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Commentary

Precompetitive Collaborations in the Pharmaceutical Industry: Process Safety Groups Work Together to Reduce Hazards, from R&D Laboratories to Manufacturing Facilities

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ABSTRACT: Process Safety scientists in the pharmaceutical industry are tasked with keeping the laboratories, manufacturing facilities, people, and environment safe from thermal runaway reactions. This group of highly trained chemists and engineers has forged an alliance stretching across company lines to help ensure the safety of the global pharmaceutical manufacturing sector. In this Commentary, we share our challenges, strategies, and opportunities for working together to ensure the safety of our respective companies and external vendors. We discuss our three platforms for collaborating and sharing ideas to help communicate the importance of pharmaceutical companies cooperating in a precompetitive space for the greater good.

KEYWORDS: *Process Safety, precompetitive collaboration, pharmaceutical industry, IQ consortium, Purdue Process Safety and Assurance Center*

INTRODUCTION

Process safety incidents in the pharmaceutical industry can result in significant deleterious consequences. These include injuries or fatalities to employees and members of the local community, facility damage or closure, environmental impact, project delay, supply chain disruption, and damage to the reputation of the pharmaceutical companies and industry to name a few.[1] For example, in 2019, the explosion caused by improperly stored nitro-compound-containing wastes in Jiangsu Tianjiayi Chemical in China injured more than 600 and killed 78 people including those in the local communities, and it caused the supply chain disruption of many pharmaceutical companies.[2] Also in 2019, a welding activity caused a catastrophic explosion at the Qilu Tianhe Huishi Pharmaceutical Co. facility in eastern Shandong province, killing 10.[3] Small-scale operations in R&D laboratories are certainly not immune to accidents.[4] However, those incidents are less reported because most media and most of the literature focus on those with severe consequences observed at the plant scale.

Pharmaceutical companies are constantly looking for collaborative opportunities to benchmark and share the best practices to resolve process safety challenges. Collaborations in a precompetitive setting can bring tremendous benefits to colleagues in the process safety field and to pharmaceutical companies, without the risk of revealing intellectual property among competitors.

In this work, we begin by discussing what concerns a process safety scientist in the pharmaceutical industry. We then describe the background on how and why these collaborative groups began and have gained momentum. Subsequently, we discuss three platforms that process safety scientists in the pharmaceutical industry use to collaborate.

PROCESS SAFETY IN THE PHARMACEUTICAL INDUSTRY

Process safety scientists in the pharmaceutical industry are chemists and engineers who dedicate themselves to identify and minimize potential risks associated with thermally unstable materials, combustible dusts, and runaway reactions from R&D laboratories to manufacturing facilities. Numerous publications illustrate such work accomplished by process safety scientists.[5−8] For example, Tian et al. evaluated thermal safety on a hydroamination reaction using DMSO as solvent, studied the potential autocatalytic decomposition with DMSO, and successfully launched the process for commercial production safely.

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Pharmaceutical companies are competitive but recognize that they share many process safety testing challenges. They must contend with regulations for shipping potentially explosive compounds that have not been produced at scale. Many of the tests used to classify compounds require hundreds of grams (or kilograms) of material, quantities that are not available until much later in the development cycle. Another challenge is to comply with constantly changing safety rules or regulations in different parts of the world. In the past two decades, one final drug process commonly requires collaborations between many stakeholders, such as Contract Research Organizations (CROs), Contract Manufacturing Organizations (CMOs) including material vendors, and companies' internal plants. These stakeholders around the globe are regulated under different jurisdictions with different safety regulations, or similar regulations are not enforced to the same extent.[9]

The worst nightmare of a process safety scientist is to witness an evaluated process result in a thermal runaway in a scale-up facility, causing personnel injury, equipment and facility damage, or environmental impact. Thankfully, such catastrophes are very rare and typically result from multiple failures related to process safety management (PSM, 29CFR 1910.119), not just solely due to the intrinsic hazardous nature of the chemical process. However, a rigorous testing methodology and proactive study during process development serves two purposes. First, it can influence the process chemists to eliminate or mitigate those potential significant safety issues prior to scale-up. Second, it can provide accurate process safety information (PSI) to the scale-up facility in order to perform a more thorough Process Hazard Analysis (PHA) or Hazard Operability Study (HAZOP). This intervention will help the facility engineers determine the engineering controls for conducting each step safely.

