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GOOD MANUFACTURING PRACTICES (GMP) / GOOD LABORATORY PRACTICES (GLP) REVIEW AND APPLICABILITY FOR CHEMICAL SECURITY ENHANCEMENTS

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Good Manufacturing Practices (GMP) / Good Laboratory Practices (GLP) Review and Applicability for Chemical Security Enhancements

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Abstract

Global chemical security has been enhanced through the determined use and integration of both voluntary and legislated standards. Many popular standards contain components that specifically detail requirements for the security of materials, facilities and other vital assets. In this document we examine the roll of quality management standards and how they affect the security culture within the institutions that adopt these standards in order to conduct business within the international market place.

Good manufacturing practices and good laboratory practices are two of a number of quality management systems that have been adopted as law in many nations. These standards are designed to protect the quality of drugs, medicines, foods and analytical test results in order to provide the world-wide consumer with safe and affective products for consumption. These standards provide no established security protocols and yet manage to increase the security of chemicals, materials, facilities and the supply chain via the effective and complete control over the manufacturing, the global supply chains and testing processes. We discuss the means through which these systems enhance security and how nations can further improve these systems with additional regulations that deal specifically with security in the realm of these management systems. We conclude with a discussion of new technologies that may cause disruption within the industries covered by these standards and how these issues might be addressed in order to maintain or increase the level of security within the industries and nations that have adopted these standards.

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NOMENCLATURE

AG	Australia Group
APIs	Active Pharmaceutical Ingredients
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CSP	Chemical Security Program
CWC	Chemical Weapons Convention
DEA	Drug Enforcement Agency
FDA	Food & Drug Administration
GDP	Good Distribution Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GSP	Good Storage Practices
GTDP	Good Trade and Distribution Practices
IBT Labs	Industrial Bio-Test Laboratories
OPCW	Organization for the Prohibition of Chemical Weapons
SOCMA	Society of Chemical Manufacturers and Affiliates
SOP	Standard Operating Procedures
USFDA	United States Food & Drug Administration
WHO	World Health Organization

1. Introduction

In this document the author will present information on the applicability of Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) for enhancing chemical risk management and the security for chemicals of concern. It will discuss how management systems provide increased oversight and tracking of materials. It will illustrate how certain operational aspects of these systems are applied to emerging industries in countries where comprehensive chemical legislation does not exist or is only beginning to emerge.

GMP and GLP are management systems utilized for quality control purposes for the manufacturing and sale of food, pharmaceutical products and material testing. The standards are designed to ensure that a set of minimal requirements for product purity and quality are met as to prevent any risk to the consumer or the general public. In addition to manufacturing, the GMP/GLP standards apply to testing standards and testing laboratories. Testing laboratories are responsible for toxicological and non-clinical testing of new pharmaceutical, medical implant, agricultural and cosmetic products.

2. Origins and History

GLP was born from the laboratory testing scandal that involved Industrial Bio-Test Laboratories (IBT Labs) in the mid-70s. IBT Labs was the major testing laboratory in North America from the 1960s through the 1970s and were utilized by dozens of major pharmaceutical and chemical manufacturers. IBT Labs accounted for over 30-45% of all product testing for non-clinical pharmaceutical efficacy, food additive safety and pesticide toxicology in the United States. In the mid-1970s questions arose concerning test data, methodologies and data handling at the IBT Labs facilities. Subsequent investigations by the United States Food and Drug Administration (USFDA) uncovered outright fraud and data falsification in a wide range of IBT Labs results. The identification of scientific fraud, called the largest scientific fraud ever, resulted in the invalidation of thousands of test results for pesticides, pharmaceutical and cosmetic products. The effects of this fraud continue today, with several popular pesticides still in use based on possibly fraudulent test data provided by IBT Labs. [1]

Due to these events, good laboratory practices were developed and became law under the USFDA on June 20, 1979.(r) The regulation may be found in the Code of Federal Regulations (21 CFR part 58). The GLP regulations cover an extensive list of requirements that a company must adopt in order to perform GLP studies. The GLP protocols include: [2]

1. Personnel and training
2. Definition and Duties of a study director, principle investigator, lab employees
3. Facility and care of animals
4. Testing operations and data collection
5. Quality systems
6. Characterization of test articles and sample accountability
7. Disqualification of testing facilities

Recently the regulations have been extended to include premarket approval submissions to the USFDA and medical device biocompatibility studies.

