

# Future issues including broadening the scope of the GLP principles

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**Summary.** When the principles of good laboratory practice (GLP) were drafted in 1982 by the Organisation for Economic Cooperation and Development (OECD) the electronic era was in its infant stages and many of the issues surrounding what may affect the environment and human health was not expected. Today, advances in technology for capturing and recording data for the reconstruction of a study are available and are being developed operating at speeds which could not have been known or understood in years past. Since that time, the United States Environmental Protection Agency (EPA) has required the conduct of additional studies in support of a pesticide registration in accordance with the GLP regulations. However, not all of these studies are required in other countries or may not require adherence to the principles of GLP. Companies are using computer models as virtual studies instead of in-life or bench type regulated research. Studies are often conducted at institutions of higher learning because of the academic expertise they offer. What is the overall impact advancing technology has on the principles of GLP? Are monitoring authorities (MAs) ready? The medical products field faces similar issues. Development and testing of these products and devices is being conducted similar to development and testing in the pesticide arena. To garner trust in mutual acceptance of data, each participating country must adhere to practices that ensure the highest standards of quality and integrity. The GLP inspector will need to have a good understanding of the science supporting the study conduct and the electronic systems that generate process and maintain study records.

*Key words:* good laboratory practice, mutual acceptance of data, global economy.

**Riassunto** (*Sviluppi futuri e ampliamento degli obiettivi dei principi di BPL*). Quando nel 1982 l'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) definì i principi di buona pratica di laboratorio (BPL) l'era dell'elettronica muoveva ancora i primi passi e molti dei problemi circa ciò che poteva influenzare la salute umana e l'ambiente erano ancora insospettiti. Oggi il progresso tecnologico rende possibile la cattura e la registrazione dei dati relativi ad uno studio ad una velocità e con modalità inconcepibili negli anni passati. Sin da allora l'Agenzia per la Protezione Ambientale degli Stati Uniti ha richiesto che ulteriori studi a sostegno della registrazione di un antiparassitario fossero eseguiti nel rispetto delle regole della BPL. Comunque, non tutti questi studi sono effettivamente richiesti in altri paesi o potrebbero non dover essere effettuati in conformità ai principi di BPL. Le aziende stanno già usando modelli computerizzati quali studi virtuali per la ricerca di tipo regolatorio su sistemi biologici o per sperimentazione da banco. Gli studi sono spesso condotti presso istituzioni di alto livello scientifico in virtù della competenza accademica offerta da queste offerte. Qual'è l'influenza globale che il progresso tecnologica ha sui principi di BPL? Le autorità di monitoraggio (AM) sono pronte? Il settore dei prodotti medici sta affrontando problemi simili. Lo sviluppo ed il controllo di tali prodotti e dispositivi vengono attualmente gestiti in modo simile allo sviluppo ed ai saggi nel settore degli antiparassitari. Per promuovere la fiducia nella reciproca accettazione dei dati, ogni paese partecipante deve adottare procedure che assicurino i più elevanti standard di qualità ed integrità. L'ispettore di BPL dovrà avere una buona comprensione degli aspetti scientifici intrinseci alla conduzione degli studi e dei sistemi elettronici che generano processi e permettono la conservazione dei documenti relativi agli studi stessi.

*Parole chiave:* buona pratica di laboratorio, accettazione reciproca dei dati, economia globale.

## INTRODUCTION

Thirty-seven years ago the United States Environmental Protection Agency (EPA) was created to address many of the nation's most pressing environmental issues. Americans were awakening to the realization

that with growing industrialization and the advent of new technology also came new challenges to human health and the environment. Sobering visions of an environment neglected, and its potentially devastating implications to human health created interest in the en-

vironment never before seen. With the creation of new environmental laws and guidelines, the United States now enjoys cleaner air, water and land. The EPA has been highly influential in shaping both national and international business practices that have not only resulted in a cleaner environment, but have also helped to create a mindset that good environmentalism equates to good business.

Through the decades, the EPA has indeed contributed to many success stories. Among them are the good laboratory practice (GLP) regulations. The GLP regulations have proven their value time and again, providing a concise, yet flexible, quality assurance model to assure that quality and valid data are developed with integrity. The popularity and utility of the GLP regulations have grown and their value was recognized by foreign countries throughout the world, leading to the development of the principles of GLP in 1982 by the Member countries of the Organisation for Economic Co-operation and Development (OECD). However, few people could anticipate many of the contemporary issues to be faced today. Few could foresee the amazing impact of burgeoning technologies such as biocides, biotechnological pesticides (Plant Incorporated Pesticides), nanotechnology, computer modeling (virtual studies), and the many GLP regulatory issues surrounding electronic data and record keeping.