The process safety testing methodology varies from one company to another in the pharmaceutical industry, depending on a company's organizational structure, portfolios (e.g., small-molecule drug substance vs large-molecule drug substance and cellular therapies), manufacturing network (e.g., in-house vs outsource), or the company's global safety engineering standards. The latter calls for an established common safety basis for each unit of operation in each process of the manufacturing plant.

Outsourcing to emerging markets in the pharmaceutical industry has become very common in the past two decades, especially with earlier intermediates which have not been fully developed in-house. Some companies without internal pilot plants may decide to outsource active pharmaceutical ingredient (API) manufacturing to contract development and manufacturing organizations (CDMOs). In this instance, the outsourcing company's own process safety lab should assess how much to do, or how much can be done, to ensure that the targeted CDMOs have adequate process safety lab capability, including testing and data interpretation to safely conduct the outsourced processes.

■ PROCESS SAFETY TESTING METHODS

Traditional process safety testing methods on thermal hazards focused exclusively on the exotherm screening, such as the control of an exotherm from desired chemistry and/or avoiding triggering the undesired secondary exotherm beyond the normal operation temperature, including the well-known Stoessel[10] methodology. In the past two decades, companies have become increasingly aware of the importance of pressure screening in thermal hazard testing, mainly because overpressurizing a vessel will cause its process safety valve (PSV) or rupture disk to open, or an explosion if the relief vent is inadequate. This pressure screening can include both the desired chemistry/process and undesired secondary decomposition for two reasons:

(1) Chemists often pay close attention to the desired reaction but neglect the quenching or workup which could also involve off-gassing. Appropriate measurement and testing in the process safety lab will provide gas identification and generation rate to the scale-up facility to benchmark against the normal vent capacity of the targeted vessel. If the anticipated gas generation rate from the desired process at scale exceeds the vessel normal vent capacity, it could cause damage to the associated equipment in the vent line (e.g., the condensers). It could also cause back pressure in the vessel, resulting in its process safety valve or rupture disk opening. An appropriate assessment of the PSV and the rupture disk adequacy is warranted in that case.

(2) Significant off-gassing from secondary thermal decomposition often occurs at a significantly elevated temperature, beyond a normal operating temperature or a temperature range from the DOE (design of experiment) for quality reasons, but potentially reaching this activity would be anticipated in upset scenarios from the PHA. Appropriate advanced calorimetry testing, such as Accelerating Rate Calorimeter (ARC), Advanced Reactive System Screening Tool (ARSST), Vent Sizing Package (VSP), or PhiTech, should be conducted carefully. An engineering simulation of these data for the scale-up and emergency vent sizing calculation based on the Design Institute of Emergency Relief System (DIERS) methodology should be performed to assess if the PSV or rupture disk on the vessel is adequate to handle the upset scenarios.

Another concern for a process safety scientist is the timing of testing. Process safety testing is typically administered before scale-up in the pharmaceutical industry.[11] However, dangers may be revealed late in process development such that the project team may not have enough time to change reagents or process conditions, let alone change the whole process route before scale-up. Earlier testing is typically preferred but may not be doable depending on the process complexity, material availability, process development stage, testing methodology rigorousness, and process safety lab resources. If testing is conducted too early, the samples tested, especially the reaction mixtures, may not be representative of the final process conditions after many modifications by the process chemists. During drug substance process development, an appropriate stage-wise approach to process safety testing is highly recommended due to limited resources of each process safety lab. Some companies use a reaction review process to flag potential significant issues in early development and/or involve a process safety lab in the commercial route definition very early on to provide input for determining a commercial route.