The history of GMP starts in 1902 with the creation of the “Poison Squad”, a group of 12 Drug Administration volunteers who sign up for a five year study regarding the effects of various preservatives. Each volunteer was provided with free, high quality, dosed meals. The materials with which the meals were dosed included borax, salicylic acid, sulfuric acid, sodium benzoate and formaldehyde. This “Poison Squad” quickly made the national headlines with reporters inundating the volunteers and chefs responsible for the meals. As the major adverse effects of these “preservatives” manifested within the volunteer group, which included nausea, vomiting, stomach aches and the inability to work, the study was halted. Because of the drama created around the event by the national press a great deal of attention was focused upon this group and the study efforts. The “Poison Squad” even had a popular song penned after them. [2]

In 1905 Colliers National Weekly ran a series of stories exposing very popular patent medicines as a complete fraud, listing false claims by manufacturers, lack of quality control and the use of addictive or poisonous components. This led to public outrage and pressure on Congress to correct the situation. This incident was quickly followed by the publication of "The Jungle", a book by author Upton Sinclair, which exposed the abuses, corruption and unsanitary conditions within the United States meat packing industry. These accumulative scandals led to the creation, in 1906, of the Pure Food & Drug (Wiley) Act. This first step towards GMP required correct product labelling and prohibited the manufacture and sale of "adulterated, misbranded, poisonous or deleterious foods, drugs and medicines". The creation of this act is considered the origin of the modern FDA. [3]

This trend of reprehensible marketing, manufacturing and sales of dangerous medicines and treatments causing injury to an unsuspecting populace, was always followed by increased attempts by the Federal Government to enforce controls and standards upon a reluctant if not rebellious industry. This rolling conflict continued until the first GMP legislation was passed by Congress. In 1962 following the tragedies of Sulfathiazole and Thalidomide the Kefauver-Harris Amendment was passed. The key points of this legislation included "Proof of Efficacy" for drugs, a requirement to report adverse events to the FDA, the requirement for "informed consent" for clinical trials, the disclosure of drug side-effects and finally an authorization for the FDA to issue GMP rules. The first drug GMPs were established in 1963 (28 CFR 6385). This list included most of the current categories of control that are utilized today, these include: [4]

1. Current best manufacturing practices
2. Premises
3. Equipment
4. Personnel
5. Components
6. Master formulas and batch production records
7. Production and control procedures
8. Product containers
9. Packaging and labeling
10. Laboratory controls
11. Distribution records
12. Stability
13. Complaint files

3. Current Applications

GMP/GLP is currently enforced in law throughout most of the industrialized world. In locations where legislation has not been forthcoming GMP/GLP is observed by most industry participants as a required voluntary standard. For companies in non-regulated countries adherence to the GMP/GLP standards is essential in order to engage in commerce within the international marketplace.

Although GMP and GLP as promoted by the World Health Organization (WHO) have no security specific components we will discuss how the implementation of several of the GMP/GLP performance categories can greatly reduce the risk of diversion, theft and adulteration of manufactured materials. In a broad review we will examine four of the implementation standards that are common to both laboratory and manufacturing sides of the standard. The four implementation standards are; Personnel, Premises, Warehousing and Distribution and Documentation.