As the progress towards a global economy continues, it will be more important than ever for nations to work together in an effort to garner respect and understanding. The US EPA is committed to partnering with the world's monitoring authorities to address the many health and environmental challenges to be faced today in assuring data quality. Governments must be willing to commit significant resources to training their regulatory personnel in an effort to maintain their effectiveness.

This paper discusses some of the future technological advances and addresses some of the challenges to be faced in the new millennium, and how regulatory entities must adapt in an ever changing world to assure the quality, validity and integrity of data used to make a regulatory decision.

### **CROSS-MEDIA ELECTRONIC REPORTING REGULATION (CROMERR)**

With the creation of the Food and Drug Administration (FDA) Title 21 CFR Part 11, the FDA helped to set forth new and innovative regulations which helped to ensure that electronic records including signatures are "considered to be trustworthy, reliable and fully equivalent to paper records" ([www.epa.gov/cromerr/](http://www.epa.gov/cromerr/)). In August 2001, EPA proposed rules on electronic reporting and record keeping known as the Cross-Media Electronic Reporting and Record-keeping Rule (CROMERR). As the name implies, CROMERR would consist of two parts; a section dedicated to electronic data reporting, which will be discussed in more detail later in this paper, and a por-

tion focusing on the issues surrounding electronic record keeping, a challenge facing many GLP laboratories today. Opposition to the record keeping aspects of CROMERR was widespread in the USA. Several companies and professional organizations resisted the proposed rule primarily sighting heavy costs and regulatory burdens. After some debate, EPA agreed with those voicing concern and jettisoned the record keeping sections of CROMERR moving forward only with electronic data reporting or Cross-Media Electronic Reporting Regulation (CROMERR).

Today the CROMERR provides the ability for entities reporting data to the EPA to do so electronically. It is EPA's intention to eventually apply CROMERR to all environmental programs within the Agency which contain regulatory requirements for data submission. These programs include: "(a) regulated entities that submit reports and other documents to EPA under title 40 of the Code of Federal Regulations, and (b) states, tribes and local governments that are authorized to administer EPA programs under Title 40. CROMERR establishes standard requirements for information systems that are equipped to receive information electronically, such as electronic signature validation, which provide the same standards of dependability and authenticity as existing traditional paper submittals" ([www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11](http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11)).

EPA is working to bring all of its systems together so that they conform to a single standard when receiving electronically submitted information such as required under the Federal insecticide fungicide rodenticide act (FIFRA) GLP regulations or any other program.

### **ELECTRONIC DATA AND THE INTERNET**

In the fast moving world of today where electronic systems have become so much apart of our daily lives, it is difficult to imagine life before electronic systems and the Internet. In fact it is difficult to think of an area of modern life were computer technology and the Internet have not made a dramatic impact.

Recently, scientists unveiled the world's fastest supercomputer which reportedly has the capability of performing 1000 trillion calculations per second. Such advances may someday allow scientists to simulate highly complex environmental fate and toxicology studies without ever stepping foot into a laboratory. Technology such as this, if ever fully implemented, will certainly raise compelling questions for the world's regulators, *e.g.*, what kind of training will the GLP inspectors require and how will they go about inspecting a virtual study? Will the GLP regulations have any relevance to such as study? And if so, how can the test substance and system be defined?

Today, EPA has converted most of its programs to Internet-based applications, which has inspired major advances in science, information management,

and other environmental programs, while greatly enhancing the public's access to EPA specific programs. As an example, the EPA's Laboratory Data Integrity Branch (LDIB) which conducts GLP regulatory inspections, has placed Standard Operating Procedures (SOPs), inspection manuals, GLP regulatory interpretation, and inspector contact information on the its web page. Recently, the LDIB added historical laboratory inspection information which includes current status information of its inspection activity.

The question we now face is, can we sustain the mostly positive influences created from electronic systems and the Internet and can the problems associated with these new and exciting technologies be solved?

Indeed, the Internet has proven to be one of history's most impressive catalysts in fostering innovation and creativity in all areas of modern life, but with its incredible benefits, there have come great challenges for maintaining privacy and security. Internet based systems used by consumers, business, and governments alike are in constant danger of attacks, which are growing in frequency and sophistication. Preventing attacks and Internet disruption will require the attention and collaboration of all entities involved, including the private sector, government, and law enforcement, and this effort must occur globally.

