

Towards an Inherently Safer Bioprocessing Industry

Nilesh Ade, Yogesh Koirala and M. Sam Mannan,

Mary Kay O'Connor Process Safety Center, Artie McFerrin Department of Chemical Engineering, Texas A&M University, College Station, TX, 77843-3122, USA

Abstract: The bioprocessing industry is regarded as one of the fastest growing sectors with an estimated compound annual growth rate of 8.6%. In the year 2017, the global market for biopharmaceuticals alone was valued at USD 727.1 billion. Due to the unique nature of bioprocessing industries where in micro-organisms are employed to manufacture the desired products, these processes are prone to additional hazards such as biological hazards and dust explosion amongst others. This necessitates the need to review the existing research in the fields of biotechnology and bioprocessing to reduce/eliminate these hazards and pave the path towards a safer bioprocessing industry. The study involves developing a framework comprising of studying the recent technologies that reduce/eliminate these hazards involved in the bioprocessing industries that include dust explosions, loss of containment of toxic chemicals, loss of containment of biohazard/active product ingredient, fire, and explosion and mapping these technologies with respect to inherent safety principles that include substitution, minimization, moderation and simplification with an overall objective of minimizing the risk associated with bioprocesses and moving towards an inherently safer bioprocessing industry.

Keywords: inherent safety, bioprocessing, fire & explosion, biohazard, dust explosion, loss of containment

Introduction

Inherent safety

Inherently safer design (ISD) philosophy has increasingly received attention since it was put forth by Dr. Kletz in his seminal paper “What you don’t have can’t leak” (Kletz, 1978). This design approach relies on the principle that hazards can be effectively reduced/eliminated in the design stage of chemical processing facilities. This reduction/elimination of hazards is generally achieved by implementation of technologies or chemicals that have innate properties that reduce/eliminate hazards. ISD has found its way in several standards and regulations as it is generally in alignment with sustainability (Li et al., 2011) and security (Hansson, 2010) of chemical facilities. The European Council directive 96/82/EC of 1996 on the control of major-accident hazards involving dangerous substances states that “Hazards should be possibly avoided or reduced at source through the application of inherently safe practices” in their guidance document. Apart from Europe, in the United States the New Jersey Department of Environmental Protection (NJDEP) and Contra Costa County, California have adopted regulations (Toxic Catastrophe Prevention Act and Industrial Safety Ordinance) that necessitate the consideration of ISD to regulate chemical facilities involving hazardous chemicals. Following the fertilizer explosion on April 27, 2013, in West, Texas, an executive order 13650 was released by the president of United States that suggested an audit to identify inherently safer technologies for processing facilities. To materialize the executive order, the Environmental Protection Agency (EPA) put forth revisions to its Risk Management Program (RMP) to include Safer Technologies and Alternatives Analysis (STAA) to regulate the risk associated with chemical facilities. However, owing to regime change, the amendments have been delayed until February 2019.

ISD is primarily based on the following principles (Amyotte et al., 2009; Anna-Mari Heikkilä, 1999):

- Substitution: Replacing a hazardous chemical (reactant, solvent or catalyst etc.) with a safer alternative
- Minimization: Limiting the quantity of hazardous chemicals in the process in absence of safer alternatives
- Moderation: Processing hazardous chemicals in less severe conditions in absence of safer alternatives and minimization of hazardous chemicals
- Simplification: Implementing simpler processes with fewer number of equipment to reduce the opportunities for failure

As observed from the definition of these principles, maximum risk reduction is better achieved through substitution followed by minimization, moderation and simplification.

Bioprocessing industry

Biotechnology differs from conventional chemical processes in the sense that it utilizes micro-organisms to manufacture the desired products as opposed to bulk chemicals. The application of biotechnology on an industrial scale for processing substrates to desired products is referred to as bioprocessing (Liu, 2017). The advancement in biotechnology and bioprocessing has been instrumental in the growth of pharmaceuticals/chemicals (specifically biopharmaceuticals and biochemicals), food (mainly fermented products), textiles (polymers) and biofuel (ethanol, biodiesel etc.) industries (Chen, 2012). The global biotechnology market size was valued at USD 369.62 billion in 2016 and is expected to rise to USD 727.1 billion by 2025 (Grandview research, 2017). This tremendous growth of the bioprocessing industries can be attributed to the increasing demands of the products that are manufactured by these industries that generally include high molecular weight organic compounds that are economically unfeasible to be manufactured by traditional chemical processing industries.

