, administering hospital unit...
Supratherapeutic acetaminophen dosing was defined as any cumulative administration of 4 g or more of the drug daily. Secondary analysis of patients who were 65 years of age or older and those with chronic liver disease was performed using a 3 g daily threshold.

Of the 14,411 patients in this study, 6.6% (955) exceeded the 4 g/day limit of acetaminophen therapy. In addition, 22.4% of patients 65 years of age and older and 17.6% of patients with chronic liver disease received dosages exceeding 3 g/day. Overall, there was a 4% (955/23,750) rate of supratherapeutic dosing in all hospitalized patients. In addition, almost half of those receiving supratherapeutic dosing actually received greater than 5 g of acetaminophen daily, 40% received supratherapeutic dosing for 3 days or longer, and 10% received supratherapeutic dosing for 10 days or longer. Averaged over the entire hospital stays, supratherapeutic acetaminophen dosing was associated with more administrations per day and a higher dose per administration.

Factors that placed patients at higher risk for exceeding the maximum recommended dose in this study included older age, chronic liver disease; white (Caucasian), a diagnosis of osteoarthritis, regularly scheduled rather than “prn” administration, use of multiple acetaminophen-containing product formulations, including formulations with 500 mg or more of the drug, and administration in surgical units and ICUs. Medicine and other units were associated with a lower risk. Of patients who received three or more different acetaminophen-containing formulations, about 21% received supratherapeutic doses.

The authors concluded that hospital policy and prescriber training are warranted to help clinicians identify acetaminophen-containing products and monitor closely acetaminophen cumulative daily doses. A decision support system implementing liver toxicity warnings displayed at order entry and during administration was suggested to mitigate the risks of supratherapeutic acetaminophen dosing. However, more judicious display of alerts might be more effective because of the risk of alert fatigue. In addition, because the practice of regularly scheduled analgesic dosing (to avoid peaks and troughs of analgesia) is considered more effective than as needed dosing for pain management, long-standing acetaminophen dosing practices involving products containing 500 mg or more should be reassessed because of the low margin of error when regimens of 1 g every 6 hours are employed. Fortunately, opioid combinations containing more than 325 mg of acetaminophen per dose are no longer available in the US although single-ingredient products are still available. Special attention also should be paid to osteoarthritis patients, particularly since acetaminophen is recommended as initial therapy for many forms of the disease and the increased risk of supratherapeutic dosing observed in this study.

In a retrospective cohort study, the frequency of acetaminophen administration in excess of 4 g daily on at least one calendar day was determined in an academic tertiary care setting. During the study period, 43,761 admissions were included in the analysis during which at least one dose of an acetaminophen-containing medication was dispensed. Of these admissions, 2.6% (1119) of patients received more than 4 g of acetaminophen daily on at least one calendar day. Doses that patients actually received were recorded via the eMAR system. The authors concluded that patients receiving a larger number of acetaminophen-containing medications were at greater risk of supratherapeutic dosing and therefore questioned the use of acetaminophen-containing combination products in inpatient settings. Because of the prescriber control over medication orders in the inpatient setting, the benefit of ordering combination formulations of acetaminophen and opioids versus ordering the component medications separately is purely a matter of convenience, but one that is associated with an increased risk of supratherapeutic dosing. Other risk factors included slightly older age, shorter lengths of stay, and admission to a surgical service (especially orthopedics). The authors further concluded that patient safety could be improved by implementing additional safeguards to prevent excessive
acetaminophen dosage.9 One such safeguard would be an automated computer-based program that tabulates a patient’s cumulative acetaminophen and fires an alert (e.g., as part of orders entered through a CPOE system) when the recommended maximum would be exceeded.4–8

These and other studies have demonstrated that several risk factors can increase the likelihood of hospitalized patients being given supratherapeutic doses of acetaminophen.1–6,8 These risk factors include (but are not limited to): being admitted to a surgical service, having a shorter length of hospital stay, being ordered multiple acetaminophen-containing products, advanced age (65 years and older), having chronic pain conditions (e.g. osteoarthritis), regularly scheduled administration vs. a “prn” basis, and using formulations containing 500 mg or more of acetaminophen versus 325 mg of the drug.

Because of the challenge of clinicians keeping track of cumulative acetaminophen doses from multiple products over 24-hour periods, which are exacerbated by clinical patient handoffs, effective CDS is needed to mitigate the risk of overdosage.1,5,8,11 Unfortunately, only about half of US hospitals were using CDS-enabled CPOE that calculated total daily doses of drugs in 2013, although almost 70% of certain hospitals stratified by bedside calculated total daily doses.13 Only about 30% of US hospitals calculated cumulative lifetime doses in 2013.13

When evaluated using an independent, standardized tool from the Leapfrog Group, CPOE systems from several small- to medium-sized community hospitals yielded evidence of the failure of these systems to adequately reduce the rates of preventable ADEs using a standardized performance tool.7 Of these ADEs, most were related to excessive dosing, either by therapeutic duplication or exceeding dosing limits, and the most frequent offenders were acetaminophen, acetaminophen-containing multiple-ingredient products, and opioids, accounting for 30, 24, and 7.4%, of all events, respectively.

3.2 Long Term Care Studies and Findings

Approximately 25–50% of older adults residing in long-term care (LTC) facilities experience pain; however, less than half of LTC residents with pain receive routinely scheduled pain medication or special services for pain management.45 Pain is a commonly undertreated condition in older adults, particularly in residents with hospice and/or palliative care needs46; age exceeding 70 years is the greatest risk factor.47 Consequences of inadequate pain control can result in depression, anxiety, impaired ambulation, decreased socialization, sleep disturbances, and increased healthcare utilization.48

According to the 2009 American Geriatrics Society pain guidelines, acetaminophen is recommended as a first-line agent in the treatment of persistent pain in older adults.49 It is contraindicated for use in liver failure and has relative contraindications for use in patients with hepatic insufficiency and chronic alcohol abuse or dependency. The usual maximum recommended daily dosage is 4 g from all acetaminophen sources, including combination products.

Acetaminophen use in older adults generally is well tolerated and efficacious for musculoskeletal pain, including osteoarthritis and lower back pain.49 In comparison with other non-opioid pain medications, such as NSAIDs, acetaminophen is not associated with significant gastrointestinal, renal, or cardiovascular toxicities.

There are several important safety concerns when prescribing acetaminophen in a LTC setting. In older adults, decreased activity of phase I conjugation reactions in the liver have been associated with decreased acetaminophen clearance, especially in frail adults who are unable to care for themselves.50 This pharmacokinetic change could result in higher acetaminophen drug concentrations and increase the risk for adverse events with cumulative doses. Although the clinical effects of these age-related
changes remain to be more fully elucidated, caution should be taken when prescribing acetaminophen to frail LTC residents.