Category of Best Practice	GMP	GLP
Pharmaceutical Quality System/Quality Assurance Program	x	x
Good Manufacturing practices for Pharmaceutical Products	x	
Standard Oparating Procedures	x	x
Sanitation and Hygiene	x	
Complaints	x	
Product Recalls	x	
Contract Production, Quality Audits	x	
Suppliers' Audits and Approval	x	
Personnel	x	x
Training	x	
Personal hygiene	x	
Premises (Facilities) (Test) (Reference Items) (Archive) (Waste) (Animal Facilities)	x	x
Equipment	x	x
Materials	x	x
Documentation	x	x
Storage and Retention of Records	x	x
Good Practices in Production	x	
Good Practices in Quality Control	x	
Test Facility Organization		x
Roles and Responsibilities		x
Test Systems		x
Test and Reference Items		x
Study Performance		x
Study Report		x

Table 1. Comparison of performance requirements GMP vs. GLP.
Annex 2; WHO good manufacturing practices for pharmaceutical products: main principles
OECD series on principles of good laboratory practice and compliance monitoring, Number 1

3.1 Review of security applicability of performance categories

3.1.1 Personnel – GMP and GLP practices place great emphasis on the skills and experience of employees operating critical manufacturing and testing tasks within the institution. Below are several main points from the U.S. Code of Federal Regulations Title 21, which is a list of employee requirements for operating within a pharmaceutical manufacturing or facility; [5]

1. Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with current good manufacturing practices (CGMP) requirements applicable to them.
2. Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.
3. There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.
4. Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.
5. Personnel shall practice good sanitation and health habits.
6. Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.
7. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.
8. Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination

thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

The eight requirements in the section above are obtained from the GMP requirements. For GLP practices, most of these requirements remain, GLP adds to the list portions concerning levels of authority and responsibility regarding individuals who carry out product or toxicology testing. GLP also has a strong emphasis placed upon data integrity, analysis and data storage, as data is the primary product for testing laboratories. [6] [7]

Only one of the points above contains subtle references to security within the GMP/GLP management system for personnel requirements. Number six, "Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas." This statement indicates that compartmentation and access control for production and other sensitive areas is observed within the standard.
Within the training requirements in the above listing it is noted that there is no provision, as there is in the Good Distribution Practices (GDP), another part of the GMP/GLP system, personnel section for "the topic of product security, as well as aspects of product identification, the detection of counterfeits and the avoidance of counterfeits entering the supply chain." is included. [8] Security training for individuals involved with handling pharmaceutical products is an obvious necessity and a large factor in the development of a "security culture" within the institutions required to implement the GMP/GLP standards. The lack of a similar requirement within the GMP regulations is puzzling.

What is noteworthy from this list of required qualifications for employees responsible for pharmaceutical production is the lack of security related background checks. Many nations that have adopted the GLP/GMP standards as law have added (at the behest of the national Drug Enforcement Agency [DEA]) extra provisions that apply to any persons involved in the handling, processing, purchasing and selling of narcotics and narcotic precursors. The anti-narcotic provisions require an extensive background review of personnel and in some cases recurring reviews depending on the time spent handling these materials and the volumes involved. In many cases, individuals involved with these materials will be required to maintain a special certification, granted by the law enforcement agency, in order to perform their job tasks with these materials. [9]

As mentioned above, many countries with GMP/GLP regulations have adopted additional regulations, usually placed by the National DEAs to require criminal background checks for all employees working within the pharmaceutical industry.

3.1.2 Premises - GMP places a great deal of emphasis on choosing, designing and constructing facilities (premises) that ensure the following points; The layout and design must ensure that the facility layout minimizes the risk of errors (work and material flow) and permit effective cleaning, decontamination and maintenance. All these activities are necessary to prevent contamination or the build-up of dust or dirt and to prevent insects or vermin from entering the

facility. For GLP, premises requirements include most of the same requirements plus additional sections on test facilities and animal laboratories, holding areas, dissection rooms, food storage and waste disposal for animal subject studies. Below is a brief summary of the requirements for GMP Premises. All of these issues are designed to protect the quality and purity of the materials produced along with all precursors and Active Pharmaceutical Ingredients (APIs). [10] They are only tangentially concerned with the physical security of the facilities.