Due to application of micro-organisms for processing of raw materials, the bioprocessing industry is prone to various biohazards as well as the chemical and physical hazards encountered in the conventional chemical processing industries (Center for Chemical Process Safety/AIChE, 2011). The associated biohazards with such facilities can pose a significant risk

to these facilities. Interestingly, Dr. David Michaels, former assistant secretary of labor for Occupational Safety and Health, USA (OSHA), has stated in the past that "We have inadequate standards for workers exposed to infectious materials" (Pollack and Wilson, 2010). ISD has been identified to reduce/eliminate hazards and this reduction/elimination of hazards generally results in risk reduction (National Research Council, 2012). Therefore, to reduce the risk associated with bioprocessing industries with respect to the physical, chemical and biological hazards, it is important to develop guidelines for the safer design of these facilities by reviewing the existing literature and identifying safer technologies and chemicals to move towards an inherently safer bioprocessing industry.

Framework

Description of framework

As a part of this study, a simple framework has been developed to analyze the recent developments towards improving the process safety associated with bioprocessing facilities by the implementation of ISD principles. The first step in this framework is to evaluate the basic processing operations in bioprocessing industries and identify the different types of hazards associated with each of these operations. The second step is to study the different types of incidents that have occurred in bioprocessing industries to assess the magnitude of risk associated with these hazards. This is followed by studying recent developments that have been made to reduce/eliminate these identified hazards. Lastly, these recent developments are classified based on ISD principles to gauge the level of risk reduction achieved by implementation of these technologies. The framework is described in the following diagram:

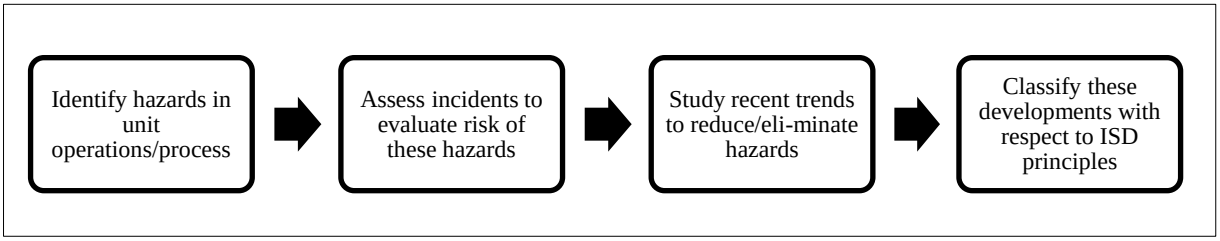

Figure 1: Framework for analyzing inherently safer technologies in bioprocessing industries

Bioprocess unit operations and associated hazards

The first step in the described approach is to identify the hazards associated with bioprocessing unit operations. The following figure describes a typical bioprocess:

