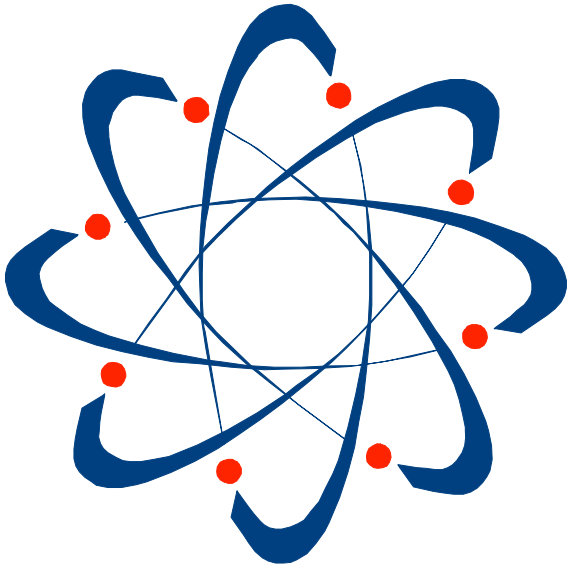
SPAQA CIRCLE



Ausgabe 8 **September 2000**

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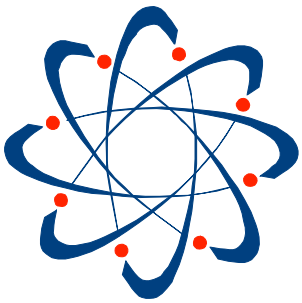

Liebe Mitglieder

Nach unserer letzten Generalversammlung durften wir drei Vorstandsmitglieder mit einem herzlichen Dank für die geleistete Unterstützung während vieler Jahre verabschieden.
Neu gewählt in den Vorstand wurden Herr St. Hagen (Aktuar) und Herr Ch. Zeugin (Beisitzer mit der Aufgabe, sich unserer Homepage anzunehmen) und als Vizepräsident wird uns nun Herr A. Edelmann mit Rat und Tat zur Seite stehen.

Die Anerkennung, welche unsere Referenten Dr. H. Galicia, Dr. Edelmann,und Fr. Dr. Studer an der GV durch die SPAQA erhielten, floss uneingeschränkt auf das Spendenkonto der Organisation "Ärzte ohne Grenzen", welche sich dafür recht herzlich bedankte.

Im Januar 2000 erschien im Deutschen Amtsblatt der Europäischen Gemeinden eine Richtlinie 1999/93/EG des Europäischen Parlaments und des Rates über gemeinschaftliche Rahmenbedingungen für elektronische Signaturen. In dem 13-seitigen Dokument sind neben den Begriffsbestimmungen, die Rechtswirkung, der Datenschutz und der Haftung die Anforderungen an qualifizierte Zertifikate und sichere Signaturerstellungseinheiten auch Empfehlungen für die sichere Signaturprüfung aufgeführt.
Eine Gegenüberstellung mit den FDA 21C FR11 wäre sicher interessant.

Im März 2000 hat die OECD ein neues Advisory Document der Working Group of Good Laboratory Praxis herausgegeben mit dem Titel: "Requesting and Carrying out Inspections and Study Audits in Another Country", worin das Vorgehen bei Länderinspektionen im Sinne des Mutual Joint Visit Programmes beschrieben ist.
Es kann von der OECD-Website heruntergeladen werden.

Unsere herbstliche Diskussionsrunde wird in diesem Jahr am 26.Oktober stattfinden. Wie immer bitten wir die Mitglieder GLP-Fragen oder Unklarheiten zur Beantwortung an unsere Vertreter der CH- GLP-Behörden bis Ende September elektronisch an mich zur Weiterleitung zu senden.

Ein grosser Teil unserer Mitglieder hat der Zahlung des diesjährigen Mitgliederbeitrages schon Folge geleistet, wofür wir uns recht herzlich bedanken.
Alle anderen möchten wir höflich daran erinnern, den Mitgliederbeitrag von SFR 50.- bitte noch zu überweisen, selbstverständlich mit Ihrem Namen und Ihrer Adresse, damit der Betrag dann von uns auch zugeordnet werden kann.

die Präsidentin

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FDA - COMPLIANCE POLICY GUIDE

Section 160.850

Title: **Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures (CPG 7153.17)**

Background:

This compliance guidance document is an update to the Compliance Policy Guides Manual (August 1996 edition). This is a new Compliance Policy Guide (CPG) and will be included in the next printing of the Compliance Policy Guides Manual. The CPG is intended for Food and Drug Administration (FDA) personnel and is available electronically to the public. This guidance document represents the agency's current thinking on what is required to be fully compliant with 21 CFR Part 11, "Electronic Records; Electronic Signatures" and provides that agency decisions on whether or not to pursue regulatory actions will be based on a case by case evaluation. The CPG does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulation, or both.