List of general requirements

1. Premises should be situated in an environment that presents minimal risk of causing risk of contamination of materials or products.
2. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of the products. They should be cleaned and disinfected (where required) according to detailed standard operating procedures (SOPs).
3. Should include appropriate lighting, ventilation and climate control for the processes and materials in use in order to protect the integrity of the product.
4. Premise should be designed to prevent the entry of insects or other animals.
5. **Premises should be designed and built in order to prevent the entry of unauthorized people.** Production, storage and quality control areas should not be used as a right of way by personnel who do not work there.

The only requirement that is security specific in the above section is number five, requiring that premises are designed to prevent the entry of unauthorized people.

Requirements for Production Areas (Premises continued)

1. Highly sensitizing materials (penicillins) or biological preparations must be produced in their own, self-contained facilities. Other sensitive products (antibiotics, hormones, cytotoxins and highly active drugs should not be produced within the same facility. The manufacture of technical poisons (pesticides and herbicides) should not take place at facilities that manufacture medical products.
2. Facility layout, in regards to equipment location and process flow should be done with an eye towards minimizing the risk of confusion between different medical products in order to avoid cross-contamination.
3. Any location where packaging materials or intermediate and bulk products are exposed to the environment, the area should contain floors, walls and other surfaces that are smooth and easily cleaned. No materials in the area can shed particulate matter and should be easy to clean/disinfect.
4. Conduits, lighting and ventilation should be designed for easy accessibility for cleaning.
5. Drains need to be of adequate size/capacity and have trapped gullies.

6. Ventilation for production areas should control internal climate for the benefit of the materials handled or produced.
7. Weighing of materials should occur in a separate weighing room designed for that use.
8. If dust is generated during any aspect of production or packaging (dust from pharmaceutical materials) provisions should be made for preventing cross-contamination.
9. Premises for packaging of medical products should be designed and laid out so as to avoid mix-ups or cross contamination.
10. Facility production areas should be well lit, emphasizing locations where visual online controls are carried out.

The GMP requirements for production areas also lack any mention of specific security provisions.

3.1.3 Warehousing and Distribution - The systems utilized for distribution and warehousing of drugs and other pharmaceuticals has been identified as a group of activities requiring its own set of good practices. Warehousing and distribution processes are known areas of vulnerability so far as diversion of materials is concerned. As a result, GDP were developed. GDP covers all aspects of the pharmaceutical supply chain, including storage, warehousing, regional and retail distribution. According to the WHO, Good trade and distribution practices for pharmaceutical starting materials, Annex 2:

> "The storage, trade and distribution of pharmaceutical starting materials are activities that are not only carried out by companies that manufacture pharmaceutical starting materials. The nature of the risks is generally that same as that of those encountered in manufacturing environment, e.g. mix-ups and cross contamination. Therefore, there are aspects in trading and distribution where the implementation of good manufacturing practices (GMP) would be beneficial. These include, but are not limited to, packaging, repackaging, labelling, relabeling, storage, distribution and documentation and record keeping practices.
>
> WHO is concerned about the quality of materials used for the manufacture of pharmaceutical products because the quality of the pharmaceutical starting materials can be affected by the lack of adequate control activities, including packaging, repackaging, labelling, relabeling, storage and distribution of materials used in pharmaceutical products.
>
> Packaging, repackaging, labelling, relabeling, storage and distribution are the usual practices of a number of parties involved in the trade and distribution of pharmaceutical starting materials, including traders, brokers and distributors. Other activities include the issuing of Certificates of Analysis. Improper trading practices (e.g. packaging, storage and distribution) can pose a significant risk to the quality of pharmaceutical starting

> materials. Experience has shown that activities such as repackaging and relabeling, in particular, can increase the risk of contamination, cross-contamination, mix-ups, degradation and changes in physical properties.
>
> To maintain the original quality, all activities such as packaging, labelling and retesting of materials should be carried out according to GMP, good storage practices (GSP) and good trade and distribution practices (GTDP)." [11]

As noted in the previous GMP section analysis, the emphasis of these practices is the maintenance of the original quality of the pharmaceutical starting materials, such as APIs, excipients (the inactive ingredients in pharmaceuticals) and other precursors. The WHO also states;

> "Member States should take appropriate measures to ensure the implementation of these guidelines. The guidelines can be used as one tool in the prevention of the trade in counterfeit and substandard medicines."