Another area of concern is the speed at which new technology finds its way into the market place. Despite the many advances inspired by electronic systems and the Internet, there still remains a divide between what software engineers are writing and the many data quality issues raised by the regulators. Although innovative in their design, some of the software fails to fully comply with some of the key components of the GLP regulations. Furthermore, the new software should be tested in the environmental conditions intended for its use, *e.g.*, software for field trials by field researchers using conventional laptop technology should be tested and validated under the environmental rigors of sun, dirt, wind, and rain. From mistakes, it has been learned that software validation must be built into the process of software development. The question then becomes how much validation and verification is enough? "The Food and Drug Administration (FDA) interprets computer system validation as documented evidence, which provides a high degree of assurance that a computer system performs its intended functions accurately and reliably. Verification of software is built upon the big picture question of whether or not the software is being written correctly. Evidence must be collected to ensure the software is performing to predefined specifications and that all required specifications are met. Validation is the process of establishing whether or not the software is doing its job correctly. In a nut shell, the software should be doing what the user expects it to do. By definition the validation process is performed during and at

the end of the software development process" [1]. In 1995 the OECD wrote the consensus document "The application of the principles of GLP to computerised systems" which helped establish harmonized polices for electronic systems. However, more work remains to sustain positive growth and maintain consumer confidence in electronic systems and the Internet internationally.

### PLANT INCORPORATED PROTECTANTS (PIPS)

Throughout history reproducing organisms have increased their chances of survival by passing along favorable heritable traits which then become more common in successive generations. Conversely, unfavorable heritable traits are discouraged eventually leading to their removal from the gene pool. This process is known as natural selection and it has been the means by which nature has created plants and animals that have gained the ability to protect themselves from parasitic organisms.

Today "scientists have been able to genetically engineer crops with pesticide characteristics to give the plant the ability to protect itself from pests. These pesticide substances within the plant, known as PIPs are primarily composed of a natural protein, that can target a very specific pest without changing the commodities basic overall character [2]. "For example, scientists can take the gene for a specific Bt pesticidal protein, and introduce the gene into the plant's genetic material. The plant then manufactures the pesticidal protein that controls the pest when it feeds on the plant" ([www.epa.gov/pesticides/biopesticides/pips/index.htm](http://www.epa.gov/pesticides/biopesticides/pips/index.htm)).

In recent years, thanks to improved communication and the speed at which consumer information is now shared and distributed, the public has taken a more active role in discovering exactly what it is they are buying. People have become very interested in finding organic food sources to help insure the quality and safety of their food supply. Today, consumers are better informed and are no longer willing to accept, without question, commodities provided to them by growers and distributors. This interest has naturally carried over to genetically modified food raising questions about the potential health and safety issues that might be associated with this relatively new technology.

The US government shares the public's concern over the quality and safety of the nation's food supply, which has resulted in several regulations written and enforced by several US. governmental entities which include; the US Department of Agriculture (USDA), FDA and EPA. The regulatory oversight and guidance from these agencies, has significantly raised the quality, and consumer confidence in the nation's food supply. Among these governmental entities is the US EPA, which traditionally, registers pesticides under FIFRA including regulatory requirements to prevent unreasonable adverse effects

on consumer health and the environment. Studies submitted to EPA, conducted in support of pesticide registration, must be performed in accordance with the GLP regulations to ensure the safety and effectiveness of all products. However, with the advancement of genetically modified products, regulators must now reconsider the way of thinking of traditional pesticides. In the past chemical pesticides were created in a laboratory, blended by formulators, and applied by growers in the field. With regard to PIPs, a plant is genetically modified with pesticidal characteristics. So the question for the world's governments is; how can one regulate this new technology to ensure continued safety and confidence of the world's food supply?