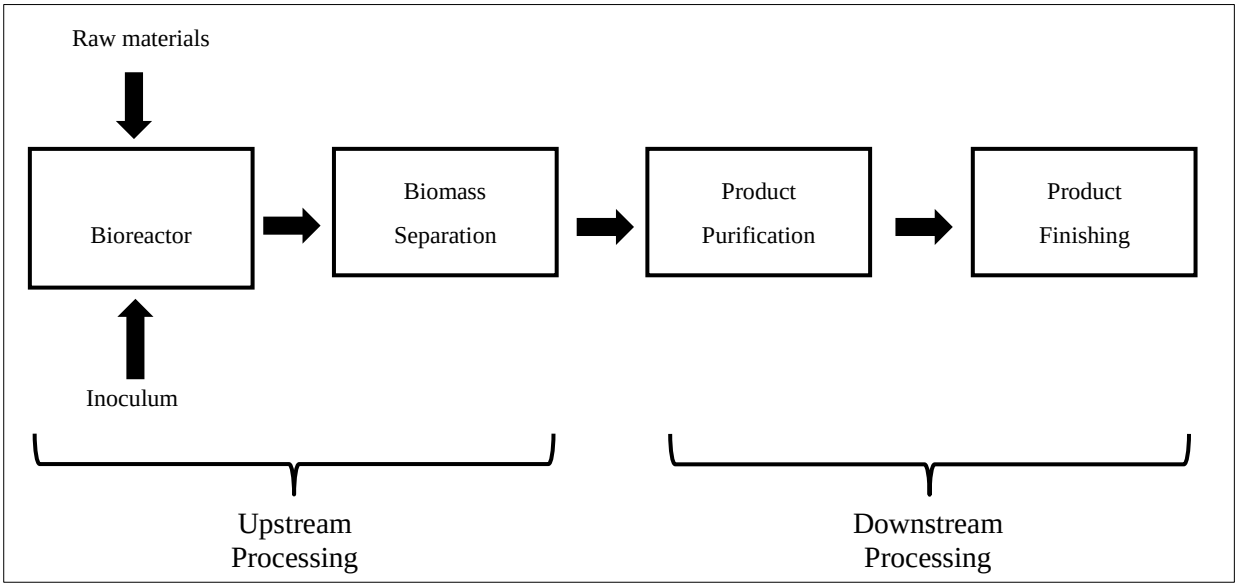

Figure 2: A typical bioprocess (Center for Chemical Process Safety/AIChE, 2011)

A Bioprocess typically consists of upstream and downstream processing. Upstream processing includes formulating a growth medium for the micro-organisms, allowing sufficient growth of the desired micro-organisms to synthesize the required product and separating the biomass (that includes the desired product) from the growth medium. This is followed by downstream processing wherein the required product is recovered from the biomass and purified. As shown in Figure 2, the growth of micro-organism in a suitable growth medium is achieved in a bioreactor. These growth media typically include organic solvents such as methanol and acetone amongst others since these organic solvents serve as a carbon source essential for the

growth of micro-organisms (Miazek et al., 2017). These solvents are used for cleaning (disinfecting) purposes as well (Center for Chemical Process Safety/AIChE, 2011). However, organic solvents can be flammable and explosive in nature. Also, a significant fraction of bioprocesses is aerobic in nature and require the supply of oxygen as a nutrient for the micro-organisms which increases the likelihood of fire and explosion. Finally, these organic solvents can be toxic (Gasco-Lopez et al., 2012) and exposure to these solvents for longer periods of time can have adverse health effects (Forte et al., 2012; Santos et al., 2013).

In downstream processing, the loss of containment of micro-organisms and/or the final bio-processed product can pose a hazard as well (Center for Chemical Process Safety/AIChE, 2011) since biohazardous micro-organisms can have respiratory, immuno-toxic, neurotoxic, sensory, dermal, and carcinogenic effects. Lastly, the finishing stage of a bioprocess may include unit operations such as material charging, milling, coating, drying and dust collection that require the processing of the materials in dust form. These materials can include both the active product ingredient (API) and the excipient (an inactive substance in a product serving as a vehicle, medium, coloring agent or any other purpose apart from the API). Both API and excipient can be combustible (Ebadat, 2012), thus introducing the hazard of a dust explosion in these facilities. Therefore, bioprocessing facilities possess the hazard of fire, explosion, dust explosion and loss of containment of toxic chemicals and biologically active substances resulting from the use of the organic solvents.

Incidents in bioprocessing industry

To assess the magnitude of risk associated with bioprocessing facilities, it is essential to study the consequences that have resulted from the incidents occurring in these facilities. To achieve this objective, a detailed analysis of the statistics provided by the Bureau of Labor Statistics (BLS), US was carried out. The analysis involved filtering the occupational fatal injuries profiles (available for the years 2011 to 2016) with respect to the bioprocessing industries. The bioprocessing industries were identified based on the North American Industry Classification System (NAICS) codes. It was observed that a total of 42 fatalities have occured in bioprocessing facilities from the year 2011 to 2016 from all possible causes. Following were the results obtained from the mentioned data analysis with respect to the hazards under consideration:

Table 1: Data analysis of fatalities from the year 2011 to 2016 in bioprocessing industries, US

Year	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Type of industries (NAICS code)	**Fatalities resulting from fire and explosion (including dust explosion) | Fatalities resulting from poisoning, toxic, noxious, or allergenic effects (including biologically active substances and toxic chemicals)**					
Pharmaceutical and medicine manufacturing (3254)	-	-	-	-	0 | 1	-
Research and development in biotechnology (541711)	-	0 | 1	0 | 1	0 | 1	-	-
Breweries (31212)	-	1 | 0	-	-	-	-
Wineries (31213)	-	-	-	-	-	-
Distilleries (31214)	-	-	-	-	1 | 0	-
Ethyl alcohol manufacturing (325193)	-	-	-	-	-	-
Medical laboratories (621511)	-	-	-	0 | 1	-	-

Note: '-' represents 0 fatalities, the number prior to '|' indicates fatalities resulting from fire and explosion (including dust explosion) and the number post '|' indicates fatalities resulting from poisoning, toxic, noxious, or allergenic effects (including biologically active substances and toxic chemicals).