Although not directly relevant to the security of these materials, any entity which has implemented the GDP practices will have acquired a strong deterrent against unauthorized access and potentially reduce the occurrence of theft and diversion of these pharmaceutical materials. There are 11 main aspects to GDP, they are:

1. Quality Management
2. Organization and Personnel
3. Premises
4. Warehousing and storage
5. Equipment
6. Documentation
7. Repackaging and relabeling
8. Complaints
9. Recalls
10. Returned goods
11. Handling of non-conforming materials
12. Dispatch and transport
13. Contract activities

From this list of GDP requirements we will examine a few that are directly or indirectly related to security. For the section on premises, again we see a statement that "measures should be in place to prevent unauthorized persons from entering the premises." Perimeter control at a minimum and some sort of access control to the premises would be preferred.

Under the section on Warehouse and storage, two subsections stand out, first, "There should be authorized procedures describing activities relating to the receipt, storage and distribution of

materials." The effectiveness of any management program relies upon the inclusion of clear, succinct and accurate Standard Operating Procedures (SOPs) and related record keeping practices. The threat of theft and diversion is diminished as the company improves any of its chemical management systems. Another sub section under warehousing continues with "highly active materials, narcotics, other dangerous drugs and substances presenting special risk of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition international conventions and national legislation may apply." This is one of the few statements within the GLP/GMP/GDP regime where segregation, control and security of pharmaceutical products are called out in the requirements. [8]

Under the section concerning documentation are two topics with security implications. "The original manufacturer and intermediaries handling the material should always be traceable and the information available to the authorities and end-users, downstream and upstream." Also, "Mechanisms should exist to allow for transfer of information including the transfer of quality or regulatory information between a manufacturer and a customer, and of information to the regulatory authority upon request." Both of these requirements follow along the path of the "Know Your Customer" programs instituted largely post the events of September 11, 2001, where it is the responsibility of the supplier to understand who their customers are in order to avoid ploys designed to divert materials to entities using deception to acquire hazardous materials.

3.1.4 Documentation - Any drug received within the United States that is not produced by a company compliant with the current GMP is automatically considered to be "adulterated" under the law. [12] This is one of the main concerns when consumers shop for drugs online. Some online sources procure their products from countries where GMP does not have the force of law backing it. As a result there are greater chances that drugs obtained in such a manner will not contain the ingredients it claims or that the concentration of ingredients is not accurately accounted for, thus presenting a risk to the end user of the product. Documentation of the analytical quality, manufacturer's origin, production SOPs and records, continuous chain-of-custody and ownership are considered essential to the safe development, approval, manufacturing and distribution of pharmaceutical products globally. Due to these requirements all aspect of the GLP/GMP/GDP management systems require strict adherence to data integrity and documentation standards. These standards cover all aspects of operations including analytical and test data, personnel responsibilities, training records, SOPs and records of change, quality control reports, shipping and receiving, batch records, adverse events, ownership of materials, test methods, specifications and logbooks.

In the GMP/GLP systems there are essentially two categories of documents required for compliance, instructions, including directions and requirements and then records and reports. These forms of records can be on any number of media types (paper based, electronic or photographic media) . The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for

sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated. Controls for the creation, distribution and storage of these documents must be implemented. The internal document system should be constructed as to include requirements for authorization signatures, revision programs, version tracking, dates of activities (production, packaging, and receipt), locations, batch numbers, document retention times and so on. These standards apply to all activities including specifications for production, packaging, batch processing, receipt, sampling, testing and written release and rejection documentation. [13]

The GMP/GLP standards operating with these strict compliance requirements provides companies and law enforcement with valuable information regarding issues of theft and diversion. Theft involving outside adversaries tends to involve a single dramatic event, such as a theft of materials from a transportation mode. This is opposed to theft by an active insider, (trusted employee) which can occur over a very long period of time with the insider removing seemingly undetectable amounts with each theft event. With accurate and up-to-date records a company has the ability to spot inventory discrepancies and discreetly investigate the cause of the inventory inconsistency. These records will also assist law enforcement in the task of tracking down and apprehending individuals who are involved in diversion.

