Is it time to revise Process Safety Legislation to include evolving manufacturing processes in the Biotechnology sector?

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Through experience of working in the consultancy sector it has been observed that large scale biological processes are increasingly used in the Pharmaceutical industry. The general misconception in the Pharmaceutical Industry is that bioprocesses result in much safer facilities than conventional chemistry based processes due to the less frequent use of flammable solvents and chemically reactive components.

A legislative framework does exist which sets out process safety standards for the bioprocessing industry. For biohazards, European Directive 2000/54/CE -biological agents at work is in place to protect workers from health and safety risks due to exposure to biological agents at work. A link between this directive and Major Accident Hazard legislation is required to ensure the potential risk of major biological accidents is assessed and mitigated against as required, in line with the expectations for all other potential Major Accident Hazards.

An example to benchmark against is that set by the Swiss Competent Authority who since 2015, have introduced into their Major Accident Legislation a threshold for Highly Active Substances (HAS). This legislation update has directed focus on the sectors of the biopharmaceutical industry where such substances are being processed. These materials include Carcinogens, Mutagens and Reproductive Toxins (CMRs) of Category 1 A and 1B.

Key Words: COMAH, Major Accident Hazards, Biological Substances

Introduction

European Directive 2012/18/EU on the Control of Major Accident Hazards (COMAH) involving Dangerous Substances aims at the prevention of major accident hazards and the limitation of such accidents for people, animals and the environment.

Industrial biological processes are increasingly used in the Pharmaceutical industry; however the COMAH Directive does not currently extend to include biohazards.

The COMAH Directive categorises the hazardous materials as set out in the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (UN, 2017) where the focus is on physical, environmental, health and safety information regarding hazardous chemicals.

Biohazards, however are classified into risk groups as defined in Article 2 of European Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. This Directive is a key piece of the legislative framework which sets out process safety standards for the bioprocessing industry. Its primary purpose is to protect workers from health and safety risks due to exposure to biological agents at work; however risks to the general population and environment are not specifically featured.

The general misconception in the Pharmaceutical Industry is that bioprocesses result in much safer facilities than conventional chemistry based processes, due to the less frequent use of flammable solvents and chemically reactive components.

The resultant focus of biosafety has been an Occupational Health and Safety one, notably at a laboratory scale where laboratory procedures, the vaccination of workers and use of appropriate containment technology are essential safeguards.

However many of the physical, chemical and mechanical hazards faced in bioprocessing facilities are comparable to those experienced in chemical synthesis and processing plants. The main difference in these facilities is the presence of biohazard, which in many cases represent extremely low risk. An example of this is recombinant mammalian cell lines used to produce antibody and protein drug therapies which are increasingly common in large scale production units. However in facilities where infectious organisms are used or where the culture may be susceptible to contamination (e.g. infecting human cell lines with a virus), the hazard may be more significant and the risk to the public and environment greater from an accidental release.

An example of such an occurrence is a loss of containment in the Pirbright Facility in the UK in August and September 2007 which led to an outbreak of foot and mouth disease (FMD). The cause of the release was found to be damage to a waste water line during construction works at the site.

The 2007 Foot and Mouth Disease Review (Anderson, 2008) provided details of 14 accidental releases of FMD virus worldwide between 1960 and 2007. These facilities also included laboratories producing FMD vaccines. It is of note that most of these releases were only detected by an outbreak of the disease near the originating laboratory/plant.

Laboratory Acquired Infections (LAIs), occur when employees inadvertently infect themselves; the net result being a health risk both to themselves and to the wider environment.

An in-depth article (Kimman, 2008) published by three specialists from the Dutch National Institute for Public Health and the Environment (RIVM), collated statistics of LAIs. This makes for sobering reading with respect to how frequent biosafety measures actually fail, in particular due to poor organisational control. For example it states:

"A recent survey of symptomatic and asymptomatic LAIs has been conducted by Harding and Byers, who reviewed 270 publications from 1979 to 2004, a period during which much has been done to improve laboratory safety while the work load in laboratories increased. A decrease in the number of LAIs would therefore be expected; however, knowledge on the total population at risk and the total number of infections would be needed. Harding and Byers found a total of 1,448 cases and 36 deaths, 6 of which were aborted foetuses".