From the above data analysis, it can be observed that from the year 2011 to 2016, 7 deaths have occurred in bioprocessing industries with respect to the mentioned hazards of fire, explosion, dust explosion and loss of containment of biologically active substance and toxic chemicals. These fatalities account for the largest fraction (~17%) of overall fatalities alone in the bioprocessing industries supporting the need to focus on these hazards to reduce the risks associated with these fatalities.

Apart from analyzing the statistics with respect to the bioprocessing industries, it is useful to examine individual incidents to gain a deeper understanding of the hazards and the associated failure mechanisms. It is also important to note that incidents in bioprocessing industries can result in serious injuries apart from fatalities. An explosion at a biotech facility owned by Amgen in San Francisco, California, US in 2013 resulted in serious injuries to an employee while inflicting minor injuries to another employee (Kurhi, 2014). One chemicals involved resulting in the explosion was identified as an ether, a commonly used organic solvent in bioprocessing industries. Similarly, an explosion at Silver Trail distillery in Frankfort, Kentucky in 2015 resulted in an employee fatality and completely demolished the processing facility (WKYT News, 2015). The incident possibly resulted from the over-pressurization of the still, employed to achieve the required alcohol content. The fire resulting from the rupture of the still seriously injured a second employee. Focusing on the loss of containment of biologically active substances, a fatality resulted from possible exposure to bacterial meningitis in Northern California Institute For Research & Education, Francisco, California, US (OSHA, 2012). The incident occurred when the employee was infected by the strain of bacterial meningitis that he was possibly working with. Similarly, loss of containment of a toxic chemical, glutaraldehyde, resulted in

minor injuries to 4 employees in International Medication System Ltd. facility, South El Monte, California, US (OSHA, 1995). Glutaraldehyde solution is generally used as a biocide for system disinfection.

Recent developments for safer design and ISD principle classification

The next step in the proposed framework is to study the recent developments made to reduce/eliminate the mentioned hazards. To track these developments, a thorough literature survey was conducted. This survey included tracking various journal articles and conference proceedings that dealt with technologies/chemicals that had innate properties that made the associated processes safer. These developments were then classified with respect to the defined ISD principles to gauge the risk reduction achieved by implementation of these technologies/chemicals. The following section describes the developments tracked in these steps and their respective classification.

1. Prevention of fire and explosion in bioprocessing industries:

As mentioned previously, the hazard of fire and explosion arises from the usage of flammable and explosive volatile organic solvents as growth mediums and disinfecting agents. A relatively safer alternative that has emerged for organic solvents are ionic liquids (Lourenço et al., 2012; Mizuuchi et al., 2008; Smith et al., 2011). Ionic liquids (molten salts) are less volatile and non-flammable as compared to organic solvents (Domańska and Bogel-Łukasik, 2005). Additionally, ionic liquids can be customized based on the desired applications by modifying their polarity, viscosity and solubility, making them suitable for various purposes such as being used as reaction and separation medium, API and catalysts (Arce et al., 2007; Bogel-Łukasik et al., 2010; Hough et al., 2007; Pârvulescu and Hardacre, 2007). Apart from the described applications, studies have concluded the applicability of ionic liquids as potential solvents for drugs with low solubility and as drug delivery vehicles (Lee et al., 2006; Smith et al., 2011). Also, it has been concluded that ionic liquids can be associated with higher solvent recovery as compared to traditional organic solvents like Toluene (Amado Alviz and Alvarez, 2017). Therefore, ionic liquids can be suitable alternatives for organic solvents and the replacement of a volatile and flammable organic solvent by an ionic liquid can be classified as an application of the ISD principle of substitution.