The consequence of a laboratory safety incident is typically less severe compared to a manufacturing plant incident. However, lab incidents occur more frequently due to the number of scientists from each organization working with numerous different reagents and reactions. It is neither possible, nor necessary, for a process safety lab scientist to

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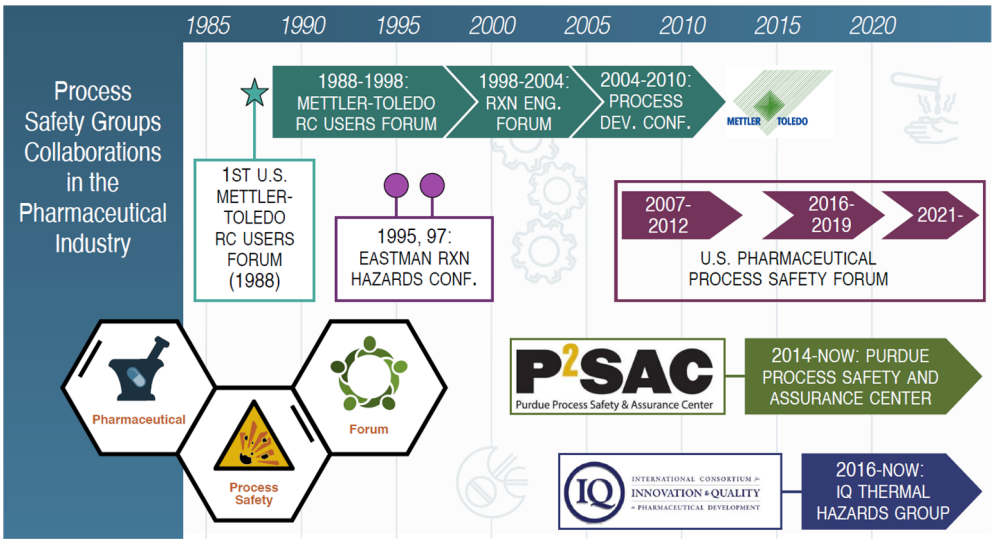

Figure 1. Timeline of process-safety-focused events. All logos used with written permission from the respective organization.

review every lab-scale chemistry, but it is advisable to establish a formal policy on reviewing hazardous reactions and using extraordinarily dangerous reagents.

Additional areas of concern often encountered by process safety scientists are

(1) environmental controlling of off-gas from the desired process (NO_x, CO_x, SO_x, HCl, ammonia/volatile amines, H_2S/mercaptan/SO_2, hydrogen, diborane, acetylene, etc.)
(2) preventing undesired reactions and overpressurization in waste streams
(3) shipping and storing of dangerous goods per UN model transportation regulations
(4) solids handling and dust hazard analyses
(5) initiating green chemistry, such as Registration, Evaluation, Authorization and Restriction of Chemicals (EU REACH) and China Ministry of Ecology and Environment (MEE), formerly called State Environmental Protection Administration (SEPA).

Given the number and the complexity of the methods and regulations, process safety scientists are finding it difficult to be an expert in every area. For this reason, cross-company collaboration is critical to the success and safety of every company involved in the manufacture of chemicals. The opportunity to share what was learned on real-world examples is critical to the success of the industry. The collaboration activities discussed in this Commentary offer process safety scientists unique opportunities to collaborate without disclosing company intellectual property.