While chemical hazards feature more predominately in the psyche of the public, the cold facts are that biological hazards can actually have a far greater and devastating impact. The 2014 – 2016 Ebola outbreak in West Africa was the largest and most complex outbreak since the virus was first discovered in 1976, yet the death toll was less than 15,000. In contrast, the influenza pandemic of 1918 - 1919 killed more people than World War I, with estimates ranging somewhere between 20 and 40 million fatalities. As published on the Political Broadcast Service website, a US Army Doctor wrote at the time about the death toll at a training base at Camp Devens near Boston.

"These men start with what appears to be an ordinary attack of LaGrippe or Influenza, and when brought to the Hosp. they very rapidly develop the most viscous type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the coloured men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up. There is no doubt in my mind that there is a new mixed infection here, but what I don't know".

The Cutter incident occurred in April 1955 after mass polio vaccination began in the US. 400,000 children were inoculated with a vaccine containing live polio virus. This contaminated vaccine was the result of ineffective inactivation of the live polio virus with formalin. The incident demonstrated the lack of oversight and safeguards in place before the vaccine was made so widely available. One contributing factor considered was the rapid translation from bench to the community of less than 6 years, the driving force for this was widespread fear of a polio epidemic. This failure led to 10 deaths and 250 cases of permanent paralysis resulting in a loss of public confidence in vaccination with uptake rates falling off nationwide (Juskewitch, 2010).

In April and May 1979, an unusual anthrax epidemic occurred in Sverdlovsk, Union of Soviet Socialist Republics. Soviet officials attributed it to consumption of contaminated meat. U.S. agencies attributed it to inhalation of spores accidentally released at a military microbiology facility in the city. Epidemiological data show that most victims worked or lived in a narrow zone extending from the military facility to the southern city limit. Farther south, livestock died of anthrax along the zone's extended axis. The zone paralleled the northerly wind that prevailed shortly before the outbreak. It is concluded that the escape of an aerosol of anthrax pathogen at the military facility caused the outbreak (Meselson, 1994).

Brucella abortus strain RB51 vaccine, is an attenuated live bacterial vaccine that was licensed conditionally by the Center for Veterinary Biologics, Veterinary Services, Animal and Plant Health Inspection Service, USDA, on 23 February 1996, for vaccination of cattle in the United States. Brucellosis is one of the most commonly reported laboratory-acquired infections in part due to the fact the organism easily forms an aerosol and has a low infectious dose (Ashford, 2004).

At that time accidental Reports were received from 26 individuals. Accidental exposure to RB51 occurred by needle stick injury in 21 people (81%), conjunctival spray exposure in four (15%), and spray exposure of an open wound in one (4%) individual. At least one systemic symptom was reported in 19 (73%) people, including three (12%) who reported persistent local reactions with systemic involvement. One case required surgery, and Brucella abortus strain RB51 was isolated from the wound of that individual.

A link between Biological Agents Directive 2000/54/CE and the COMAH Directive 2012/18/EU is really required to ensure that the potential risk of major biological accidents is assessed and mitigated against. Indeed, one could comment that this would be in line with the general public's expectations for control of potential Major Accident Hazards.

There are products of the biotechnology sector that while no longer biologically active they are of very high activity physiologically and that the inclusion of the category above into Major Accident Hazard legislation has to be seen as sensible in adapting to technical progress.

It is worth noting that emerging technologies in bioprocessing are leading to a considerable increase in large scale bioprocessing facilities worldwide. These include therapeutic stem cells, gene therapy vectors and the development of new vaccines. It is vital that the legislative framework is fit for purpose in light of this upsurge in activities.

Definitions of Biological Agents

Classification of Biological Agents

The Classification of Biological Agents in the EU is set out in Annex III of Directive 2000/54/EC and provides detailed information on the criteria for classification of biological agents into risk groups, plus a list of classified biological agents collated into:

Bacteria and similar organisms,

Viruses,

Parasites and;

Fungi

Member States also provide additional information. For example in Ireland biological agents are classified in the Code of Practice for the Safety, Health and Welfare at Work (Biological Agents) Regulations (Health and Safety Authority, 2017), which provides a non-exhaustive classification list of biological agents.