Although ionic liquids can serve as a substitute for the organic solvent, their application may not always be economically feasible and competitive with organic solvents. Therefore, in such cases, it might be beneficial to utilize the organic solvent under less hazardous conditions. These relatively safer conditions can be achieved by controlling the oxygen concentration in the reactor *i.e.*, maintaining the oxygen concentration below the limiting oxygen concentration (LOC). However, this will require the accurate knowledge of the LOC of the organic solvent under the reactor operating conditions since reducing the oxygen concentration substantially can lead to a loss in production of the bioprocess (Garcia-Ochoa and Gomez, 2009). Fortunately, the LOC for nine commonly used organic solvents in aerobic oxidations in pharmaceutical industries has been studied (Osterberg et al., 2015) and the results are as follows:

Table 2: LOC % for commonly used solvents in aerobic oxidations in pharmaceutical industries

Solvents	**T (ºC)**	**1 bara**	**20 bara**
		LOC (%)	
Acetic acid	200	10.6	9.6
N-methyl pyrrolidone	200	8.1	7.6
Dimethyl sulfoxide	200	3.9	-
Dimethyl sulfoxide	100	6.4	-
Tert-amyl alcohol	100	9.6	10.1
Ethyl acetate	100	9.4	9.9
2-methyltetrahydrofuran	100	9.4	9.1
Methanol	100	7.6	6.9
Acetonitrile	100	-	11.9
Toluene	100	10.4	9.9

However, the LOC data for the organic solvent at the required operating conditions may not always be available. In such cases, it might be advisable to determine the LOC at the required condition experimentally. Also, the LOC values can be estimated using various prediction models within acceptable error limits (A. Lazzús, 2011; Gharagheizi, 2010; Pan et al., 2009). Operating the bio-process at oxygen concentrations below LOC *i.e.*, lesser severe conditions of oxygen concentration, can be classified as the implementation of the ISD principle of moderation.

Another technology that can contribute to risk reduction in bioprocessing industry is the application of continuous processing reactors. These reactors typically have higher production rates as compared to batch reactors and therefore, require storage of lesser quantities of hazardous raw materials at the processing facilities for a given capacity of the product. Their superior production capabilities have been demonstrated for fermentation applications (Ercan and Demirci, 2015). Also, continuous reactors can either be utilized in packed bed or fluidized bed configurations with biocatalysts as the packing and they have been widely used in industrial bio-processes such as the production of enzymes (Klein et al., 2013; Schöffer et al., 2013;

Yewale et al., 2013; Zhou et al., 2014). The packed and fluidized bed configuration for continuous reactors have demonstrated the ability to produce the required products with sufficiently high yields (Lorenzoni et al., 2015). An emerging technology for bio-process intensification that has emerged recently is the continuous micro-reactors. These micro-reactors have proven to be superior from the conventional large reactors operating in batch mode due to the presence of more favourable mass and heat transfer, large surface area to volume ratio and the ability to operate in continuous mode (Thayer, 2005; Watts and Wiles, 2007; Yoshida et al., 2011). Micro-channel reactors have been applied successfully for the production of cholesterol oxidase, an intermediate for steroid manufacture (Marques et al., 2012). Another bio-process intensification technology of interest is the continuous membrane reactors. These reactors are an improvement as compared to the conventional reactors in the sense that they combine the chemical reaction process and the separation process of the unreacted reactants and products through the utilization of a membrane surface while operating in continuous mode. These reactors have already been widely implemented in bioprocessing facilities such as wastewater treatment (López et al., 2007, 2004; Méndez-Hernández et al., 2015; Taboada-Puig et al., 2015). The application of membrane reactors can be classified as an application of the ISD principle of simplicity as the number of equipment required in the process are decreased since the reaction and the separation are achieved in a single equipment *i.e.*, the membrane reactor. Also, the application of a continuous reactor can lead to an increase in the production rate due to an increase in yield thus, decreasing the amount of hazardous raw materials/catalysts required at the bioprocessing facility and therefore, the application of continuous reactors will fall under the ISD principle of minimization.

