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## The Science of Safety – An Emerging Concept in Medication Use and Research

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## The Science of Safety – An Emerging Concept in Medication Use and Research

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### Abstract

Most published reports of patient safety in clinical practice focus largely on the culture of safety in complex health systems, separate from pre-approval and postmarketing research-related safety considerations for drugs, biologics, and other medical products. The science of safety requires a linked integrated perspective, i.e., an iterative process examining and relating safety concerns from drug or biologic discovery and development in preclinical stages, clinical trials and post-market use, research, surveillance, and potential regulatory changes. This commentary addresses the science of safety across the lifecycle of drug and biological products, regulatory considerations, barriers, and research needs. This paper provides a brief overview on how the functioning of healthcare systems affects the safety environment and describes how stakeholder involvement, research participation, and targeted education and training can help facilitate better safety measures and practices, provide improved quality of care to patients, and contribute to the science of safety.

### Science of Safety along the Lifecycle

The emerging concept of the science of safety is new to most pharmacists, physicians and other clinicians. Our conceptualization of the science of safety for medication use is envisaged as a linked and iterative process along the lifecycle of prescribed drugs and biologics in Figure 1.<sup>1-17</sup> The distinguishing feature of the science of safety is its all-encompassing, systematic lifecycle approach to drug safety, rather than focusing on separated knowledge spheres. Combined efforts in the science of safety are needed to decrease adverse drug events -- both serious adverse drug reactions and medication errors.<sup>18</sup>

The science of safety for medication use aims at methods to prevent adverse events by targeting use of specific agents for patients in whom benefits are maximized over risks and identifying safety concerns quickly.<sup>2,3,16</sup> Across the lifecycle of drugs, the framework of the science of safety incorporates advances in toxicology screenings, pharmacogenetics, and pharmacogenomics with the envisioned goals of effective treatment and reduced drug toxicity in providing personalized medicine to diverse patient populations. The science of safety includes disease awareness of molecular medicine (recognizing promising therapeutic benefits and adverse risks) and novel methods of signaling, data mining and analysis for drug/biologic safety.<sup>14</sup> It enables hypothesis generation about the existence and causes of safety problems and exploration of genetics and biomarkers that may help promote individualized drug treatment regimens.<sup>14,16,19</sup> The

science of safety calls for a transformational, team-oriented, multidisciplinary approach in delivering high quality of care and improving patient safety. This involves preclinical and clinical studies, regulatory review, postmarketing surveillance, and risk management. The science of safety also considers human factors, organizational cultures, informatics, and clinical practices and communications that help guide clinical treatment, regulatory decisions, and research through effective communications, programs, and processes.<sup>2,6,10,12,14</sup>

Since the 1999 publication of *To Err is Human* by the Institute of Medicine (IOM),<sup>20</sup> progress in achieving safer healthcare systems has been noted 5-years,<sup>21,22</sup> 10-years,<sup>23,24</sup> and 15 years<sup>25</sup> following the landmark report. Progressive awareness of patient safety considerations is increasingly conceptualized through a “total systems approach” involving providers and engaged consumers, rather than less deliberative piecemeal interventions.<sup>25,26</sup> Despite efforts such as root cause analysis in healthcare systems and implementing interventions to reduce risks, occurrence of sentinel adverse events persist. The initiatives and goals proposed by IOM in 1999 are commendable although the healthcare system has lacked strategic models and tailored mechanisms to achieve them.<sup>21</sup> The concept of the science of safety is not necessarily individually driven but involves a system driven approach to bring about changes in the current healthcare system and implementation of new health quality forums. Tremendous impact of transformative change could be witnessed when the concept is viewed by a single vision with the prime motives of patient safety and better quality care.<sup>1,6</sup>

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### Drug approval and regulation