In the UK, there is an approved list of biological agents (Advisory Committee on Dangerous Pathogens, 2013)

In Germany, the Statutory Accident Insurers maintain a Biological Agents Database.

Classification into Risk Groups

Directive 2000/54/EC on the protection of workers from risks related to exposure to Biological Agents at work is one of the 'Individual' Directives to the Framework Safety Directive 89/391/EEC. Biological Agents are defined in Article 2 of the Directive as micro-organisms, including those which have been genetically modified, cell cultures and human endoparasites, which may be able to provoke any infection, allergy or toxicity. Biological Agents are classified into four risk groups, according to their level of risk of infection:

- Group 1 Biological Agent means one that is unlikely to cause human disease.
- Group 2 Biological Agent means one that can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available.
- Group 3 Biological Agent means one that can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available.
- Group 4 Biological Agent means one that can cause severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available.

General Biosafety Requirements for large scale work

Following on from the definition of risk groups the basic concepts involved in the selection of equipment and other protection measures and procedures within a facility are defined using those risk levels;

GLSP (Good Large Scale Practices) is sufficient for organisms that are not pathogenic and do not produce compounds that are toxic, allergenic or biologically active. These are Risk group 1 agents that have been used safely over a period of time, or have been designated as safe, and will not survive in or cause adverse effects in the environment. For GLSP there are no specific biosafety containment requirements.

Biosafety level 1 -Large scale is used for Risk Group 1 agents, non-pathogenic organisms, but can include organisms that can cause sensitisation or are opportunistic pathogens. This is comprised of Risk Group 1 organisms that do not meet the criteria for work at GLSP. Operations should be designed to prevent release of viable organisms. (E Coli is an example of this type of agent).

Biosafety level 2 -Large scale is used for Risk Group 2 agents, i.e. common pathogens. Operations should be designed to prevent release and prevent employee exposure by means splashing, spraying and subcutaneous exposure routes. (Lyme disease is an example of this group of agent).

Biosafety level 3 -Large scale is used for Risk Group 3 agents that may be transmitted via aerosol route, have the ability to be spread by insect vectors and cause serious disease in humans and animals. Equipment and facilities must be designed to prevent employee exposure and aerosol release within the facility and release of the agent outside the facility and prevent employee exposure by means splashing, spraying and subcutaneous exposure routes. (Tuberculosis is an example of this type of agent).

Biosafety level 4 - is used for Risk Group 4 agents is highly specialised, tends to be laboratory scale with very few of these facilities existing across the world.

These agents may be transmitted via aerosol route, have the ability to be spread by insect vectors and cause life threatening disease in humans and animals. (Ebola Virus is an example of this type of agent)

Biohazards within Swiss Major Accident Legislation

To explore the treatment of major accident regulation for bio-hazardous material from jurisdictions outside of the European Union, Switzerland may be one step ahead of their neighbours in this regard.

The Swiss Major Accidents Ordinance (Swiss Federal Council, 2018) was introduced in 1991 as a response to the disastrous Sandoz agrochemical warehouse fire in Basel, which more than thirty years later is still considered to be one of the worst environmental disasters in Europe. It has been updated regularly since then, but an important point to note that its scope was

never limited to stationary installations. It includes major rail lines, roads and pipelines used for transporting hazardous goods, in addition to what would be seen as the traditional installations of the chemical process sector. While even in the original 1991 version the scope made reference to hazardous microorganisms. A strong point of this legislative act is that it was never treated in isolation, but rather demonstrates a strong integration to other national and international legislative measures related to chemical safety, transportation of dangerous goods, genetically modified organisms, etc.

The current 2018 version of the Major Accidents Ordinance includes within its scope:

Establishments where an activity involving genetically modified or pathogenic organisms or alien microorganisms subject to compulsory containment is carried out which is to be assigned to Class 3 or Class 4 in accordance with the Swiss Ordinance on Handling Organisms in Contained Systems (Containment Ordinance) (Swiss Federal Council, 2015).