2. Prevention of dust explosion in bioprocessing industries:

The bioprocessing industries particularly the biopharmaceuticals are prone to the hazard of dust explosion. As mentioned previously, the hazard originates from the processing of materials in a solid form wherein these solid dust materials serve as fuel for a dust explosion. A study focusing on summarizing the dust explosion characteristics of commonly encountered pharmaceutical dust revealed that major fraction of API, intermediates, and formulated pharmaceuticals can lead to dust explosions under favorable conditions (Richter, 2012). In order to assess the hazard (and the resulting risk) of dust explosion for a particular material, it is essential to determine its dust explosion characteristics that are generally defined by the following parameters (Malizia et al., 2016; Wilén and Rautalin, 1993):

a) Minimum Ignition Energy (MIE)

b) Minimum Ignition Temperature (MIT)

c) Thermal Stability

d) Minimum Explosive Concentration (MEC)

e) Maximum Pressure (P_{max})

f) Maximum Rate of Pressure Rise $(dp/dt)_{max}$, and Thermal Stability Explosion Severity (K_{st})

g) Minimum Oxygen Content $(O2)_{min}$

The characterization of dust based on the mentioned parameters is followed by estimating the level of risk posed by the material based on the dust explosion parameters. A classification for pharmaceutical dust has been put forth (Meszaros and Sethi, 2007) that qualitatively estimates the level of risk based on the parameters MIE, MIT, K_{st} and thermal stability. The classification is as follows:

Table 3: Classification of the risk associated with dust based on dust explosion parameters

Parameter	**Low risk**	**Medium risk**	**High risk**
MIE	>100 mJ	25-100 mJ	<25 mJ
MIT	$> 500^0$ C	300 -500^0 C	<300 ^{0}C
K_{st}	<50 bar-m/s	50-200 bar-m/s	>200 bar-m/s
Thermal stability	No exotherm	Exotherm > 200^0C	Exotherm < 200^0C

One of the origins of dust explosion hazard is the formation of hybrid mixtures (solid-gas mixtures) encountered in bioprocessing industries. One such hybrid mixture is that of an excipient (in dust form) and the vapors of an organic solvent. A study (Hossain et al., 2014) focusing on determining the MIE of two commonly used excipients lactose (L) and microcrystalline cellulose (MCC) mixed with vapours of commonly used solvents in pharmaceutical industries such as methanol (M), ethanol (E) and isopropanol (I) yielded the following results:

Table 4: MIE of commonly encountered hybrid mixtures in pharmaceutical industries

Material	MIE (mJ)
MCC	30-100
MCC + M	30-100
MCC + E	10-30
MCC + IPA	30-100
L	30-100
L + M	10-30
L + E	10-30
L + IPA	10-30

As observed from the Table 4 and the suggested classification in Table 3, a mixture of microcrystalline cellulose and methanol will fall under the medium-risk category whereas, a mixture of lactose and methanol will fall under the high-risk category. Since both lactose and microcrystalline cellulose are used as excipients in drugs for their compressibility properties, lactose can be substituted with microcrystalline cellulose for bioprocesses involving methanol to reduce the risk of dust explosion. This approach of implementing hybrid mixtures with innate properties that reduce the risk of dust explosion can be classified as an application of the ISD principle of substitution.

Another common approach to prevent dust explosion is to process the explosive material in slurry form as opposed to dust form (Amyotte et al., 2007). An example of this approach can be the manufacture of naproxen, a nonsteroidal anti-inflammatory drug that can be manufactured through bioprocessing (Liu et al., 2010). A novel process has been recently developed that involves the precipitation of naproxen by supercritical CO_2 on excipient slurries of mannitol or silica (Subra-Paternault et al., 2014). Processing excipient or API in slurry form eliminates the hazard of dust explosion completely and can be classified as an application of moderation wherein the severe operating conditions resulting from the usage of solid materials in dust form are eliminated by processing the material in slurry form.

Dust explosions can also be prevented by inerting (Amyotte et al., 2009). Inerting involves mixing the dust with powdered inert prior to possible ignition. The fundamental principle behind this approach is to deny the availability of the necessary heat required for combustion (Amyotte et al., 2009). The approach can be classified as an application of the ISD principle of moderation as well (Amyotte et al., 2009), wherein the severity of the operating conditions resulting from the low MIE of the solid explosive dust is decreased by inerting it with another non-explosive dust. This approach has been proven for excipients such as cornstarch wherein inerting cornstarch with inert solid dust such as limestone or monoammonium phosphate (in sufficient proportions) resulted in the elimination of the hazard of dust explosion (Dastidar and Amyotte, 2017).