"One approach has been to focus specifically on the characteristics and the safety of products and not necessarily the technology through which the product was derived. It also does not require the producer or vendor to provide specific information to the consumer about the technologies used. In 1997 public concerns about genetically modified food led the European Commission to adopt a directive requiring specific labeling of products containing or produced from genetically modified organisms (GMOs)" ([www.oecdobserver.org/news/categoryfront.php/id/540/OECD\\_Observer.html](http://www.oecdobserver.org/news/categoryfront.php/id/540/OECD_Observer.html))

"As it is well known, before any pesticide can be registered by the US EPA, there must be extensive testing performed on the pesticide, under the GLP regulations, to demonstrate its effectiveness and safety to human health and the environment when properly used. Up to this point, EPA regulatory oversight has primarily focused its efforts on residue contaminants and not the actual commodity. EPA has determined that genetically engineered products, when used in accordance with approved label directions, and use restrictions, would not pose unreasonable risk to human health and the environment during their time-limited registration. To make this claim, EPA sponsored extensive testing that focused its efforts on exploring any potential risks to human health and the environment, including studies designed to examine the effect on non-target organisms and the development of crop management plans" ([www.epa.gov/pesticides/biopesticides/pips/index.htm](http://www.epa.gov/pesticides/biopesticides/pips/index.htm)). These studies must be conducted in accordance to the principles of GLP.

#### **BIOCIDES (ANTIMICROBIALS) AND PUBLIC HEALTH HAZARDS**

EPA's mission of protecting human health goes beyond the obvious mandate to ensure the safety and effectiveness of agricultural pesticide products used in the USA. EPA must also consider the use of pesticides for protecting human health against pests known to be public health hazards. Over the last several years, consumers have also become increasingly aware of microorganisms in or on the many items used each day. This awareness has raised the con-

cern of many consumers, resulting in an upsurge of new cleaning products claiming to kill "99.99% of all germs!". In addition, many of the familiar products used each day have been "improved" with the addition of antimicrobial pesticides promising to keep families and individuals safer. Everything from counter tops to sponges, door handles to children's play toys are now treated with antimicrobial pesticides. EPA's definition of treated articles typically refers to "articles or products that are treated with an antimicrobial pesticide to protect the articles or products themselves. The pesticides are usually added to the products (*e.g.*, plastic shower curtain) during manufacture; however, they may be added after manufacture but before use of the article" [3].

EPA's required efficacy testing prohibits a company from making any public health claims regarding a pesticide distributed or sold in the USA before it has been adequately tested and registered. Furthermore, this required testing must be carried out in a laboratory following the GLP regulations and established testing guidelines. Laboratories must allow EPA to inspect their registration data and all laboratory facilities utilized in the research.

In addition to antimicrobials, vector borne diseases are another major public health problem both in the USA and abroad. "A vector-borne disease is one in which a microorganism is transmitted from an infected individual to another individual by an arthropod or other agent, sometimes with other animals serving as intermediary hosts. The transmission depends upon the attributes and requirements of at least three different living organisms: the agent, either a virus, protozoa, bacteria, or helminth (parasitic worm); the vectors, which are commonly arthropods such as ticks or mosquitoes; and the human host. In addition, intermediary hosts such as domesticated and/or wild animals often serve as a reservoir for the pathogen until susceptible human populations are exposed" ([www.ciesin.columbia.edu/TG/HH/veclev2.html](http://www.ciesin.columbia.edu/TG/HH/veclev2.html)). As before, EPA requires GLP-compliant efficacy testing of all pesticide products designed to eradicate pest vectors, such as ticks and mosquitoes, that have the potential to affect human health. Scientists must consider the impacts of vector-borne disease versus the pesticides potential toxic effects to human health and the environment, and weigh how any regulatory decision will impact the USA and other countries affected by EPA's decisions.

#### **STUDIES INVOLVING HUMAN EXPOSURE**

Throughout the years, research using human subjects has provided valuable data to scientists working to understand and control any potential risks to human health. However, using such data raises many ethical questions regarding the welfare of human test subjects and the role this kind of research should play in the evaluation of pesticide products.

Before any discussion on human exposure studies



can begin, it must be first established that EPA does not require or encourage any research involving the intentional exposure of human subjects to test substances known to have toxic effects. This is especially true for any study submitted to EPA in support of pesticide registration under FIFRA. Despite this policy, some regulated entities have conducted these types of studies in the past. "It is EPA's position to consider all available, and relevant, and scientifically sound research, including data generated using studies with human subjects, provided all research was conducted ethically. The EPA, therefore, promulgated regulations for the protection of human subjects in research which are found at 40 CFR Parts 9 and 26. These new rules, developed in partnership with the National Academy of Sciences and the Department of Health and Human Services significantly strengthen and expand protections for subjects of "third party" human research (*i.e.*, research that is not conducted or supported by EPA).

The US Department of Health and Human Services (HHS) is responsible for the promulgation of the Basic Federal Policy for Protection of Human Research Subjects or Common Rule and historically been responsible for its enforcement" [4]. However, regulators recognized the need for revision of the Common Rule as research using human subjects is now supported by EPA and several other federal departments and agencies. As previously mentioned, any testing used to support the registration of a pesticide, including that which involves human test subjects, must be performed in strict accordance with the GLP regulations.