While pharmacists monitor medication use in a LTC setting, there is a concern when OTC acetaminophen-containing products (e.g., combination cold, pain/fever, allergy products) are used without a recommendation from a LTC provider. Daily ingestion exceeding 4 g may result in an overdose and is a concern in this setting. Patient education on acetaminophen sources, maximum daily dose limits, and signs and symptoms of hepatotoxicity are key in preventing acetaminophen misuse and overdose.

Alcohol is commonly used in persons 65 years of age and older. In nursing homes, the rate of alcohol use varies from 8–46%. Regular alcohol use and/or abuse will increase the formation rate of acetaminophen’s toxic metabolite, \( n\)-acetyl-\( p\)-benzoquinone (NAPQI), thus increasing the risk for hepatotoxicity. In older adults with hepatic insufficiency or known regular alcohol use and/or abuse, an acetaminophen dose limit of 1–2 g daily is recommended.

When considering other opioid and non-opioid medications, acetaminophen is usually the “best” choice as a first-line agent to treat mild persistent pain; however, medications should ideally be used in combination with other non-pharmacologic interventions (e.g., physical therapy, meditation, biofeedback). Although acetaminophen is generally well tolerated by older adults, it is important to consider the potential safety risks of using this medication in a LTC setting. Patient education regarding potential harm is essential in preventing acetaminophen misuse and abuse.

4. Background and Current State

Publication of NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen Version 1.0 published May 2011 elucidated the clinical finding regarding acetaminophen overdose and the need for complete spell out of acetaminophen and the presence of warning labels addressing liver damage and concomitant use with other acetaminophen-containing products on prescription container labels. These recommendations aligned with FDA recommendations for OTC products containing acetaminophen. The subsequent White Paper, Version 1.1 published January 2015 provided a review of stakeholder response and made recommendations for further action.

4.1 Interventions and Initiatives

NCPDP, in its original White Paper on improved acetaminophen prescription container labels, as well as FDA and other stakeholders, have put in place or are currently exploring several interventions to help lower the risk of acetaminophen supratherapeutic ingestion. These include:

- Educational initiatives
  - Teaching patients and consumers about acetaminophen as an ingredient in many prescription and OTC medications and the importance of not using more than one acetaminophen-containing medication at any time
  - Promoting the importance of reading and following the medication labels of acetaminophen-containing products
  - Raising awareness of the risks associated with acetaminophen overdose
  - Instructing patients about their own role in medication safety, particularly the importance of maintaining updated medication information/lists, the need to share this...
information with primary care givers, and the importance of always carrying it with
them in the event of an emergency.\(^{30}\)

- Educating healthcare providers about the hepatotoxic risk of acetaminophen and the
importance of not exceeding the recommended daily doses of the drug. Importantly,
they also should be educated about the need to consider the cumulative doses that
could result from simultaneous use of multiple acetaminophen-containing products,
including the many formulations of analgesic, cold and cough, sleep-aid, and other
combinations that include acetaminophen.

- Formulation changes limiting the amount of acetaminophen contained in oral prescription
combination pain relievers to 325 mg per dose
- Addressing health literacy issues on medicine labels containing acetaminophen in a patient-
centered way
- Changes to pharmacy-generated prescription container labels and to outpatient e-prescribing
and inpatient CPOE systems to remove the abbreviation “APAP” and fully spell out
acetaminophen
- Exploring the use of an acetaminophen label icon that can serve as a global indicator of the
presence of acetaminophen in medications with the goal of improving awareness of
acetaminophen as an active ingredient and to help prevent the use of multiple acetaminophen-
containing products.\(^{34,55}\)

Some of the resultant interventions and initiatives pursued by stakeholders and the FDA can be
accessed at the following links:

FDA links
- [http://www.fda.gov/drugs/drugsafety/safeuseinitiative/ucm188762.htm#acetaminophen](http://www.fda.gov/drugs/drugsafety/safeuseinitiative/ucm188762.htm#acetaminophen)

Know Your Dose links
- [http://www.knowyourdose.org/?s=acetaminophen](http://www.knowyourdose.org/?s=acetaminophen)
  these are related links

Consumer Health Products Association (CHPA) link
- [http://www.knowyourotcs.org/ingredient/acetaminophen/](http://www.knowyourotcs.org/ingredient/acetaminophen/)

American Pharmacists Association (APhA) link

National Council on Patient Information and Education (NCPIE) links
- [http://www.talkaboutrx.org/acetaminophen/](http://www.talkaboutrx.org/acetaminophen/)
- [http://www.talkaboutrx.org/acetaminophen/teen-influencers-landing.jsp](http://www.talkaboutrx.org/acetaminophen/teen-influencers-landing.jsp)
- [http://www.mustforseniors.org/acetaminophen_safeuse.jsp](http://www.mustforseniors.org/acetaminophen_safeuse.jsp)

Centers for Disease Control (CDC) link
- [http://www.cdc.gov/MedicationSafety/protect/protect_Initiative.html#Results](http://www.cdc.gov/MedicationSafety/protect/protect_Initiative.html#Results)
4.2 Healthcare Environment

In recent years, healthcare providers have been faced with many initiatives aimed at increasing patient engagement, increasing use of technology - especially for electronic communication and records and automation of functions - improving patient outcomes, and controlling costs. In addition, there has been a steady move from a sick care (hospital focus) to a greater focus on disease prevention and wellness programs.

Legislative and regulatory policies have placed increased emphasis on enhanced technology, particularly use of EHRs, and incentivized providers with pay-for-performance measures. As part of their medication-use process, hospitals typically employ various medication safety technologies, including CPOE, CDS, and various types of medication administration (e.g., BCMA systems, eMAR systems). CDS is employed to generate interruptive alerts, notifications, and explicit care suggestions. Other technologies employed to optimize pharmacy practice models in hospitals include automated dispensing cabinets (ADCs) and robotic systems. Combined, these technologies are employed to optimize medication therapy management (MTM) and safety and to improve patient outcomes.

In 2013, more than 75% of US hospitals reported having implemented a CPOE system and prescribers entered at least 50% of orders into CPOE systems in 80% of hospitals. Of US hospitals with CPOE systems, about 60% reported concurrent implementation of CDS within their CPOE system. In addition, about 70% of US hospitals that provided care in ambulatory care settings used e-prescribing systems. BCMA systems to verify patient identity and electronically check doses administered by nurses were reported in about 90% of US hospitals in 2014, up from about 75% in 2013. Almost 95% of US hospitals used an eMAR system in 2014. In addition, combined use of eMAR, BCMA, and electronic nursing documentation was reported in almost two-thirds of US hospitals in 2013. Smart infusion pumps were used in about 80% of US hospitals in 2014.