3. Prevention of loss of containment (LOC) of biologically active substances:

The hazard of exposure to biologically active substances such as API and pathogens is unique to bioprocessing and allied industries. The National Institute of Health and the World Health Organization have put forth a qualitative classification for the risk posed by micro-organisms. The classification is as follows:

Table 5: Risk classification of micro-organisms based on individual and community risk

Risk group	**Effect on humans** (NIH Office of Science Policy, 2002)	**Level of individual risk** (World Health Organization, 2004)	**Level of community risk** (World Health Organization, 2004)	**Availability of treatment and preventive measures** (World Health Organization, 2004)
1	no possibility of disease	no/low	no/low	-
2	may cause rarely serious disease	moderate	low	yes
3	can cause serious/lethal disease	high	low	yes
4	likely to cause serious/lethal disease	high	high	usually no

The above classification serves as a pathway for the ISD principle of substitution, wherein a micro-organism associated with higher risk can be substituted by a relatively safer micro-organism (in a lower risk group), provided that the safer micro-

organism performs the required function in the bioprocess with similar efficiency. An example of this approach is the suggested modification of the anit-tuberculosis medicine armamentarium by 2013 Paris Bettencourt team in the iGEM Competition (International Genetically Engineered Machine Competition, 2016). The team used mycobacterium smegmatis (a risk group 2 micro-organism) instead of mycobacterium tuberculosis (a risk group 3 micro-organism) for developing the desired antibiotic.

Also, one of the common routes of exposure to biologically active substances is through aerosols containing these substances leaking from various equipment in these facilities (Liu, 2017). One of the simpler ways to prevent aerosol formation from leaks is by applying the ISD principle of moderation by storing these substances under refrigerated conditions. However, it is important to evaluate whether the biologically active substance (API or micro-organism) lose its functionality under refrigerated conditions. An example of this approach can be the refrigerated storage of commonly used pathogen Escherichia coli (E. coli). E. coli is widely used in the manufacture of biopharmaceuticals mainly because of its growth rate, high yield of the bio-product, cost and easy scaling-up process (Baeshen et al., 2015). It has been recently established that pathogenic E. coli strains can survive in refrigerated conditions (around 4 ^{0} C) in brine solutions for as long as a period of a month (Lu et al., 2013).

4. Prevention of loss of containment (LOC) of toxic chemicals:

As mentioned previously, organic solvents used as growth mediums and disinfecting agents pose the hazard of toxicity in bioprocessing industries. The 4 most commonly used solvents in pharmaceutical industries are methanol, toluene, dichloromethane and acetonitrile (Perez-Vega et al., 2013; Raymond et al., 2010), all being associated with the hazard of toxicity. Interestingly, ionic liquids that are emerging as a substitute for organic solvents are often relatively less toxic and are referred to as 'green solvents' in pharmaceutical industries (Smiglak et al., 2014). Moreover, the toxicity of ionic liquid can be controlled by appropriate selection of anions and cations in the molecule (Smiglak et al., 2014). Such ionic liquids formed by a mixture of Lewis-Bronsted acid and bases containing a variety of cations and anions are referred to as deep eutectic solvents. The application of deep eutectic solvents (DES) has been established for various bioprocesses such as the enzymatic synthesis of phosphatidylserine (Yang and Duan, 2016). Thus, in addition to reducing the hazard of fire and explosion resulting from the use of organic solvents, ionic liquids (specifically DES) can reduce the hazard of toxicity as well and this utilization of ionic liquids can be classified as the application of the ISD principle of substitution.

Another possible implementation of the ISD principle of substitution can be for toxic excipients in biopharmaceutical industries. Interestingly, excipients that are deemed to be relatively inert in nature as compared to the API in a drug have been identified to be toxic and exposure to these excipients have been reported to cause significant health hazards. For example, diethylene glycol exposure can lead to renal failure and death and propylene glycol can lead to cardiotoxicity (Osterberg and See, 2003). A possible solution for these synthetic excipients are natural excipients (Jain et al., 2014). Since, excipients serve an auxiliary purpose in a drug formulation such as binders, diluents, flavorings etc., they can be easily substituted with relatively safer natural excipients (*e.g.* ricin and keyhole limpet hemocyanin). This approach will eliminate the hazard of toxicity resulting from the usage of toxic excipients.