■ PHARMACEUTICAL INDUSTRY COLLABORATION

The concerns facing a process safety scientist are commonly shared by those practitioners working in the pharmaceutical industry. The instruments used today to measure and quantify hazards (reaction calorimeter, accelerating rate calorimeter, etc.) became more widely available and implemented during the late 1980s and early 1990s. With the uptake of technology like the Mettler RC1 reaction calorimeter, the RC1 User's Forum was hosted annually by Mettler, in both the U.S. and Europe, for their customers and interested parties. These scientific forums focused on the application of technology to solve hazard evaluation challenges. They were instrumental in setting the stage for technical discussions among industry colleagues in a precompetitive environment where participants were free to discuss practices and challenges without the encumbrances of disclosing intellectual property. In the U.S., the first RC1 was purchased by Burroughs Wellcome in 1987. The following year, the first user forum was held in Williamsburg, Virginia, with a small attendance of 16 participants.[12] In addition to scientific presentations, an early feature introduced in these agendas was a Tips and Hints section, which promoted the sharing of methodologies and approaches to technical challenges, further enhancing collaboration. As the fora matured, scientific communications began to feature complementary techniques and application of process analytical tools, used in conjunction with the RC1. Examples included automated laboratory reactors and the implementation of Applied Systems Inc. (ASI) "ReactIR" FTIR and Lasentec FBRM particle-size analysis probes.[13] Interestingly, the RC1, ReactIR, and Lasentec technologies are all now part of the same company, and the business plan to combine these tools certainly might have been influenced by the knowledge sharing and common interest shared by Pharma and fine chemical process safety scientists.

In the mid-1990s, the RC1 User Forum became a biannual event and by 2000 had evolved into the Reaction Engineering Forum, indicating a widening scope. With a strong interest remaining within the U.S. pharmaceutical process safety community for annual interaction, the Eastman Chemical Company (one of the early RC1 adopters) hosted two user forum events with good attendance at their Batesville, AK, and Kingsport, TN, sites during alternate years. By this time, the Mettler-hosted conferences had grown in attendance to well over 100 participants. The event continued until 2010 as the Mettler Process Development Conference.[14] While attendance had decreased over the last few cycles, likely due to cost and travel budget restrictions in the modern era, the conference remained a good option for high-caliber, scientific contributions in the field of process safety, reaction engineering, and process development.

As a result of the relationships forged during the Mettler forums, three significant collaboration activities have evolved in the U.S. pharmaceutical process safety community over the

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past ∼20 years. These are discussed in greater detail below and represented chronologically in Figure 1.

U.S. PHARMACEUTICAL PROCESS SAFETY FORUM

In 2007, after attending a pharmaceutical industry environmental, health, and safety (EHS) benchmarking forum, several process safety scientists proposed the start of a U.S. Pharmaceutical Process Safety Forum[15] focused on topics of common interest, as detailed in the section above, with the main driver being collaborative information sharing and discussions in smaller groups of experts facing similar challenges. This collaboration has been running successfully since that time and has given rise to an associated Innovation and Quality (IQ) Thermal Hazards working group, which discusses technical methodologies and conducts benchmarking activities across the industry.

The inaugural meeting of the U.S. Pharmaceutical Process Safety Forum was hosted by Merck, with subsequent meetings hosted in the following years (two in 2008), by Pfizer, Wyeth, Sanofi, GSK, BMS, and Janssen. Agenda items for the initial meetings focused mainly on benchmarking, while later forums included topics on heat of reaction modeling, emergency vent sizing, dust hazards, outsourcing, transportation safety issues, and the determination of thermal stability safety limits. After running successfully for six years, the forum suspended from 2013 to 2015, likely due to restructuring among participating companies and the industry in general. Individual collaborations continued among pharmaceutical process safety scientists during this period; a forum reboot occurred in 2016, with GSK hosting at its Upper Providence (Philadelphia) site. The meeting featured ∼20 participants, with a half dozen pharmaceutical companies represented. Reflective of the times, several presentations focused on hazard evaluation of continuous (Flow) processes and process safety support for projects placed with external partners (outsourcing) .[16] By 2019, increasing interest saw a doubling of both attendees and pharmaceutical company representation compared to the experience of just four years earlier. Presentations included familiar topics on outsourcing support and hazardous chemistry scale-up but also featured hazard evaluation strategies for early phase development, support for nontraditional processes, powder explosion hazards, incident sharing, and offerings from equipment and software manufacturers.[17]