In 2013, about one-third of US hospitals reported having a complete EHR (no paper records) and two-thirds reported complete clinical documentation with an EHR.
Use of Electronic Health Records (EHRs) in US Hospitals 2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete EHR</th>
<th>Pharmacists View Complete EHR*</th>
<th>Complete Clinical Documentation Components*</th>
<th>Pharmacists Document and Make Recommendations in EHR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and children’s medical–surgical hospitals (by staffed beds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>50–99</td>
<td>49</td>
<td>32.7</td>
<td>51</td>
<td>66.7</td>
</tr>
<tr>
<td>100–199</td>
<td>88</td>
<td>26.1</td>
<td>89</td>
<td>64.8</td>
</tr>
<tr>
<td>200–299</td>
<td>65</td>
<td>29.2</td>
<td>66</td>
<td>64.2</td>
</tr>
<tr>
<td>300–399</td>
<td>43</td>
<td>37.2</td>
<td>44</td>
<td>65.9</td>
</tr>
<tr>
<td>400–599</td>
<td>51</td>
<td>35.3</td>
<td>50</td>
<td>58.0</td>
</tr>
<tr>
<td>≥600</td>
<td>35</td>
<td>57.1</td>
<td>35</td>
<td>78.8</td>
</tr>
</tbody>
</table>

*S of hospitals with an EHR.

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Meaningful use in the US was an ongoing effort to drive adoption and use of EHRs in a way that improves patient outcomes and health information exchange. Notably, meaningful use included core and menu measures for exchanging clinical information among providers, medication reconciliation and drug formulary checks, summary-of-care records for transitions of care, and electronic formulary query and transmission of discharge prescriptions. In addition, HIE is an important infrastructure component of current and future meaningful use that will allow providers and patients to share medical information.

More granular analysis of medication safety technology use (EHRs, CPOE, BCMA, smart infusion pumps) reported in ASHP’s national hospital survey for 2009–2014 can be found in “Appendix B: ASHP National Survey”.

Medication safety technologies offer some of the most important tools for decreasing medication errors, preventing adverse drug effects, and improving drug use and patient outcomes, given the complexity of the drug-use process and number of potential failure points.

### 4.3 Hospital Medication-Use Systems

The medication-use system is defined as the provision of medication by the pharmacy to patient-care units and ultimately administration to the patient. The process includes activities associated with product selection, prescribing, transcribing, dispensing, and administration such as drug choice, order entry and transmission, pharmacist evaluation of the order, drug verification at dispensing and administration, and recording in the MAR. The medication-use system also includes monitoring and patient education.

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**Note:** At the time this White Paper was submitted for publication, CMS announced the replacement of Meaningful Use with the new Merit-Based Incentive Payment System (MIPS) under provisions of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), but details were not available.


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Medication therapy monitoring includes assessment of the drug’s therapeutic and adverse effects and involves transition-of-care services, medication history and reconciliation, medication order review and entry, implementation of medication-use system technology, and ambulatory care transitions. As part of medication use monitoring, proactive patient assessment includes monitoring for therapeutic duplication in the patient’s medication regimen (e.g., multiple simultaneous use of various acetaminophen-containing products) and for the appropriateness of the dose. In addition, an ongoing, systematic program for quality assessment and improvement in the medication-use system should be in place.

Hospital medication distribution systems define the provision of medication delivery from order entry to the pharmacy to clinical units, until it is administered to the patient. Whether the distribution is from a centralized pharmacy department or decentralized pharmacy satellites or automated dispensing devices (e.g., decentralized medication ADCs), the key overarching medication-use system components are the same.

- **Prescribing**
  - Data to support clinical decisions for drug choice and regimens
  - Medical record documentation by prescribers, pharmacists, nurses, and clinical staff or CPOE
  - Ideally decision support functionality

- **Transcribing**
  - Medication order received (verbal, written, or CPOE)
  - Order evaluated (e.g., drug choice, dosage, adverse drug reactions, medication reconciliation, lab results) and verified by pharmacy and nursing staff
  - Documentation in the MAR; includes procurement and storage

- **Dispensing**
  - Data entry, screening and verification, and dispensing in the MAR
  - Drug preparation (includes procurement and storage) by the pharmacy staff
  - Dispense to patient care units or verify inventory levels in decentralized automated dispensing devices such as ADCs

- **Administration, nursing staff**
  - Drug procurement and preparation (as needed)
  - Medication verification, including dosage
  - Administration to patient with documentation on the patient’s MAR; BCMA and eMARS provide an added level of safety

- **Monitoring**
  - Therapeutic drug monitoring includes assessment of medication therapeutic effects (including identification of any potential duplication) and any adverse drug reactions (treat and report to medication safety officer as needed)
  - Review of laboratory results as needed by pharmacy, medical, and nursing staff

In addition, the medication-use system supports outcome measurement documentation in compliance with the facility quality improvement standards.

Technologic solutions (e.g., CPOE, EHR/EMR, CDS, eMar, BCMA) are critical components in an ideal medication-use process. Such technologies should be designed to support clinicians and

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promote improved patient care processes, combining process, information systems, and supporting technologies that work together to allow desired improvements. As noted elsewhere in this white paper, current technologies support identification and alerting of cumulative acetaminophen dosage as part of the medication-use process and system.

4.4 Medication Errors in the Inpatient Setting

Medication errors can occur at various steps in the medication-use process as depicted in the following:

Errors in the Medication Cycle

<table>
<thead>
<tr>
<th>Medication Management Processes</th>
<th>Ordering</th>
<th>Transcribing</th>
<th>Dispensing</th>
<th>Administering</th>
</tr>
</thead>
<tbody>
<tr>
<td>E R R O R S</td>
<td>Wrong Dose</td>
<td>Wrong Route</td>
<td>Wrong Dose</td>
<td>Wrong Patient</td>
</tr>
<tr>
<td></td>
<td>Wrong Drug</td>
<td>Wrong Drug</td>
<td>Wrong Route/Form</td>
<td>Wrong Patient</td>
</tr>
<tr>
<td></td>
<td>Wrong Route/Form</td>
<td>Wrong Patient</td>
<td>Wrong Time</td>
<td>Wrong Time</td>
</tr>
<tr>
<td></td>
<td>Allergy, Drug Interaction</td>
<td>Wrong Drug</td>
<td>Incorrect Labeling/Omitted</td>
<td>Wrong Route</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Primary catch for Allergy, Drug Interaction</td>
</tr>
<tr>
<td>Percent of Errors</td>
<td>39%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept Rate</td>
<td>19%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True Error Rate</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis of the error distribution in the 1995 landmark study on medication errors showed that the highest rate of errors is in ordering and administering: ordering 39%, transcribing 12%, dispensing 11%, and administering 38%. In two follow-up studies, it was shown that a substantial reduction in medication errors could be achieved by implementation of CPOE. Research indicates that implementation of CPOE systems in non-rural US hospitals could prevent 3 million ADEs annually.