In drug and biological product approval and postmarketing surveillance efforts, the U.S. Food and Drug Administration (FDA) determines safety and effectiveness. The Agency also

considers optimal trade-offs with respect to access, risk, and value in product use for labeled indications in specified populations. The FDA Amendments Act of 2007 (FDAAA)<sup>27</sup> provided mechanisms for more resources to facilitate the science of safety across the lifecycle of drugs, biologics and devices.<sup>11</sup> Implementation of Title IX of FDAAA on March 25, 2008 enhanced FDA's authority in post-market drug safety initiatives including expanded Risk Evaluation and Mitigation Strategies (REMS), postmarketing studies/clinical trials and surveillance, and safety-related labeling changes.<sup>28-30</sup> REMS plans (updated list available online<sup>31</sup>) allow drug/drug classes or biologics with serious safety risks to be approved for marketing or to remain available on the market for patients who could benefit from them. Implementation and management of REMS, specifically those with Elements to Assure Safe Use (ETASU), can exact a burden on healthcare practitioners due to the lack of standardization and time-consuming nature of the requirements.<sup>29</sup> ETASU include training or specific certification of prescribers; certification of pharmacists or other practitioners and/or pharmacies or other dispensing sites; restricted dispensing outlets; dispensing under conditions of safe use such as required laboratory testing; patient monitoring; and/or enrollment of each patient in a registry. Stakeholder feedback regarding experiences with REMS/ETASU and associated challenges is encouraged by FDA and would build upon the iterative science of safety process.

FDA plays an important role in mitigating medication risks and identifying risks for preventable errors that can occur at any point in the complex U.S. healthcare system.<sup>14</sup>

Stakeholder involvement is crucial as it increases transparency and communication<sup>32</sup> and helps maintain scientific integrity and credibility. Stakeholders also help disseminate information produced through research, and their role towards science of safety is illustrated in Figure 2. The Agency's intersection with the industry, healthcare providers, and other governmental public health agencies help enable FDA to facilitate this collaborative process. Examples of stakeholders for FDA in the science of safety include:

- pharmaceutical industry; federal agencies, such as the Drug Enforcement Administration (DEA), the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), and the Centers for Medicare and Medicaid Services (CMS); healthcare professionals and their professional societies; patients and patient advocates (including consumer groups), and others.

### Healthcare Systems

Transitioning to safer healthcare practices requires that healthcare practitioners understand the challenges faced in complex healthcare environments, human factors contributions to adverse events, qualities of "high reliability organizations" and other resources for patient safety.<sup>33</sup> With the escalating demand to ensure safety, quality, efficacy and efficiency, it becomes essential for interdisciplinary healthcare teams to collectively share the common goal of patient safety.<sup>34,35</sup> Problematic professional relationships and communication gaps among health professionals have an impact on the quality of care provided.<sup>36-38</sup> For example, in physician-nurse interactions, doctors tend to perceive good working relationships more often than do nurses, possibly due to lack of understanding about challenges nurses face in hierarchical system roles.<sup>36</sup> Inadequate collaboration and communication is also seen between physicians and administrators, as well as physicians and pharmacists. When provided with access to data-rich environments (e.g., electronic medical records) and identifying preferred contact modes (e.g., fax, telephone, electronic) and times, pharmacists are better enabled to communicate effectively with physicians and others.<sup>39</sup> Collaborative support for improved communications is needed across three levels -- individuals, healthcare teams and organizations (leadership and culture).<sup>40</sup> Embedment of an interdisciplinary approach into the healthcare system can raise awareness of the value of cooperative teamwork and application of consistent patterns among health professionals to achieve positive patient outcomes.<sup>34,35,37</sup>

More research is needed to evaluate the impact of socialization on healthcare work environments and quality of care provided to the patients.<sup>36</sup> Effective patient-provider communications results in improved patient knowledge, adherence, satisfaction, and safety, as well as reduced healthcare costs.<sup>41-43</sup> Recommendations for patient-centered communications are readily available,<sup>44-46</sup> including resources for communicating with patients about harm.<sup>47</sup> Despite strong evidence on the benefits of patient engagement in healthcare decisions, the practice is not mandated or perhaps not yet followed to a large extent in healthcare systems.<sup>48</sup>