As far as is known, other countries may not require human studies/ testings to be done according to the principles of GLP.

## NANOTECHNOLOGY

Nanotechnology is another new and exciting technological advancement that has the potential to improve many of the things commonly used today, such as electronics, medicine, transportation, energy and agriculture. "Nanotechnology is the science of creating or modifying materials at the atomic and molecular level to develop new or enhanced materials and products. A nanometer is one billionth of a meter or about one ten-thousandth the diameter of a human hair, a thousand times smaller than a red blood cell, or about half the size of the diameter of DNA" [5].

As one would expect, EPA is very interested in the potential benefits of nanotechnology to the environment. It is hoped that nanotechnology may lead to new and innovative ways of reducing and managing contaminants in the environment. As with any other technology used in the USA, EPA's concern is to better understand any potential risks from exposure to materials containing nano-scale particles. With respect to pesticides, nanotechnology has already begun changing the nature of some pesticides.

"There are consumer products on the market today using engineered nanoparticles of active ingredients, such as silver, to achieve antimicrobial effects, and many more are likely. Even as these consumer products are introduced, agricultural chemical producers are developing new pesticide products using nanotechnology to enhance the effectiveness or delivery of those pesticides. Among the uses of nanotechnology in agriculture currently being explored are agrochemical delivery (delivery of pesticides and other chemicals only when needed or for better absorption), nanosensors, and new or modified active pesticidal ingredients" [6].

The EPA has created a workgroup which has the responsibility of identifying the major environmental benefits that nanotechnology may offer, while identifying potential environmental risks. Indeed, nanotechnology has evolved from an innovative idea to a present day reality, and yet another challenge for the world's GLP programs to train GLP inspectors to inspect and audit these types of studies.

For additional readings on this subject matter refer to [7-12].

## CONCLUSIONS

The regulatory process begins and ends with EPA's responsibility to protect human health and the environment. The important question for the regulators is: what should the government regulate and how?

With the amazing speed at which new technology is introduced, it will be more important than ever for the world's regulatory agencies to recognize the value of staying ahead of modern innovation. For good regulations to be passed and work successfully, there must be a logical balance between the interests of the producer and the needs and concerns of the consumer. It is time for countries around the world to work together in an effort to broaden the scope of their respective GLP programs and realize the great value of global harmonization. Nations whose borders were historically closed to foreign interaction are now beginning to realize the benefits of policies that promote openness, providing them access to vast experience from experts around the world, while promoting a spirit of cooperation and partnership. Despite these changes, there still exists several challenges that lie ahead.

In the modern age of rapid technological advancement, people have become accustomed to hearing about new and exciting scientific discoveries. However, when a new innovation has the potential to affect human health and the environment, as it has been seen with simulated (virtual) studies, GMO's or nanotechnology, regulatory review and oversight must follow, compelling governments to commit significant resources to training their regulatory personnel. The GLP inspector of the twenty-first century must have the appropriate qualification and training, not only in the basic science, but also in the new technologies. He/she must first have a ba-

sic knowledge of the study design, before he/she can inspect the facilities and audit the new technology studies.

Along this line, there remains disharmonization among nations regarding appropriate levels of government oversight and testing required to make regulatory decisions on the risks and benefits of pesticide products. These inconsistencies have created data gaps and uncertainty about the integrity of foreign data, resulting in the loss of valuable research time and money.

Still another challenge facing receiving and regulatory officials within the US EPA is an increased trend of data submissions consisting of only cited study literature. This information is sometimes very old and, in most cases, not performed in accordance with the GLP regulations. In some situations the laboratory identified in the literature as having generated the data is unknown or may no longer exist.

Challenges such as these examples will be solved in time and organizations such as the OECD are a log-

ical place in which to discuss them. OECD's mutual acceptance of data (MAD) program has been highly successful in translating the principles of GLP and procedures, while promoting better data consistency throughout the world. These programs have helped governments establish their own procedures for monitoring GLP compliance through regulatory inspections, global training, and study audits.

The authors believe this is the best way to solve the most pressing issues in new millennia, while fostering friendship, respect, and harmonization between nations, and assuring the quality and integrity of data in regulatory decision making.

#### Disclaimer

Opinions presented in this paper reflect those of the authors and should in no way be perceived as official EPA interpretation.

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