The landmark 2006 report, “Preventing Medication Errors” from the Institute of Medicine, asserts that errors injure 1.5 million Americans each year at a cost of $3.5 billion in lost productivity, wages, and additional medical expenses. It is estimated that

- 100,000 people die/year resulting from medication errors
- More than 400,000 drug-related injuries occur each year in the hospital setting
- 800,000 drug-related injuries occur in long-term care
- 51.5 million medication errors occur during the filling of 3 billion prescriptions each year
- 530,000 medication errors among Medicare recipients in outpatient clinics
Errors in the Hospital Medication-Use Process

- Prescribing: 39%, wrong dose/drug/route and allergies, interactions
- Transcribing: 12%, wrong dose/route/patient/time/drug
- Dispensing: 11%, wrong dose/route/patient/time, incorrect labeling/drug identification, primary allergy and drug-drug interaction identified
- Administration: 38%, wrong patient/dose/drug/route/time, and omissions, including infusion pumps.

Given the potential benefits for both patients and healthcare expenditures, healthcare quality and patient care experts recommended that the Leapfrog Group select CPOE as one of its initial hospital safety standards.64

5. Technology

Medication safety technologies such as EHRs, CPOE, CDS, eMAR, BCMA, ADCs, and smart infusion pumps have great potential in mitigating potential medication errors and associated adverse consequences, including inadvertent supratherapeutic dosing of drugs like acetaminophen that have narrow therapeutic indexes.13,14,56,57,59,60 As described earlier in this White Paper, gaps in optimal deployment of such technologies can reduce their effectiveness in preventing adverse consequences of medication use in the inpatient environment.

5.1 Tools available to help the hospital clinician monitor the accumulation of acetaminophen

Data embedded for use within prescribing and dispensing systems/applications are commercially available for clinicians in a variety of healthcare settings.13,14,22,56,57,59,60 Advanced dosing support systems employing rules-based processes provide accurate dosing recommendations, including adjustments, by utilizing patient attributes such as age, indication for use, renal function, comorbidities, and weight or body surface area (when applicable).59 In addition to dose screening, existing systems provide protocol data and standard order sets such as predefined order sentence (also known as the Sig) pick lists. Dosing rules are written by clinical editorial staff to account for daily dose limits, maximum single doses, and cumulative lifetime limits based on clinical references. Dosing clinical support systems support healthcare providers when dosing drugs with narrow therapeutic ranges or well-defined daily maximum doses. Application programming interface (API) technology allows for calculation of acetaminophen doses within and across prescribed drug products, allowing maximum daily dose screenings to be performed across products. This feature is in addition to the basic dose/duration/frequency screening.

Institutions utilizing flat file data in legacy systems have the potential to use ingredient record flags for products containing acetaminophen. This could be used when developing a dose accumulator to be displayed on the MAR for nursing to see at the time of administration. Proper implementation of the functionality of drug knowledge base tools is necessary to optimize such features for patient safety.

Referential products offer comprehensive drug information to help improve patient outcomes and to help treat and diagnose patients at the point of care. Content is available online and via smartphones and tablets as well as traditional print versions. Using web links, online referential content can be integrated into electronic health information systems for minimal interruption in workflow. Many of the well-respected referential offerings go beyond the dosing provided by manufacturer labeling to include off-label dosing from primary literature and special alerts (FDA, Institute for Safe Medication Practices [ISMP], and manufacturers) for neonates through geriatrics.
5.2 Drug Database Companies

The drug database companies provide robust drug data, patient education materials, auxiliary label text, and referential content for use within electronic prescribing, CPOE, pharmacy dispensing, and other applications. The drug database companies (e.g., First Databank, Elsevier Gold Standard, Wolters Kluwer) have played a prominent role in assisting healthcare professionals by providing valuable acetaminophen recognition and labeling tools that have standardized the prescription and OTC warning labels for medications containing acetaminophen. Additionally, they offer data and software tools to support prescribing, dispensing, and administration of acetaminophen by

- Providing age- and weight-based dosing alerts
- Calculating the 24-hour acetaminophen dose across all prescribed drug products

These medication safety tools are designed to supplement the capabilities of the various EHR applications used in the inpatient setting. These tools are commercially available for integration into EHR systems companies from the drug database companies.

5.3 Characteristics of an Ideal System

Today there are a number of EHR vendor applications companies in use in the US hospital inpatient marketplace, including Cerner, Epic, McKesson Pharmacy Systems, Allscripts, and MEDITECH. These EHR vendors provide clinical support systems that support dosing data alerts from drug database vendors such as First Databank, Wolters Kluwer, and Elsevier Gold Standard. Institutions should dialogue with their EHR vendors to fully understand the drug accumulator possibilities within their systems. Inpatient systems must mix and match the available capabilities in a manner consistent with their medication management process flow. The key to successful utilization of these tools resides in the following factors:

- Education of hospital staff so they have thorough knowledge of systems and tools capabilities and operation
- Activation of acetaminophen dosing accumulators and alert functionality
- Evaluation of CPOE systems for their ability to reduce the rates of preventable overdosage errors using systematic, standardized tools whenever possible
- Integration of dispensing robotics (e.g., Accudose, Omnicel, Pyxis) with alerts and accumulator tools
- Seamless data transfer during all transitions of care from admittance to discharge
- Use of BCMA systems since they are less prone to alert overrides
- Provision of functionality for documentation of necessary overrides
- Use of periodic vendor retraining for staff as system version updates become available
- Harmonization of systems operation with facilities medication management process for consistency
- Implementation of safeguards to address alert fatigue
- Expanded clinical pharmacist role to include monitoring of liver function testing (LFTs) for patients on acetaminophen
During multiple interviews, users consistently attributed system failures to poor training and the lack of user knowledge of the capabilities and functionality of their total systems. Intimate involvement by clinical informatics staff in the system selection and implementation is needed so they can educate bedside clinicians (prescribers, pharmacists, nurses) on tools available for their use. Many institutions have physician and/or pharmacy “champions” that dialogue with the informatics staff to ensure that clinician issues are being addressed. This is especially important when an institution goes “live” with a new EHR system and when upgrades are applied.