### Education and Training

Momentum is building on the need to contemporize health professions education and related training programs to meet changing population needs and prepare students in efforts to emphasize quality and safety, decrease errors, and utilize evidence-based practices and health informatics.<sup>5,49</sup> Little is known on a nationwide basis about the extent of curricular incorporation of methods to decrease adverse events and improve patient safety in health professions degree programs.<sup>4,50,51</sup> Descriptions of curricular aspects of patient

safety, error reduction, and quality improvement for individual programs are published in regard to undergraduate medical education,<sup>4,12,52,53</sup> postgraduate medical training,<sup>54-56</sup> nursing education,<sup>33,50,57,58</sup> pharmacy education,<sup>9,59-62</sup> and interdisciplinary health education.<sup>34,63</sup> Efforts directed toward integration of concepts supporting the culture of safety and the science of safety should involve raising awareness and expanding offerings, rather than major curricular revision.<sup>1</sup> Education and training about postmarketing surveillance, pharmacoepidemiology, and FDA's role in product safety and adverse event reporting should be advocated.<sup>64-66</sup>

The American Association of Colleges of Pharmacy (AACCP) and FDA partnered to determine the 2010 baseline status on integration of the science of safety in professional degree curricula for pharmacy students.<sup>17,67</sup> Findings demonstrated that curricula in colleges of pharmacy provided aspects of the science of safety, though gaps exist.<sup>17</sup> Didactic learning and experiential teaching strategies can help pharmacy students understand the complexities involved in real-world environments and need for safety design considerations for risk identification, assessment and mitigation. To foster awareness of safety concerns and knowledge dissemination learned from adverse event reporting, novel teaching strategies should be incorporated in health professions education to help prepare students for the challenges they will face in practice.<sup>65</sup> Relevant continuing education and lifelong learning are paramount for healthcare practitioners to keep knowledge and skills up-to-date. The IOM recommended all practicing clinicians demonstrate continued competency through periodic assessments.<sup>5</sup>

### Research

Research programs on drug safety have focused primarily on sick individuals with respect to treatment of disease processes. New paradigms necessitate the need for enhanced safety considerations for both healthy subjects and patient-subjects in research processes as novel drugs are evaluated for outcomes on cognitive functioning, impact on major organ systems, and health-related quality of life.<sup>19</sup>

Improved and validated, clinically-appropriate metrics are needed to measure adverse drug events, which rank among the leading causes of iatrogenic harm to patients.<sup>68</sup> Development of a common hazard taxonomy in management and risk identification methods such as root cause analysis (RCA), failure modes and effects analysis (FMEA) or situational briefing models can help prevent the hierarchical structure of an organization from impeding its ability to achieve better patient safety models.<sup>38,61,69-71</sup> The AHRQ addressed evidence-based patient safety strategies through commissioned reports in 2001<sup>72</sup> and updated 2013,<sup>73</sup> with strong encouragement for adoption. More research is needed

to effectuate implementation of evidence-based safety practices, build new tools to assess safety measures, and disseminate knowledge among healthcare professionals, payers, patients, and other audiences.<sup>74-76</sup>

Through the Institute for Safe Medication Practices (ISMP) Medication Error Reporting Program, MedWatch, FDA Adverse Event Reporting System (FAERS), related vaccine error reporting programs or other mechanisms, healthcare professionals and consumers can voluntarily report adverse events associated with drugs, biologics, and medical devices.<sup>13,14</sup> The pharmaceutical industry is mandated to report adverse drug events to FDA.<sup>77</sup> Review and research on nationally-reported adverse events can identify causes and/or contributory safety concerns, strengthen monitoring, and generate recommendations and policies to prevent future occurrence.

### Barriers to the Implementation of Science of Safety

Individual barriers such as poor communication abilities and inadequate knowledge about pharmacovigilance, error reporting, or research processes obstruct efforts to improve the science of safety.<sup>78-80</sup> Lags in timely reporting and dissemination of evidence-based patient safety practices impede efforts to develop safer healthcare systems.<sup>81</sup> Lack of information technology, insufficient standardization in error definition, insufficient staffing, and limited access to clinical data are recognized as system barriers that impede delivery of quality of care to patients. Culture of blame in healthcare systems and fear of punishment deter error reporting, representing additional barriers in developing the science of safety.<sup>33,82</sup> While increased attention is directed to the science of safety regarding prescription drug products and biologics, less stringent regulations, oversight and evidence-based practices exist for non-prescription drug products<sup>83</sup> and compounded drug preparations.<sup>84</sup>