Results and discussion

From the current study, it can be observed that incidents in bioprocessing industries can lead to fatal consequences. However, by applying the developed framework it can be observed that considerable progress has been achieved in terms of improving the inherent process design of bioprocesses in terms of safety. Also, classifying these developments in terms of ISD principles can help in gauging the level of risk reduction achieved by implementation of these developments as the principle of substitution can typically lead to maximum risk reduction followed by minimization, moderation, and simplicity. The following figure provides a summary of the analysis deduced by applying the suggested framework:

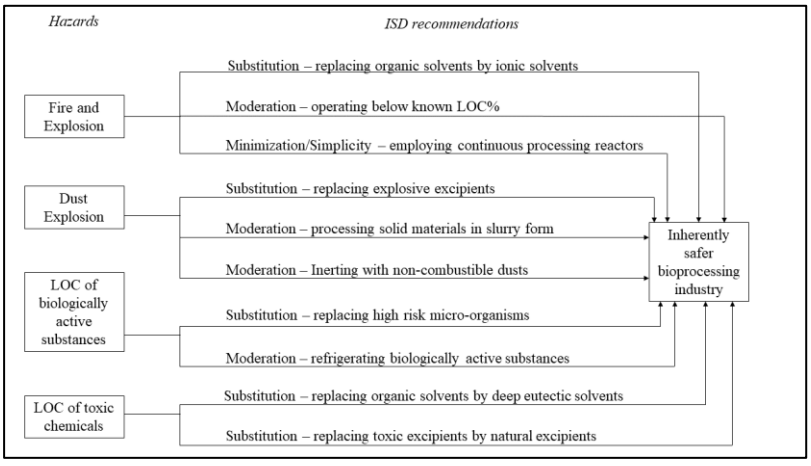

Figure 3: Recommendations for inherently safer design of bioprocessing facilities

As observed from the figure, a large fraction of the ISD recommendations fall under the ISD principle of substitution. This infers that the risk associated with bioprocessing facilities can significantly be reduced by implementation of these measures as substitution typically tends to be superior from other ISD principles in terms of the level of risk reduction achieved. Also, many of the hazards are found to originate from common sources such as excipients and organic solvents. Thus, finding safer

substitutes for these materials can be an emphasis for further studies in terms of improving the process safety of the facilities using these materials. Also, a significant fraction of the ISD recommendations is classified as moderation. Since moderation involves changing the operating conditions of the process, it is relatively easier to implement as opposed to other ISD principles and can lead to substantial risk reduction.

Although the ISD recommendations resulting from this study might reduce/eliminate the associated hazard, it is vital to understand that the ISD philosophy itself has certain drawbacks and challenges. One of the well-known drawbacks of ISD is risk transfer wherein trying to reduce the risk associated with a particular hazard might lead to an overall risk increase in the system due to a resulting risk increment from another hazard (Hendershot, 2006). This resulting risk aggravation caused by the implementation of ISD can contribute to undesirable environmental impacts as well, since a process associated with low risk is generally synonymous with an environmentally friendly process. Also, an inherently safer alternative might compromise the reliability of the overall system (Ade, 2017).

It is also of utmost importance to understand that the properties of chemicals and technologies that make them relatively hazardous tend to be the same properties that make them more desirable in terms of their applicability and efficiency in the process. Therefore, an ISD alternative has the potential to negatively impact the profitability of the process. It is also important to note that ISD principles can usually only be applied feasibly to grass-root facilities as implementing them for existing facilities will require significant equipment and process changes leading to substantially high investments. Therefore, it is important to support every ISD recommendation with a detailed cost-benefit (specifically, risk-benefit analysis) for both grass-root and existing facilities.

Conclusion

The study has revealed that the bioprocessing industries are prone to hazards of fire and explosions, dust explosions and loss of containment of toxic chemicals and biologically active substances. However as observed from this study, by applying the principle of inherently safer design, these hazards can be reduced/eliminated and the resulting risk from these hazards can be reduced. It is, however, important to note that inherently safer design philosophy is itself susceptible to various drawbacks. Moreover, the recommendations resulting from the application of inherently safer design philosophy may not always improve the economics, environmental impact and even safety of the overall process. Therefore, it is essential to support these recommendations with thorough economic, environmental and safety analysis to establish their fruitfulness and reduce any undesirable repercussions.

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