As a number of hospital pharmacy directors were interviewed about their department’s system capabilities regarding the safe handling and administration of acetaminophen, it became apparent that total systems integration was prerequisite for a successful implementation of the technology and systems tools necessary to achieve the safety and efficiency intended. The integration of automated dispensing systems with the pharmacy processing system (e.g., Omnicell, Pyxis, Accudose) into the medication-use process flow can enhance the administration safety for all medications, especially acetaminophen. Individually, each of these systems can potentially enhance safety, but if not properly integrated into the flow process, they can provide dangerous gaps in the monitoring of acetaminophen containing medication and other medications that require precise dosing and monitoring.

6. Process

Multiple hospital pharmacy directors interviewed for this White Paper cited the importance of developing a comprehensive and well-documented process flow outlining the sequence of events associated with a patient in the inpatient setting from pre-admittance, admittance, and all transitions of care through discharge.

6.1 Process Flow

This process flow encompasses the activities from preadmission medication review through reviews at transition between units, medication orders, dispensing and administration to discharge medication review. Hospital medication distribution systems define the provision of medication order and delivery from the pharmacy to clinical units, administration and discharge review and reconciliation. To support this flow, hospital systems need to provide support for:

- Clinical decisions for drug selection and administration
- Medical record documentation of orders, reviews, verifications, and administration by clinical staff at the point of action
- Monitoring of patient response to treatment and laboratory results
- Outcome measurement documentation in compliance with the facility quality improvement standard
- Patient education
The process flow procedures must be integrated into the pharmacy prescription processing system technology with special emphasis on identifying points of process disruption that can compromise administration safety of acetaminophen and other targeted drugs. These points of disruption can also be transformed into points of healthcare intervention that can safeguard patient safety. Some points of disruption identified in process flow charts that can lead to potential acetaminophen overdose episodes include:

- “prn” dosing of acetaminophen
- Non-integrated automated dispensing devices (e.g., ADCs)
- Absence of bar code technology (e.g., BCMA)
- Transitions of care gaps
- Undocumented alert overrides associated with hard stops
- Institution-specific acetaminophen accumulator dosing thresholds
- Continuous IV maintenance acetaminophen therapy
- Use of opioid and acetaminophen combination products
- Alert fatigue
According to an independent report released by Avalere Health, pharmacists and pharmacy technicians can play an integral role in support of patient safety and improved outcomes throughout the continuum of care. The study cited five areas in which pharmacists could enhance coordinated care:

- Medication management
- Medication reconciliation
- Preventive care services
- Education and behavior counseling
- Participation in collaborative care models

This enhanced role strengthens the continuum of care in the inpatient hospital’s operating procedures. These procedures should be centered in a totally integrated decision support system that utilizes all of the medication safety technology tools.
Transitions of Care Processes Used by Pharmacists or Pharmacy Technicians

- Manufacturer patient assistance programs: 27
- Participation in discharge planning: 24
- Discharge medication counseling by pharmacists: 22
- Facilitate filling of prescriptions at an outpatient pharmacy: 17
- Communicating orders for home infusion services: 12
- Discharge prescription services: 12
- Prior authorization: 11
- Handoff to community pharmacy at discharge: 10
- Design a patient-specific medication-related action plan: 5

2012 National Survey © ASHP

Primary Responsibility for Medication Regimen Information*

### Collecting at Admission
- Nurse: 79.4%
- Physician: 6%
- Pharmacy Tech: 2.9%
- Multidiscipline: 9.8%
- Pharmacist: 2%

### Disseminating at Discharge
- Nurse: 81.4%
- Physician: 7.2%
- Pharmacist: 1.6%
- Multidiscipline: 9.8%

*Neither pharmacy residents or pharmacy students were reported having primary responsibility

2012 National Survey © ASHP
6.2 Medication Reconciliation

Medication reconciliation is a key priority in safe medication use within the US. Critical in optimizing safe medication use is reconciliation at transitions of care. Lack of communication at care transitions has clearly been shown to adversely affect patient care. As described in this White Paper, the need for optimal medication reconciliation during transitions of care is particularly important for drugs like acetaminophen that have a narrow therapeutic index and that inadvertently can be duplicated in potentially toxic amounts because of their availability in numerous multiple-ingredient products.

There is evidence that medication discrepancies can adversely affect patient outcomes, and an effective process for medication reconciliation can reduce medication errors and support safe medication use by patients. Medication reconciliation is the process of identifying the most accurate list of all medications by comparing medications a patient is taking (and should be taking) with newly ordered medications in order to identify and resolve discrepancies or potential problems. The comparison addresses duplications, omissions, dosage changes, and interactions as well as the need to continue current medications. Discrepancies include omissions, duplications, contraindications, unclear information, and changes. The purpose is to obtain and maintain accurate and complete medication information and to use it within and across the continuum of care to ensure safe and effective medication use. Reconciliation is considered complete when each medication has been actively continued, discontinued, substituted (e.g., under formulary guidelines), held, or modified at each transition point.

The importance of medication reconciliation in the inpatient setting was affirmed when the Joint Commission introduced a national patient safety goal (NPSG.03.06.01) aimed at maintaining and communicating accurate patient medication information, with the goal of reducing negative patient outcomes associated with medication discrepancies. Included in this care process are coordination of information during transitions of care within (e.g., from surgical to medical units, from intensive care to medical units) and outside (e.g., home, LCT facilities) the hospital, patient education on safe medication use, and communication with all providers. The importance of medication reconciliation also was affirmed by CMS as part of meaningful use stage 2 and EHR incentive programs for eligible professionals, eligible hospitals, and critical access hospitals in 2015–2017, and was to continue with meaningful use stage 3 in 2018.

Complicating optimal transitions of care is the lack of adequate communication among various healthcare providers, including prescribers, pharmacists, and nurses. For example, communication between hospitalists and the patient’s primary care provider occurs infrequently (3-20%). As a result, various professional societies (e.g., American College of Physicians, Society of Hospital Medicine, American Geriatrics Society, Society of Academic Emergency Medicine, American Society of Health-System Pharmacists) have identified the need for adequate communication at transitions of care as an important element in optimizing patient care, including medication use. In particular, pharmacist collaboration should be encouraged, and systems and technologies that enable collaboration should be enhanced; medication reconciliation across the continuum of care is an important element of such collaboration.