As regards the above, the scope of the Major Accidents Ordinance recognises an exemption from Class 3 activities with organisms which, due to their properties, cannot spread uncontrollably among the public and in the environment; and due to their hazard potential, cannot seriously harm the public or the environment. However, at the discretion of the authorities, establishments with activities involving organisms according to Class 2 of the Swiss Containment Ordinance can also be included, if it is foreseen that there is a risk to the public or environment.

The Major Accident Ordinance is therefore co-ordinated with the Containment Ordinance. There is a Swiss commentary on this Containment Ordinance, which explains its relation to European Legislation, namely the Biological Agents Directive 2000/54/EC and Directive 2009/41/EC on the contained use of genetically modified micro-organisms. Although the scope of the Swiss Containment Ordinance does go beyond Directive 2009/41/EC, which refers only to genetically modified microorganisms (GMMs), by the additional regulation of genetically modified macro-organisms and pathogenic and alien organisms.

See Table 1 for Comparison of Containment Ordinance and Major Accident Ordinance Requirements for Operations with biological hazard potential (Federal Office of the Environment, 2017).

Since 2015, the Swiss have also introduced into their Major Accident Legislation a threshold for Highly Active Substances (HAS). This legislation has directed focus to encompass sectors of the biopharmaceutical industry where materials such as Carcinogens, Mutagens and Reproductive Toxins (CMRs) of Category 1 A and 1B are being processed.

The Major Accidents Ordinance 2015 amendment has included a threshold of 20 kg for ‘highly active substances’ defined as:

- Workplace inhalation threshold in the air (MAK, TLV, OEL, IOEL, etc.) ≤ 10 µg/m3.
- Effect dose (ED50) ≤ 10 mg. This corresponds to the effect dose ED50 of 0.17 mg/kg at a body weight of 60 kg. The effect dose relates to the worst effect of the substance/preparation according to the self-assessment by the person responsible.
- Carcinogenic, Mutagenic or Reproductive Toxicant (CMR) substances with major accident potential of Categories 1A or 1B according to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging (CLP).

However legislating solely on thresholds as a trigger would be insufficient when dealing with organisms that have the ability to grow/replicate and infect multiple hosts, as only very small quantity of a pathogenic organism can cause widespread harm. Therefore, it is also necessary to follow the Swiss approach and specify activities with high risk organisms without including a quantity threshold.

Table 1 Comparison of Containment Ordinance and Major Accident Ordinance Requirements for Operations with biological hazard potential

	CO (classes 3 and 4)	**Major Accidents Ordinance**
Object to be protected	People and the environment	
Goals	Protection from hazards and impairments as a consequences of the release of organisms from handling such organisms	Protection from serious damages as a consequence of handling organisms Coping with major accidents as a consequence of handling such organisms
Risk considerations	Organism and activity related	Operation and location specific (on the basis of major accident scenarios)
Safety measures	General safety measures	
	Particular stage specific safety measures	Safety measures for operations Operations specific measures dependent on the totality of the activities being implemented Operational planning (pre-emptive measures and practices for the case of a release) Response measures in the case of a release
Implementation processes and controls	Monitoring of the operation by implementation authorities (cantons or federal)	
	Notification or permitting of individual activities (Projects)	Short report and at most a risk evaluation for the operations
		Coordination of the emergency services by the cantons.
Competent authorities for activities requiring notification and permitting requirements	Federal	
Implementation authorities	Federal and cantons together	Either cantons or federal

Details of Implementation of Swiss Major Accidents Ordinance

The handbook that supports the implementation of the Major Accidents Ordinance includes a Module for activities with biological hazard potential and a Module for installations which work with highly-active substances. For the latter there is also an Excel based 'Tool-Box' with whose help the relevant, i.e. realistically to be expected worst possible, accident scenarios for different operational areas (e.g. storage or production) can be deduced. The damage impacts of these scenarios, for the indicator of injured persons, can on the basis of dispersion and effects be evaluated by means of the model "Simulation of Effects caused by Incidents with HAS (SEIHAS)", which is used as a basis for this implementation guidance.