### Conclusion

This paper describes the science of safety through a conceptualized process. It provides an overview on the lifecycle of drug/biologic approval and regulation and the roles played by diverse stakeholders in implementing better patient safety systems and measures. The need for ongoing education and training programs, as well as robust research, is underscored. This paper also emphasizes the need for collaborative, interdisciplinary care provision by health professionals and effective communications (within healthcare systems and via patient-provider interactions) to ensure optimal quality care. Collectively, these practices can reduce barriers and promote safer medication use. Developing a medication-use system based on the science of safety should be an aspirational goal to achieve exceptional levels of patient safety, quality care, and effectiveness.

Figure 1. Science of Safety in Lifecycle of Drugs/Biologics

### The Science of Safety: A Lifecycle Approach

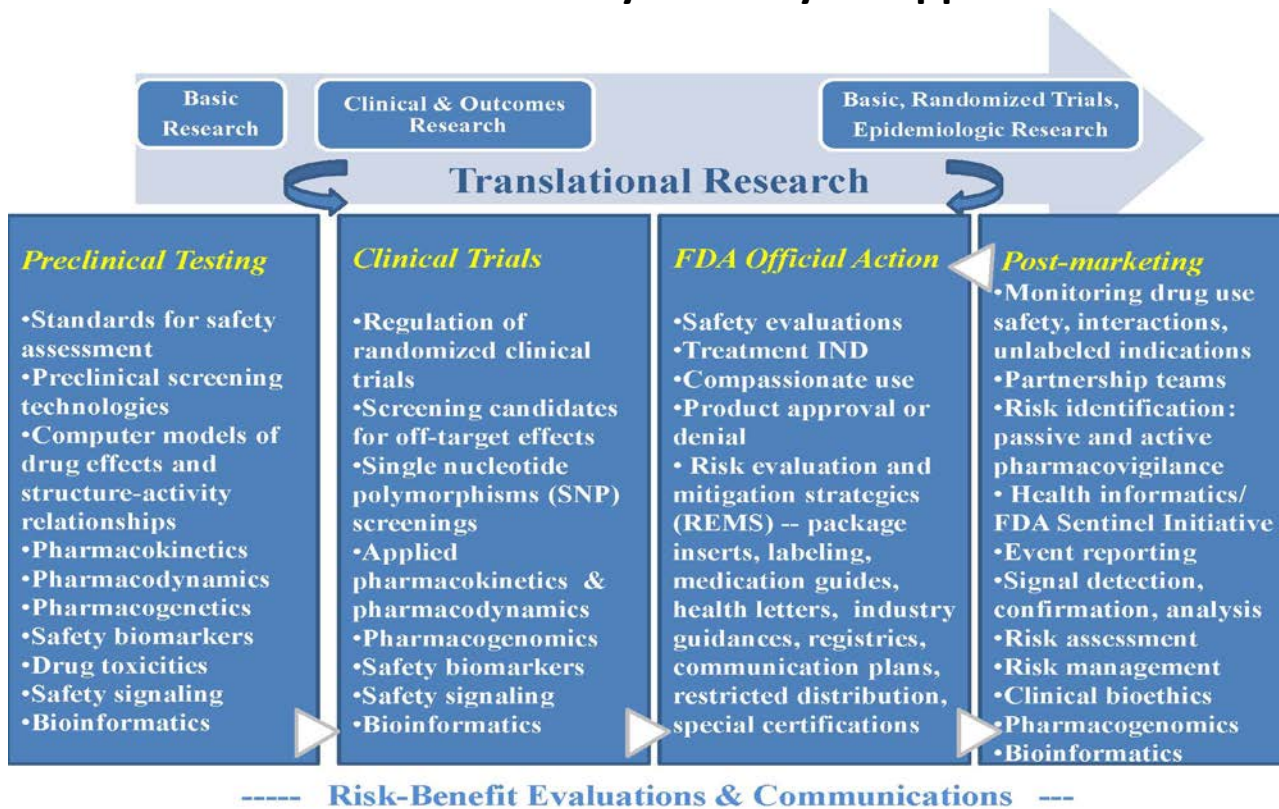
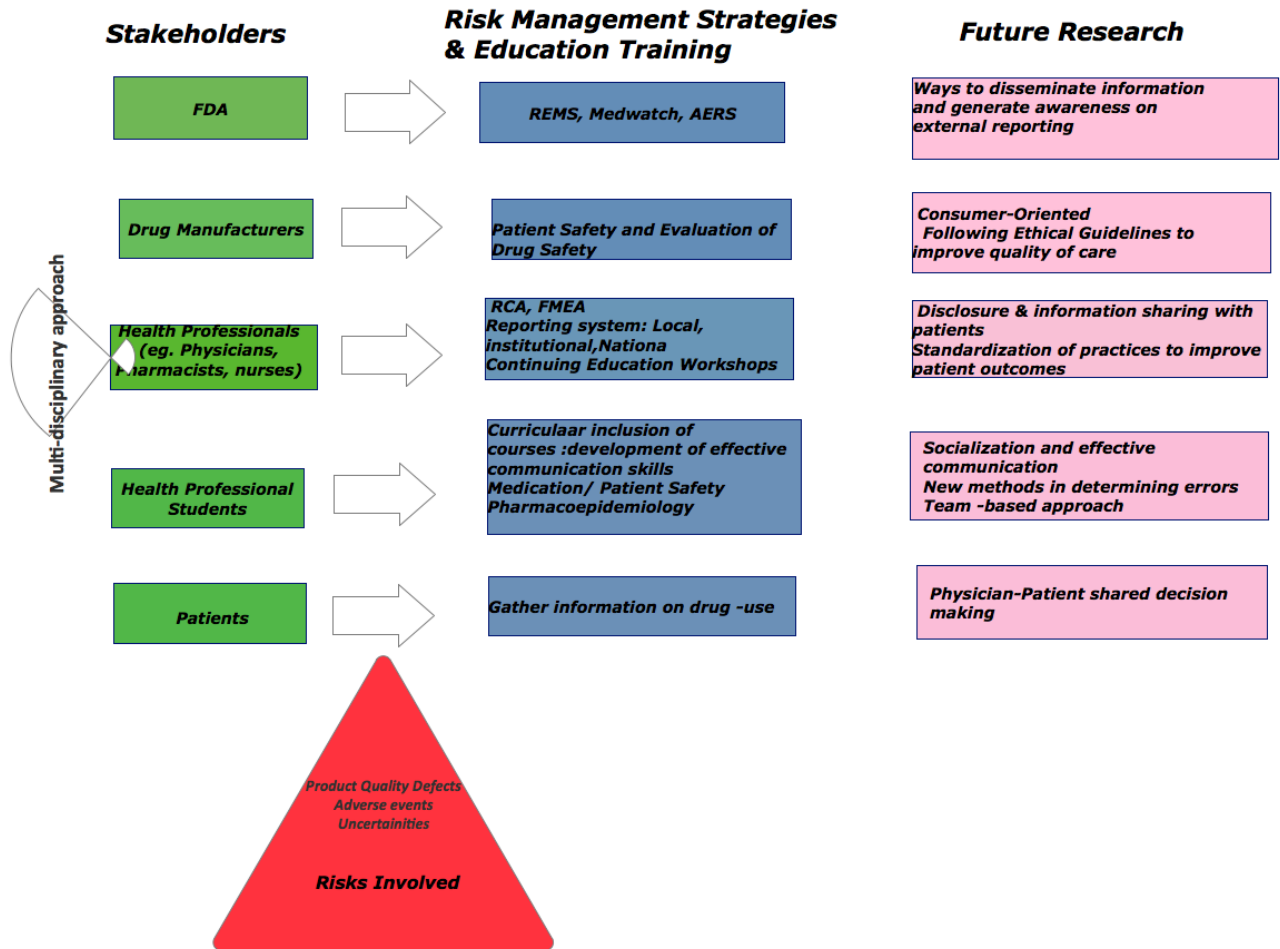


Figure 2. Major Stakeholder’s Role in the Science of Safety



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