As part of the Affordable Care Act (ACA), the Department of Health and Human Services (HHS) was charged with developing a National Quality Strategy (NQS). Priorities for the NQS were developed initially by a broad base of stakeholders convened by the National Quality Forum (NQF) and later turned over to the Agency for Healthcare Research and Quality to implement. One of the six priorities under

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The NQS initiative is the promotion of effective communication and coordination of care leading to better long-term health outcomes as demonstrated in part by fewer conflicting medications and better patient understanding of the purpose for each medication.\textsuperscript{73} Similarly, CMS’ EHR incentive program emphasizes advanced use of EHR technology to promote improved patient outcomes and health information exchange.\textsuperscript{22}

The medication reconciliation process involves three steps:

- Verification (collection of medication history),
- Clarification (ensuring that medications and their doses are appropriate), and
- Reconciliation (documentation of changes in the orders).\textsuperscript{27}

Preventing ADEs is the impetus behind medication reconciliation.\textsuperscript{26,27} Approximately 50–70% of medication errors occur during transitions of care.\textsuperscript{13,24,26,27} Substantial experience has shown that poor communication of medical information at care transition points is responsible for up to 50% of all medication errors and up to 20% of ADEs within hospitals.\textsuperscript{13,26,27} Likewise, two-thirds of adverse events occurring within 3 weeks of discharge from the hospital to outpatient setting are drug related.\textsuperscript{24}

Whenever a patient moves from one setting to another or from one care provider to another where medication orders change or must be renewed, clinicians should review all previous orders against new orders and care plans, and should reconcile any differences.\textsuperscript{22,23,26,27} Failure to implement standard processes for ensuring complete reconciliation will result in medication errors that can lead to ADEs and patient harm.\textsuperscript{26,27}

The Institute for Healthcare Improvement (IHI) recommends the following methods for improvement in reconciling medications at points of transition: \textsuperscript{26}

- Reconcile admission orders with home medication lists and advise the patient’s primary care provider of any changes.
- Reconcile medication orders when patients are transferred to other units, particularly if the patient is moving from one level of care to another. The patient’s provider should be advised of any pre-transfer medications that are not reordered or are deemed inappropriate and any omission should be documented as deliberate.
- Reconcile discharge instructions and prescriptions with the medication administration record (MAR.)
- Reconcile medications in the outpatient setting.

The most effective methods for implementing effective medication reconciliation in the hospital setting are those that employ pharmacy staff and focus on patients at high risk for adverse events.\textsuperscript{23,74,75}

Important elements in pharmacist-related interventions included:

- Performing a comprehensive medication history at admission,
- Medication reconciliation at admission and discharge,
- Patient counseling,
- Discharge communication with outpatient providers, and
- Post-discharge communication with the patient.\textsuperscript{23,75}
Obtaining an accurate preadmission medication history appears to be the most critical step in avoiding propagation of potential harm throughout the care transitions of hospitalization and after discharge, and errors during this step are the most common reasons for preventable ADEs secondary to medication discrepancies.\textsuperscript{75,76} However, it is difficult to distinguish the impact of an accurate medication history from the impact of successful medication reconciliation.\textsuperscript{75}

Targeting interventions to a subset of patients at greatest risk of an ADE, such as geriatric patients, patients taking multiple medications, and/or patients with multiple comorbidities, may have the highest yield.\textsuperscript{75} In fact, a targeted approach by pharmacists has been recommended as an important means of preventing inadvertent acetaminophen overdosage in hospitalized patients.\textsuperscript{5,6} As part of this approach, interdisciplinary communication and education of prescribers and nurses by pharmacists (e.g., about maximum acetaminophen dosage and presence in multiple-ingredient formulations) should be emphasized.\textsuperscript{5,6,18}

7. **Recommendations and Stakeholders Call to Action for Dose Accumulation Monitoring for Medicines Containing Acetaminophen**

The NCPDP Acetaminophen Best Practices Hospital Safety Sub-Task Group call to action is directed to all pharmacy system stakeholders, to further explore implementation of solutions that target use of point-of-administration state of the art clinical decision-support module systems.

All stakeholders are encouraged to enter into a dialogue to find synergies in utilizing existing programs and to collaborate on future initiatives.