This Tool-Box is a simple and easy to use worksheet, which could well find applicability over a wider range of scope than just highly active substances. For instance if the system failure is a reactor experiencing a 'Runaway', then the source strength factor is 0.5, i.e. 50% of the material is discharged. If there is as a system barrier a 'Blow-Down Tank' then this has a source strength factor of 0.1, i.e. only 10% of the inlet material is released. If we were to assume a mean poly dispersed particle size of ≈ 50 µm, then for a direct release to air the source strength is 1. So the total factor then becomes 0.05, i.e. if we had 20 kg of highly active material in the reactor, 1 kg would be released to air. Similar estimations can be made for dust explosions, fire, vessel failures and leakages of packaging.

The SEIHAS model is then presented in the Module for Highly Active Substances (HAS) as a series of nomograms, which allow the estimation of the exposure on the population, which are being affected by the dispersion from the source scenario. Temporary Emergency Exposure Limits (TEELs) are then used to estimate the impact on the population, where these are a three scale guideline value similar to ERPG and AEGL values, the 1 hour TEEL value being the decisive value. For compounds for which there are no official TEEL values published, the Module for Highly Active Substances (HAS) provides a means of estimation based on Occupational Exposure Limits values.

The Module for Biological Hazards is less analytical, as befitting the nature of the subject matter. It is also co-ordinated with the Swiss Containment Ordinance.

The Module for Biological Hazards inherently recognises that many of the measures for accident avoidance are already covered by the Containment Ordinance. However, for activities with Class 3 and Class 4, the Major Accidents Ordinance requires further measures for prevention of occurrence of accidents, as well as additional measures for limiting and managing their effects. In contrast to the more prescriptive measures defined in Containment Ordinance, these major accident measures are individually influenced by the location and surroundings of the establishment. However, in the same manner in which the Major Accidents Ordinance is supported by additional guidance, so too is the Containment Ordinance.

The terminologies Laboratory Biosecurity and Biosafety are used in the Module for Biological Hazards, where Laboratory Biosecurity describes the protection and control measures as well as the responsibilities in the handling of biological material of value, which should prevent the loss, theft, misuse, unauthorised access or the deliberate unauthorised release. Biosafety describes the containment principles as well as the technologies and practices, which should prevent an unintended exposure to organisms and toxins or respectively their unintended release.

As the Module on Biological Hazards also points out since the 21st Century there is further aspect to the Laboratory Biosecurity programme mentioned above in relation to 'dual-use research'. This "encompasses biological research with legitimate scientific purpose, the results of which may be misused to pose a biologic threat to public health and/or national security."

The safety concept for installations which are subject to the Major Accidents Ordinance therefore combines the areas of biosafety for normal cases, as per the Containment Ordinance, and for the prevention and management of serious emergencies, as per the Major Accidents Ordinance. Such latter measures include redundant systems, fire protection, emergency escape routes and ventilation, retention of firewater, decontamination and disinfection, information plan, etc. While all of these issues are standard to an industrial facility, they need far more in-depth consideration with respect to the biological risks associated with Class 3 or 4 establishments. Naturally reduction of risk at source takes priority, in that hazardous micro-organisms should so far as possible be replaced by those which are less hazardous, such as those which have less of a chance to survive in the surrounding environment. Additionally vectors could be applied, which are poorly mobilised and genetic material, used to inhibit carry over to other organisms.

The Major Accidents Ordinance requires the preparation of a 'Short Report' and the Module on Biological Hazards provides a sample contents list for such a 'Short Report'. Some additional information is then provided on technical and organisational measures, which support the contents list. However, it must be recognised that this is a technology area which is still developing and requires considerable rigorous risk assessment from essentially first principles.

International Standards, Legislation and Guidance

There is currently no published international standard for managing biological risks. The European Committee for Standardisation Workshop Agreement, CWA 15793 Laboratory Biorisk management (European Committee for Standardisation, 2011) was initially published in 2008 and included International contributors. The agreement was revised in 2011 but it has not been updated since and with a usual lifespan of 3 years for such agreements it was due to lapse in 2014.