What is striking within the requirements for documentation control is the lack of any language that deals specifically with the security of documents and intellectual property. With documents and data in many formats both physical and electronic, there are no physical security or cyber security requirements listed within the standards.

Even though the management standards for GMP/GLP do not include security specific performance categories; many nations have included such controls within their national GMP/GLP regulations. The adoption of additional GMP/GLP security practices in law has been largely driven by the threat of illegal narcotics. Within the United States, the DEA has added sections to the list of GMP practices that concern the handling, registration, accounting, manufacturing, storage and distribution of narcotic materials within the pharmaceutical industry.

The additional narcotics related security requirements include the registration and certification of any person involved with the handling, importation, exportation, sales, or packaging of these sensitive materials. These regulations also include the requirement for on-site inspections by the DEA. The onsite inspection serves several purposes. The DEA personnel need to examine the physical layout of the facility (interior and exterior) and assess the procedures and security measures for receiving, storing and distributing listed chemicals. The DEA personnel will also review with responsible members of the firm pertinent federal law and regulations concerning regulated chemicals to ensure that the applicant has full understanding and knowledge of federal requirements. [14]

4. Current issues with GMP/GLP

As described in the analysis of each of the four principles chosen (above) to illustrate the security intentions of GMP/GLP, many of the security aspects within the individual principles of these standards are not overtly written for security but come into existence as a secondary or tertiary effect of the implementation of the quality based management system. Noting that the GMP/GLP standards are quality based I will discuss some current trends and future challenges with the application of these standards and the influx of new technologies for the pharmaceutical and chemical industry and how these are potential issues for material and manufacturing security.

4.1 Proliferation of small chem-lab equipment - One issue that is just now receiving attention from the non-proliferation community involves the substantial proliferation of small pharmaceutical specialty batch manufacturers. This phenomenon is occurring mostly in wealthier areas of Asia, although small batch producers of APIs and precursors are located on every continent except Antarctica. The continuing global expansion in hi-tech manufacturing has led to the introduction and production of small to medium sized, glass lined, stainless steel reaction vessels. These chemical synthesis devices are assembled with other scaled down pieces of chemical production equipment and assembled within a small foot print. The common term for these systems is “a chem lab on a pallet”. These reaction vessels and palletized production platforms, by their nature, are easily mobilized, representing a potential for dual use activities. Most of this type of equipment is produced in China and elsewhere in Asia. This equipment is notable in that the size of the containers and other synthesis equipment is a fraction of the size of common, industrial batch production equipment. The availability of these inexpensive and now readily available synthesis systems has led to an explosion in the number of small start-up pharmaceutical and specialty batch chemical production companies.

Additionally, countries such as China produce over one hundred eighty thousand chemists and chemical engineers per year, this includes undergrads through PhDs. [15] [16] This situation has led to a dramatic increase in the creation of small start-up chemical and pharmaceutical “job shops”. These small start-ups have been a boon for larger pharmaceutical companies that wish to offload some of their production runs. Larger companies choose to eliminate the unprofitable products, such as, small batches of specialty drugs with limited patient populations, more costly or unprofitable production runs for APIs and other chemical pre-cursors. The motivation for the larger manufacturers to utilize these small start-ups is the reduced costs associated with the elimination of marginally profitable or unprofitable, though necessary, product lines and facilities. This is occurring at a greater frequency throughout both the chemical and pharmaceutical industries and raises concerns on just how closely the GMP standards are being followed by these new small companies. The quantity of equipment being produced and the amount of under-utilized expertise (under-employed PhD Chemists) present a potential challenge for both non-proliferation and narcotics interdiction agencies. [17] Both chemical synthesis and

biological/pharmacological batch work, most of which is un-registered, provides a large and varied market of opportunities for the individuals who are looking to profit through narcotics production or worse, production of CWC or dangerous biological products.