<table>
<thead>
<tr>
<th>Recommendation: Minimize use of multiple-ingredient products containing acetaminophen.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stakeholders:</strong> Director of Pharmacy, Pharmacy &amp; Therapeutics Committee</td>
</tr>
<tr>
<td>• Clearly identify all acetaminophen-containing products and their associated dose in computerized prescriber order entry (CPOE) and other clinical decision support (CDS) systems</td>
</tr>
<tr>
<td>• Evaluate acquisition cost and risks associated with use of a multiple ingredient product vs multiple single-ingredient products</td>
</tr>
<tr>
<td>• Remove multiple-ingredient, acetaminophen-containing products from formularies where possible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation: Implement physician and nurse education with emphasis on maximum daily dose for medications at risk for overdose.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stakeholders:</strong> Director of Pharmacy, Clinical Staff Pharmacists, Pharmacy &amp; Therapeutics Committee, Nursing Education</td>
</tr>
<tr>
<td>• Renewed emphasis on maximum 4 g and/or weight-based (75 mg/kg for patients weighing less than 50 kg) daily dosage of acetaminophen</td>
</tr>
<tr>
<td>• Awareness of multiple sources (e.g., single- and multiple-ingredient products) contributing to the accumulated dose</td>
</tr>
<tr>
<td>• Awareness that maximum daily dose of acetaminophen is based on all routes of administration</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
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</tr>
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|   | administration (IV, oral, and rectal)  
|   | • Awareness of the risks involved with exceeding the recommended maximum daily dosage  
|   | • Awareness that some patients (e.g., the elderly, patients with chronic liver diseases) may not tolerate the usual maximum recommended acetaminophen dosage of 4 g daily |
| 3 | **Recommendation: Provide patient education on medication use and the risk for overdose.**  
| **Stakeholders:** Clinical Staff Pharmacists & Pharmacy Technicians (Medication Reconciliation), Nursing Staff, & Nurse Case Managers upon discharge |
|   | • Validated discharge instruction sheet  
|   | • Drug specific maximum doses and warnings  
|   | • For acetaminophen-containing medication  
|   |   - Information on over-the-counter (OTC) drugs  
|   |   - Warnings for example on  
|   |   - Concomitant use of multiple products containing acetaminophen  
|   |   - Co-morbidities  
|   |   - Liver toxicity  
|   |   - Alcohol intake  
|   |   - Safe use education  
|   |   - Possible icon use |
| 4 | **Recommendation: Establish standardized Inpatient Medication Management Protocols.**  
| **Stakeholders:** Director of Pharmacy and Clinical Informaticist, Chief Information Officer, EHR Vendors |
|   | • Integrate with pharmacy management system  
|   |   - Including management of robotic dispensing and automated dispensing cabinets (ADCs)  
|   | • Dialogue with EHR vendors regarding availability of drug accumulator tools  
|   | • Activate full alert functionality available in internal software or as part of the drug database in use  
|   | • Revise protocols that potentially result in duplicate therapy |
| 5 | **Recommendation: Establish pharmacists as the primary actor in the Medication Reconciliation Process.**  
<p>| <strong>Stakeholders:</strong> Director of Pharmacy, Pharmacists, Pharmacy Technicians, Pharmacy &amp; |</p>
<table>
<thead>
<tr>
<th><strong>Therapeutics Committee, Chief Nursing Officer, &amp; Nursing staff</strong></th>
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<tr>
<td>- Comprehensive medication review on admission and discharge</td>
</tr>
<tr>
<td>- Pharmacist oversight of all medication use activities during inpatient stay, emphasizing areas of greatest risk such as during clinical handoffs and transitions of care</td>
</tr>
<tr>
<td>- Communication of reconciled drug regimen and recommendations to the patient’s outpatient pharmacy and caregivers</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>6 Recommendation: Integration of health information technology solutions that minimize the risk of inadvertent overdosage for high-risk medications into all process flows and decision support.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stakeholders:</strong> Director of Pharmacy, Clinical Informaticist, Pharmacists, Pharmacy Technicians, Chief Information Officer &amp; IT staff, EHR vendors, Medical staff via Pharmacy &amp; Therapeutics Committee, Chief Nursing Officer &amp; Nursing staff</td>
</tr>
<tr>
<td>- Customize and monitor CPOE and clinical decision support (CDS) systems to optimize rate reductions in medication errors and adverse drug events (ADEs) associated with inadvertent overdosage of high-risk medications</td>
</tr>
<tr>
<td>- Review policies for order entry that aim for increased safety (e.g., reviewing current medications before entering new orders)</td>
</tr>
<tr>
<td>- Update existing medication databases as necessary to prevent duplicate order errors</td>
</tr>
<tr>
<td>- Install and activate dose accumulator, alert, and monitoring tools</td>
</tr>
<tr>
<td>- Target all medications with a narrow therapeutic margin</td>
</tr>
<tr>
<td>- For acetaminophen, implement a “never event” strategy for daily dosages exceeding 4 g, including for any combination of IV, oral, and rectal administration</td>
</tr>
<tr>
<td>- Customize alerts to target users in order to avoid “alert fatigue”</td>
</tr>
<tr>
<td>- Whenever possible, evaluate CPOE systems for their ability to reduce the rates of preventable overdosage errors using systematic, standardized tools</td>
</tr>
</tbody>
</table>

In addition to the recommendations for stakeholder action:

**Recommendation to NCPDP:**

- Identify a “model hospital” that
  - has adopted most of this White Paper's recommendations and
  - is willing to participate in an acetaminophen safety study.
- Conduct a safety study.
8. Conclusions

Despite the use of numerous medication safety technologies such as EHRs, CPOE, CDS, eMAR, BCMA, ADCs, and smart infusion pumps, the incidence of acetaminophen overdose and other associated sentinel events continue to be a serious problem in many hospitals and long-term care treatment settings. Even though beneficial, the technologies implemented at the tertiary care hospitals in two recent studies were not of themselves sufficient to prevent supratherapeutic dosing of acetaminophen. Without optimal deployment of such technologies and robust and well-developed processes that emphasize staff knowledge and responsibility and effective health information exchange, including drug reconciliation at all transitions of care from admission through discharge, many situations are created that lead to gaps in care related to dose accumulation and monitoring in the safe use of acetaminophen in the inpatient setting.

Along with recommendations on the adoption and integration of available technologies and use of documented processes, these recommendations emphasize continuing education of the patient care staff on the dosing safety requirements for the administration of acetaminophen, particularly the recommended maximum daily dose and the special care required when the drug is administered to the elderly, patients with liver dysfunction, and patients being treated for specific disease states such as osteoarthritis.

Inpatient facilities (hospitals, skilled nursing and others) do have available to them all of the technology tools needed to monitor and employ dose alerts, accumulators, and warning systems and to integrate such medication safety tool capabilities necessary to reduce inadvertent overdose episodes. For optimal patient safety outcomes, full functionality of these tools needs to be configured to meet the institution’s policies and processes, and then implemented and integrated with the other systems in use. Equally important is the training of the staff on the functionality, operation, and utilization of the technical capabilities of the inpatient system as well as recommended dosages and sources of acetaminophen. Special emphasis must be placed on the initial training and re-training of all staff that use these systems. Additionally, the White Paper describes the development and implementation of a process map that provides for guidance and documentation of the drug reconciliation process from admittance to discharge and specifically the special attention needed to successfully execute safe patient passages through the various transitions of care that patients routinely navigate in the inpatient setting.

Finally, the clinical pharmacist must play a prominent role in the entire drug reconciliation process with particular emphasis in participating in the transitions of care as they relate to drug therapy.
9. Reference Citations


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Centers for Medicare & Medicaid Services. Regulation and Guidance Meaningful Use Stage 1 and stage 2:
10. Appendices

Appendix A: Online Educational Resources

This appendix supplements *Section 9, References*, to provide additional acetaminophen educational websites for the reference and education of healthcare professionals.

The public educational websites are provided to facilitate the efforts of healthcare professionals to educate their patients. Most of the materials can be obtained at no cost or can be downloaded and printed; some materials are also available in Spanish.