In addition to knowledge sharing and discussion on topics of interest, the forum features other opportunities for collaboration among participants, including poster sessions, case studies, hazard evaluation laboratory tours, and roundtable discussions. The suggested topics of interest for the agenda and additional features are scheduled at the discretion of the host, returning a significant reward for their commitment, with the opportunity rotating among the participating companies approximately annually. With the success of the forum reliant on in-person interactions at the host site, the 2020 meeting was postponed due to the COVID-19 pandemic; however, continued interest and discussion among participating members indicates that the proceedings will likely resume in late 2021.

PURDUE PROCESS SAFETY AND ASSURANCE CENTER (P2SAC)

During the past 20 years, industry support for academic centers of excellence in the field of process safety has grown significantly, with Texas A&M and Purdue Universities emerging as two premier institutions. The latter, Purdue Process Safety & Assurance Center (P2SAC), has evolved since 2014 to include a portion of its program focused specifically on pharmaceutical research and collaboration.[18]

P2SAC began with a modest 4 sponsor companies, all members of the department's Industrial Advisory Committee, now having grown to 20. Sponsors represent a broad array of industries, from oil and gas, chemicals, pharmaceuticals, manufacturing, risk management consulting firms, and others. Conferences free of charge are held each semester (fall and spring of each year), generally starting with a half-day of industry-led tutorials, followed by a day of general process safety topics, with the final day focused on the pharmaceutical industry. The program generally contains a 50−50 split of industry and academic presentations. At each conference, members solicit industry's process safety challenges and potential topics of future research. Over 50 companies registered for the December 2020 and May 2021 virtual conferences (online due to COVID-19).

Students of all academic levels—doctoral, professional masters, and undergraduate—participate in P2SAC's process safety research. Most projects are suggested by industry, with the Executive Board of sponsor representatives voting on which Ph.D. projects to fund, following a series of proposals by faculty during conferences and industry/faculty dialogue. These projects have expanded to ∼10 as sponsor funding has risen. The projects also provide a unique opportunity for industry members to collaborate and define funded projects. If several companies support a given project, the decision may be made to engage multiple companies, as often happens with undergraduate and master's student projects. This was the case for an undergraduate project on heats of reaction that eventually became a project within the Professional Master's Program (PMP) involving seven companies.

Table 1 provides a list of example projects conducted at each academic level. Associated companies are also listed, providing the mentor for PMP projects and/or who suggested an undergraduate project and remained a resource during the research. The success of the Center has led to numerous peer-reviewed publications at all levels.

The P2SAC conferences have evolved over the past few years to now include a full day devoted to process safety research related to the pharmaceutical industry. There has been an abundance of industry presentations, combined with current ongoing research in P2SAC and various departments at Purdue. Membership in P2SAC is not a requirement to attend the meetings. To date, P2SAC meetings are the only events outside of the Pharmaceutical Process Safety Forum meeting that dedicate an entire day to pharmaceutical process safety.

Like the Pharmaceutical Process Safety Forum, principal managers and experts in the field make P2SAC presentations, resulting in rich discussions, as participants speak from decades of experience. These individuals are personally committed to collaborating with their industry peers, and their companies empower them by supporting high-quality and thought-provoking process safety presentations. The forums are single track to keep all of the experts in the same room, rather than a