4.2 Production of Active Pharmaceutical Ingredients (API) – The active pharmaceutical ingredients are the substance(s) within a medication that is biologically active. APIs are of concern to regulators due to the fact that many pharmaceutical companies rely upon outside suppliers, as mentioned above, to provide the precursors for the production of APIs. Due to globalization within the chemical and pharmaceutical industry, pharmaceutical companies can obtain APIs from nearly every continent on the planet. The pharmaceutical companies prefer to outsource this part of the process in order to save funds that would otherwise be used within their organization for the costs of additional facilities and production of these precursors. Regulators are concerned that the level of quality and the potential for impurities within APIs sourced in various locations may lead to adulterated products. Currently regulators are considering whether to compel pharmaceutical manufacturers to produce their own APIs through the "long" or "short" synthetic routes in the manufacturing of pharmaceuticals. It is also one of the drivers behind the debate on long tail versus short tail product synthesis and whether larger manufacturers should be required to perform more in house production of pre-cursors, thus becoming more "long tail" in their manufacturing process. [18]

Pharmaceutical companies are tending to prefer the short route, purchasing feed stocks and precursors from what are hopefully reliable suppliers.

Long Tail Synthesis – The pharmaceutical company produces most if not all of its APIs, excipients and precursors in house, establishing total control over production quality and eliminating the hazardous steps of transportation and relying upon outside chemical suppliers.

Short Tail Synthesis – The pharmaceutical company only produces a minimal number of APIs, excipients and precursors. Which are then blended and combined in the final production steps. Instead the company largely relies on outside manufacturers to produce and supply materials that meet GMP/GLP practices. Generally conducted as a cost savings measure.

4.3 Micro-Chem synthesis – Chemical production is on the verge of a revolutionary change in technology. Chemical companies have been under pressure since the late 1980s to reduce their ecological footprint. The overarching goal has been to become more "green" in all aspects of their business models. As a result, research has led to the development of chemical micro process technology. In effect the development of a chemical factory on a chip. From the initial research, it was discovered that performing chemical reactions through this technology resulted in reactions occurring faster, requiring less materials, less energy and generating (for exothermic reactions) far less heat. Yet another benefit of the technology is that reactions occur more efficiently with fewer side reactions and resulting unwanted byproducts. Micro-chem synthesis is being fully embraced by the chemical industry for research and development, pilot plant

studies and, like massively parallel computing, its' ability to be scaled up for full mass production of chemicals. Micro-chem technology has the potential to produce a wide array of chemicals with better quality control and greatly reduced process safety risks as compared to current techniques. It will eventually allow for the elimination of large batch production equipment such as massive reactor vessels and the associated hazards of high pressures and temperatures and large volumes of hazardous chemicals.

In locations where micro-chip production is concentrated, primarily Asia, mass production of these chem-chips has reduced the costs to that of semi-conductors, making the price of entry into this technology affordable to a greater array of end-users. As with most new and disruptive technologies, micro-chem synthesis can also be utilized by state and sub-state actors. Consideration of the multiple ways this new technology could be used nefariously includes narcotics production, explosives synthesis and the potential ability to create chemical weapon compounds. Another disruptive aspect of this technology is the enormous reduction in production footprint. With the savings in energy, reduction in waste and diminished floor space required to produce materials, micro-chem synthesis has the ability to eliminate the classic intelligence "gives" that national intelligence agencies and police forces utilize to detect unlawful activities. A facility that used to require large energy supplies, vast production and storage space, smoke stacks, heat exchangers and other "classic" chemical production equipment can, theoretically, now be accomplished in a quiet commercial office development, or other small clandestine location. [19]