The draft International Standards Organisation (ISO) standard 35001 Biorisk management for laboratories (ISO, 2018) and other related organisations seems to be positioned to take its place. The draft reproduces much of the guidance previously contained in CWA 15793, albeit without as many examples, and while the title suggests it applies to "other related organisations" there is no specific guidance relating to Industrial operations.

Industrial operations are specifically legislated for in Directive 2000/54/EC however the containment measures required for Laboratories and Industrial Processes are counter-intuitive.

Some containment measures that are "Recommended" for a specific Containment level at Laboratory scale are "Optional" for Industrial Processes. This may indeed be due to the complexity of implementing the measures at a larger scale, but with larger inventories at risk of release they should surely receive equal if not more consideration. Indeed, one could argue that as a minimum they should require risk assessment in conjunction with cost benefit analysis, since the statistics presented earlier clearly demonstrate the Lab infections occur even with small quantities and with stricter containment requirements.

German Ordinance on Safety and Health Protection

Taking a look at how other EU states have transposed the applicable EU Directives in their national legislation we can see that some Member States, for example Germany, have considered that given that EU Directive only specify minimum requirements, that these can be improved on if their own experience and expertise deem necessary.

Sections 13(3) and (4) of the German ordinance on Safety and Health Protection at workplaces involving Biological agents (Federal ministry of Justice & Consumer Protection, 2017) contains specific requirements (not contained in the EU Directive) for protection Levels 3 and 4. Levels 3 and 4 require the operator to draw up an internal plan to address the risk arising from failure of containment measures resulting in a release of biological agents and this plan must be submitted with the licence application required for level 3 and 4 activities. In addition level 4 activities require details on safety drills if they have been deemed to be required and communication and coordination with rescue and security services.

Annexes II and III also contain stricter requirements for containment measures than contained in the corresponding EU Directive Annexes V and VI. Some measures that are not required in the EU Directive are "recommended" in the German ordinance, similarly some "recommended" measures in the EU Directive are "mandatory" in the German ordinance. It goes further again in stating that if a measure is "recommended" then it "Shall" be implemented if there is a reduction in risk to employees.

The Technical Rules for Biological Agents (TRBAs), which support the implementation of the above Ordinance (BioStoffV) provide more specific technical details considered as best practice for compliance with the ordinance. Of particular interest is TRBA 130 Occupational Safety Measures in Acute biohazard situations (Committee for Biological Working Materials (ABAS), 2013). It applies to biohazard situations arising from accidental releases of biological agents as well as situations arising from deliberate bioterrorism or criminal actions. It details a logical approach to setting up hazard zones but the basis for the approach is not provided and again the focus is very much on localised treatment and clean-up rather than any external threat to the public. Unlike the requirements for emergency plans it is not a requirement of the licence application process.

UK Guidance

The HSE publication: The large-scale contained use of biological agents (HSE, 1998) was intended to be supplementary guidance to "Categorisation of biological agents according to hazard and categories of containment" (HSE, 1995). The 1998 document acknowledges the potential for major accident hazards resulting from such operations and the need for Emergency Planning in this regard. It also contains detailed information on containment measures. However it has not been updated in line with the updates to the 1995 document which has been replaced by the 3 documents listed below and it remains unclear whether the 1998 document still stands for large-scale facilities:

- The management, design and operation of microbiological containment laboratories (HSE, 2001), which is aimed at those responsible for the management and operation of Containment Level 2 and 3 (CL2 and CL3) laboratories;
- Biological agents: Managing the risks in laboratories and healthcare premises (HSE, 2005), which is aimed at the healthcare sector; and
- Biological agents: The principles, design and operation of Containment Level 4 facilities (HSE, 2006) – this document is aimed at high-hazard containment facilities however it must be noted that the title is misleading. The guidance does not apply to all facilities handling CL4 substances, merely to Laboratories. It does however require such facilities to have Emergency plans in place to deal with unplanned releases of biological material that is likely to cause harm to persons outside the facility.

What are the policy makers doing?