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Table 1. Examples of P2SAC Process Safety Research Projects Undertaken at Each Academic Level

academic level	project title (sponsor)
doctorate	Hazardous property prediction via machine learning
	Dusts—modeling and uncertainty analysis; concentrations by imaging
	Optimal placement of gas and fire detectors, *published*[19]
	Safety in Academic & Industrial Laboratories (Corteva), *published*[20]
professional masters	Analysis of 73 global process safety incidents in the pharmaceutical industry, *published*[22]
	Heat transfer modeling in Accelerating Rate Calorimeter (Dow)
	Assessing thermal hazards in pipe flow reactors (Merck)
	Thermal Hazards in the Pharmaceutical Industry (Amgen)
undergraduate	Comparison of heat of reaction data for common pharma reactions with model predictions (Amgen, Corteva, GSK, Lilly, Merck, Vertex)
	Use of ARSST Calorimeter to Study Reagents Common to the Pharmaceutical Industry
	Comparison of global process safety regulations, *published*[10]
	Process hazard analysis shortcomings leading to major incidents

multitrack format, which leads to competing presentations that tend to scatter experts. These provide invaluable opportunities to present and discuss challenges faced in the pharmaceutical industry, while at the same time serving as mentors for future generations of process safety professionals.

INTERNATIONAL CONSORTIUM FOR INNOVATION AND QUALITY (IQ) THERMAL HAZARDS GROUP

It is now well recognized that pharmaceutical companies continue to experience process safety incidents,[21] especially in emerging markets, leading to catastrophic loss of life and capital losses along with severe disruption to the supply chain, delaying much needed medicine for patients. Safety is a cornerstone to the entire pharmaceutical community, and a collective goal to all companies involved is avoiding incidents such as fires and explosions at the innovator companies' facilities and their partners. The industry effort to collaborate in process safety was hindered by two factors: the infrequency of the U.S. Pharmaceutical Process Safety Forum meetings, and the lack of a framework that would facilitate best practices for sharing without liability concern from participating companies. The two gaps led to the creation of a working group within the IQ International Consortium for Innovation and Quality in Pharmaceutical Development (www.iqconsortium.org) to meet frequently, almost monthly, while other venues at the time were yearly. In addition, IQ provided the legal and technical tools to allow the pharmaceutical industry to share challenges among their scientists and even the wider pharmaceutical and fine chemical industries.

The working group was quickly endorsed by IQ Drug Substance Leadership. Then, a recruitment effort followed, and SMEs in process safety from 15 companies joined the effort. Group members represented the major pharmaceutical companies in the United States and Europe. In 2020, the group published a paper[22] on companies' different approaches to thermal hazard evaluation that was well received by the community and won the ACS Editor's Choice Award. Future work will focus on platforms used to carry these important testing methodologies. In addition, the group is planning to share best practices in the field of dust explosivity. The benefit of sharing and publishing information on process safety can even extend further beyond the innovator company's facilities to their strategic partners around the globe, the wider chemical industry, and even academic laboratories.

CONCLUSIONS

Process Safety scientists in the pharmaceutical industry are tasked with arguably the most important responsibility in the drug manufacturing lifecycle: protecting the lives of research and manufacturing personnel performing the chemistry that produces our medicines. In addition to protecting lives of the workers inside the facilities, the environment, and the surrounding communities, we are also responsible for keeping multi-million-dollar facilities from experiencing damage during production. Damage to facilities, besides the financial consequences, can also result in significant project delays, thus resulting in medicines not making it to the patients waiting for these transformative therapies.

In an era of high competition between pharmaceutical companies looking to be first-to-market or to develop the best-in-class medicine, process safety scientists have assembled a community that is solely focused on keeping all manufacturing sites safe in the pharmaceutical industry. This effort also includes external partners. Many pharmaceutical companies use the same set of external partners to help deliver their portfolio of medicines. A process of one company resulting in damage to a facility at an external supplier can have a ripple effect across several other companies.

In this Commentary, we have described the challenges we face as process safety scientists. We use a set of consortiums and external programs to routinely share our findings and best practices for handling challenging chemistry and processes. We strongly believe that these opportunities for openness are beneficial to not just our profession but also every company and the greater scientific community, as they provide a means for us to share our results and the challenges we face. This community of scientists is always open to share our challenges in a precompetitive space for the greater good. We hope this example can inspire further collaboration in other fields as well in the pharmaceutical industry.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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