Under the US CFR part 211, equipment, no special recognition of micro-chem equipment is made. A review of the US DEAs "Special Surveillance List of Chemicals, Products, Materials and Equipment Used in the Clandestine Production of Controlled Substances or Listed Chemicals" contains no provisions for the recognition or control of micro-chem equipment. As a result, this new and currently un-controlled technology is not regulated at this time. Consideration must be made by suppliers of this equipment on how to track these products through import control regimes, know-your-customer programs and voluntary best practices. Care should be taken in any attempts to control this largely beneficial technology as micro-chem has the potential to greatly reduce the safety, health and environmental risks associated with bulk chemical production. Additional benefits to this technology could include considerable cost savings to all sections of the supply chain and consumers. In 2009 the Australian Group (AG) established a working group to study the potential threat of micro-chem technology. There have been conversations within the Organization for the prohibition of Chemical Weapons (OPCW) concerning options for which to regulate or control this emerging technology.

Due to the significantly improved aspects of safety, reduced environmental footprint and increase in production efficiency it will be difficult for any overarching regulation to appear in order to control micro-chem technology. One possible additional control would be the implementation, by the micro-chem manufacturing and use community, to establish a set of

voluntary, self-regulating best practices (similar to Responsible Care) to drive responsible sales and usage of this equipment.

5. Conclusions and Discussion

In this document we have reviewed aspects of the GMP/GLP/GDP management programs with an eye toward their applicability to increase chemical security. What has been identified through this assessment is that the GMP array of standards is steadfastly a quality assurance program. Comparing U.S. and international versions or variations to the GMP standards indicate a global solidarity regarding the uniformity of the specifications within these standards. This uniformity is a necessity for all global participants to engage within the ever more entwined world of international trade and co-support between and amongst the pharmaceutical and analytical test communities. The necessity of protecting the integrity of drugs and medicines is the highest priority for the continued confidence in the ability of trans-national corporations to provide safe and effective medications to a world-wide audience.

Although the inclusion of specific security related performance aspects is very limited within the standards. The author can state unequivocally that the adoption and successful implementation of these systems will, by their nature of uniformity of operations and controls, provide an increase in the security of materials and information within the entire supply line of these vital industries.

Despite the omission of security specific performance mandates within the standards, we have noted that many countries with interests in the pharmaceutical, chemical and material testing trades have enacted regulations complimentary to the GMP standards that sufficiently fill a number of these missing security principles. These additional regulations are largely driven by the international communities' attempts to suppress the illegal global narcotics trade. Additionally, national regulations regarding the export and import of materials and equipment act as an additional legal "sieve" for screening trade in these materials, some of which have dual use implications.

Implications for cooperative threat reduction programs such as the U.S. State Departments Chemical Security Program (CSP) are difficult to assess. These standards have been enacted on a global scale due to the cooperation of numerous governmental and supra governmental agencies. The ability to have an influence within this community at this point in the timeline of integration and implementation of these well-established standards would be difficult. The ability to assert changes that would include additional security requirements could possibly be influenced by the promotion of other well established voluntary standards such as the American Chemical Associations Responsible Care Program or the Society of Chemical Manufacturers and Affiliates (SOCMA). Cooperative engagement programs such as the CSP do have the ability to promote higher levels of security awareness and acceptance through education and promotion of these standards within professional or manufacturers' trade unions and associations. If the priorities within the CSP programs shift to include a greater emphasis on the pharmaceutical industry, a number of pathways may be available to increase influence within the industry. The Bureau of Economic and Business affairs may be an excellent conduit for reaching key, in-country economic partners in order exchange information and opinions on the roll and necessity

for increased security within the industry. The use of industry “champions”, individuals within the countries of interest who have already played an important role in supporting and promoting CSP interests and priorities within the current CSP programs could be recruited to support the cause of greater security awareness and the promotion of future security standards.

GMP/GLP/GDP standards have been tremendously successful in providing uniformity and harmonization within an industry that spans nations, cultures and languages. As such it has provided for healthier lifestyles and longer lives for countless inhabitants around the globe by providing safe and economical medicines and related materials for those with medical needs. As noted several times in this document, the full control of facilities, personnel, and materials via this set of quality control systems provides a solid ground floor for additional security controls should they be needed in the future.

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