The Organisation for Economic Co-operation and Development (OECD) are very active in the area of chemical safety, including guidance on chemical accident preparedness and response. Their work on biosafety unfortunately has to-date been focused on environmental protection.

In Germany, the responsible body for technical rules in the area of Hazardous Incident Ordinance is The Commission for Plant Safety (Kommission für Anlagensicherheit, KAS). Contact with the KAS, following a review of their online publications, would appear to confirm that major accident prevention for biological agents is not a current area of focus for them.

Information from the US Centre for Disease Control with respect to Emergency Preparedness and Response is limited to Chemical Accidents and Bioterrorism with an all too familiar gap in the area of accidental biological releases.

The CCPS have recognised, and indeed have gone a long way to address, the lack of guidance for Large Scale Biosafety facilities in their book "Guidelines for Process Safety in Bioprocess Manufacturing facilities" but the focus is on personnel and environmental protection (CCPS, 2011).

The European Commission Action Plan to enhance preparedness against chemical, biological, radiological and nuclear (CBRN) security risks also looks only at deliberate biological risks rather than accidental industrial releases (European Commission, 2017).

Learning from Previous Incidents

Following the 2001 FMD outbreak in the UK the government announced an independent inquiry into the lessons to be learned from the foot and mouth disease outbreak of 2001 and the way the Government should handle any future major animal disease outbreak (Anderson, 2002). The resulting report included many damning recommendations. Many improvements followed both in the UK and the EU. Those with most relevance to the prevention of major industrial biological accidents include improvements to Emergency Preparedness and the Legislative Framework. The Animal Health Act was amended in 2002, the provisions under the Civil Contingencies Act 2004 provided for wider civil emergencies co-ordination which greatly improved the response during the 2007 outbreak and EU legislation was updated with the passing of 2003/85/EC Community measures for the control of FMD.

While, admittedly, these improvements did not prevent the 2007 UK outbreak it did significantly reduce the impact. Some examples of this reduced impact are provided below (Anderson, 2008):

Table 3: Selected Comparative Impacts of 2001 –vs- 2007 FMD Outbreaks

	2001	**2007**
Cost to Government	£3 billion	£47 million
Duration	221 days	58 days
No. of infected premises	2026	8
No. of animals slaughtered	> 4 million	2160

A subsequent review following the 2007 outbreak (Anderson, 2008) was undertaken to determine if lessons were learned since 2001. It was again chaired by Dr Iain Anderson. The review acknowledged the many improvements that had been made since 2001 alongside recommendations for further improvements and some new lessons to be learned.

Outlook

The precedent set by the origin of the majority of safety related legislative frameworks speaks for itself. Major Accident legislation for the chemical industry was implemented following a number of major accidents resulting in thousands of fatalities.

Releases of Class 3 and 4 biological materials are already happening. We are in a unique position where we may not have to improve by learning from our mistakes, we can introduce legislation to minimise the effect of the first major industrial biological accident.

Public concerns to date with the biotechnology sector has been on the deliberate release of GMO into the environment such as GM foods, while in terms of actual hazard to the public the potential for an accidental release from Class 3 and 4 material from Industrial and Laboratory facilities is actually far greater.

Making predictions is always difficult. Biotechnology offers many promises with greatly improved medicinal products, but to develop these, research is required on Group 3 and 4 microorganisms. Therefore the number of research scale facilities utilising these agents will definitely increase as will their use on an industrial scale as they emerge from the R&D cycle.

These are indications that recent developments in biotechnology are such that the successful antigens produced as a result of such research, which induce the sought after immune response in the body, may well be less hazardous than the organisms from which they are derived. This may well help reduce the risk associated in the resulting large scale production that occurs. However there are no guarantees that this will occur in all cases. For example, large scale production of polio vaccines occurs in facilities, which have to be designed for Group 3 biological agents.

What is lacking to date is a unified structure that addresses:

- The identification of MAH scenarios
- The development of suitable control measures
- The establishment of appropriate preparedness for emergencies and associated requirements for remediation

Practical examples of such measures do exist within the body of technical knowledge to date but there is no obligation to identify and implement them. Such measures are always easier to implement in the design rather than retrofitting after an incident or accident has occurred.

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