A. Acetaminophen Websites Targeted to Healthcare Professionals

- **Acetaminophen Information**, from the US Food and Drug Administration (regulatory documents, advisory committee documents, consumer education, related resources)
  
  http://www.fda.gov/acetaminophen

- **FDA Safe Use Initiative – Acetaminophen Toxicity**, from the US Food and Drug Administration
  
  http://www.fda.gov/Drugs/DrugSafety/ and search for acetaminophen toxicity

- **NCPDP: Providing Guidance on Improved Prescription Container Labels for Acetaminophen**, held March 1, 2012. NCPDP members and non-members can access this CE webinar from the NCPDP without cost.
  
  http://www.ncpdp.org/members/audio/03-01-12NCPDP.wmv

- **Using Acetaminophen and Nonsteroidal Anti-inflammatory Drugs Safely**, from the US Food and Drug Administration
  
  Articles; brochures; fact sheets; audio, print and video public service announcements; internet banners and widgets; and tutorials; materials in Spanish
  
  www.fda.gov/otcpaininfo

Acetaminophen Resources for Specific Audiences

- **Acetaminophen continuing pharmacy education program**, for pharmacists from the American Pharmacist Association
  
  http://www.pharmacist.com/acetaminophen-continuing-pharmacy-education-campaign

- **Proper Acetaminophen Use: Resources & Handouts**, from McNeil Consumer Healthcare
  
  http://www.tylenolprofessional.com/tips-for-proper-use.html

- **An Interdisciplinary Look at Labeling Changes for Acetaminophen and the Implications for Patient Care**, from the Geriatric Society of America
  

Using Prescription Medicines Safely

Manufacturers’ websites can also provide useful materials for use by healthcare professionals to use with their patients, such as *the ones listed below available from McNeil Consumer Healthcare* 

http://www.getreliefresponsibly.com, and
http://www.tylenol.com

B. Drug Alerts

- JCAHO Sentinel Event Alerts
  http://www.jointcommission.org/assets/1/18/SEA_11.pdf
- ISMP High Drug alerts 2014 includes Acute Care & Community Ambulatory setting
  https://www.ismp.org/tools/highalertmedicationLists.asp
Appendix B: ASHP National Survey
Medication Safety Technologies (2009-2014)

- Use of Electronic Health Records (EHR) Systems
- Use of Computerized Prescriber Order Entry (CPOE) Systems
- Use of Barcode-Assisted Medication Administration
- Use of Smart Infusion Pumps
Use of Electronic Health Records (EHR) Systems

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Electronic Health Record (EHR) Systems
(Acute care hospitals with <50 staffed beds)

Year
2014
2013
2012
2011
2010
2009

Percentage
44.5%
28.2%
22.1%
4.9%
6.3%
9.5%

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Electronic Health Record (EHR) Systems
(Acute care hospitals with 50-99 staffed beds)

Year
2014
2013
2012
2011
2010
2009

Percentage
30.4%
25.4%
15.4%
6.9%
5.9%
8.3%

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Electronic Health Record (EHR) Systems
(Acute care hospitals with 100-199 staffed beds)

Year
2014
2013
2012
2011
2010
2009

Percentage
18.7%
21.7%
8.2%
9.7%
9.7%
11%

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Electronic Health Record (EHR) Systems
(Acute care hospitals with 200-299 staffed beds)

Year
2014
2013
2012
2011
2010
2009

Percentage
37%
31.5%
15.9%
5.3%
7.3%
5.4%
Use of Electronic Health Records (EHR) Systems

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Electronic Health Record (EHR) Systems
(Hospitals with 350-599 staffed beds)

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Use of Electronic Health Record (EHR) Systems
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Use of Electronic Health Record (EHR) Systems
(Hospitals with more than 600 staffed beds)

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Use of Computerized Prescriber Order Entry (CPOE) Systems

**ASHP National Survey**
Medication Safety Technologies (2009-2014)

Use of Computerized Prescriber-Only-Entry (CPOE) Systems
(Hospitals with less than 50 staffed beds)

Year | Percentage
--- | ---
2014 | 77.6%
2013 | 57.7%
2012 | 50.5%
2011 | 26%
2010 | 12.8%
2009 | 8.3%

Year | Percentage
--- | ---
2014 | 74.1%
2013 | 53.2%
2012 | 52.3%
2011 | 24.1%
2010 | 14.9%
2009 | 11.1%

**ASHP National Survey**
Medication Safety Technologies (2009-2014)

Use of Computerized Prescriber-Only-Entry (CPOE) Systems
(Hospitals with 50-99 staffed beds)

Year | Percentage
--- | ---
2014 | 83.1%
2013 | 76.7%
2012 | 52.5%
2011 | 38.9%
2010 | 16.9%
2009 | 17.8%

Year | Percentage
--- | ---
2014 | 91.3%
2013 | 68.5%
2012 | 53.6%
2011 | 38%
2010 | 23.2%
2009 | 15.1%
Use of Computerized Prescriber Order Entry (CPOE) Systems

**ASHP National Survey**
Medication Safety Technologies (2009-2014)

Use of Computerized Prescriber-Only-Entry (CPOE) Systems
(Hospitals with 300-399 staffed beds)

- 2014: 81%
- 2013: 69.8%
- 2012: 67.6%
- 2011: 53.1%
- 2010: 29.9%
- 2009: 29.6%

Use of Computerized Prescriber-Only-Entry (CPOE) Systems
(Hospitals with 400-599 staffed beds)

- 2014: 90.8%
- 2013: 79.4%
- 2012: 61.4%
- 2011: 44.6%
- 2010: 31%
- 2009: 23.5%

**ASHP National Survey**
Medication Safety Technologies (2009-2014)

Use of Computerized Prescriber-Only-Entry (CPOE) Systems
(Hospitals with more than 500 staffed beds)

- 2014: 87%
- 2013: 75%
- 2012: 83%
- 2011: 64.1%
- 2010: 58.8%
- 2009: 51.6%
Use of Barcode-Assisted Medication Administration

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Barcode-Assisted Medication Administration
(Hospitals with 300-599 staffed beds)

Year
2014
2013
2012
2011
2010
2009
Percentage
91.4%
75.5%
72.1%
61.9%
43.8%
42%

Use of Barcode-Assisted Medication Administration
(Hospitals with 600-999 staffed beds)

Year
2014
2013
2012
2011
2010
2009
Percentage
90.8%
77.9%
67.1%
57.6%
41.8%
37.2%

ASHP National Survey
Medication Safety Technologies (2009-2014)

Use of Barcode-Assisted Medication Administration
(Hospitals with more than 1,000 staffed beds)

Year
2014
2013
2012
2011
2010
2009
Percentage
89.1%
77.3%
60.4%
65.6%
35.8%
35.5%

November 2015
Use of Smart Infusion Pumps

**ASHP National Survey**
Medication Safety Technologies (2009-2014)

Use of Smart Infusion Pumps (Hospitals with less than 50 staffed beds)

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Use of Smart Infusion Pumps (Hospitals with 50-99 staffed beds)

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## Appendix C: Contributors to This White Paper

Note: the organizations listed below should not be considered endorsers of this White Paper.

### Contributors to Version 1.0

<table>
<thead>
<tr>
<th>Task Group/Co-Leads</th>
<th>Members</th>
</tr>
</thead>
</table>
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