In the Federal Register of March 20, 1997, at 62 FR 13429, FDA issued a notice of final rulemaking for 21 CFR, Part 11, Electronic Records; Electronic Signatures. The rule went into effect on August 20, 1997. Part 11 is intended to create criteria for electronic recordkeeping technologies while preserving the agency's ability to protect and promote the public health (e.g., by facilitating timely review and approval of safe and effective new medical products, conducting efficient audits of required records, and when necessary pursuing regulatory actions). Part 11 applies to all FDA program areas, but does not mandate electronic recordkeeping. Part 11 describes the technical and procedural requirements that must be met if a person chooses to maintain records electronically and use electronic signatures. Part 11 applies to those records required by an FDA predicate rule and to signatures required by an FDA predicate rule, as well as signatures that are not required, but appear in required records.

Part 11 was developed in concert with industry over a period of six years. Virtually all of the rule's requirements had been suggested by industry comments to a July 21, 1992 Advance Notice of Proposed Rulemaking (at 57 FR 32185). In response to comments to an August 31, 1994 Proposed Rule (at 59 FR 45160) the agency refined and reduced many of the proposed requirements in order to minimize the burden of compliance. The final rule's provisions are consistent with an emerging body of federal and state law as well as commercial standards and practices.

Certain older electronic systems may not have been in full compliance with Part 11 by August 20, 1997, and modification to these so called "legacy systems" may take more time. As explained in the preamble to the final rule, Part 11 does not grandfather legacy systems and FDA expects that firms using legacy systems will begin taking steps to achieve full compliance.

Policy:

When persons are not fully compliant with Part 11, decisions on whether or not to pursue regulatory actions will be based on a case by case evaluation, which may include the following:

1. Nature and extent of Part 11 deviation(s). FDA will consider Part 11 deviations to be more significant if those deviations are numerous, if the deviations make it difficult for the agency to audit or interpret data, or if the deviations undermine the integrity of the data or the electronic system. For example, FDA expects that firms will use file formats that permit the agency to make accurate and complete copies in both human readable and electronic form of audited electronic records. Similarly, FDA would have little confidence in data from firms that do not hold their employees accountable and responsible for actions taken under their electronic signatures.

2. Effect on product quality and data integrity. For example, FDA would consider the absence of an audit trail to be highly significant when there are data discrepancies and when individuals deny responsibility for record entries. Similarly, lack of operational system checks to enforce event sequencing would be significant if an operator's ability to deviate from the prescribed order of manufacturing steps results in an adulterated or misbranded product.

3. Adequacy and timeliness of planned corrective measures. Firms should have a reasonable timetable for promptly modifying any systems not in compliance (including legacy systems) to make them Part 11 compliant, and should be able to demonstrate progress in implementing their timetable. FDA expects that Part 11 requirements for procedural controls will already be in place. FDA recognizes that technology based controls may take longer to install in older systems.

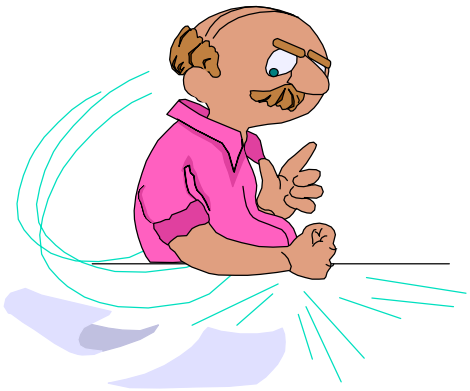
4. Compliance history of the establishment, especially with respect to data integrity. FDA will consider Part 11 deviations to be more significant if a firm has a history of Part 11 violations or of inadequate or unreliable recordkeeping. Until firms attain full compliance with Part 11, FDA investigators will exercise greater vigilance to detect inconsistencies, unauthorized modifications, poor attributability, and any other problems associated with failure to comply with Part 11.

Regulatory Action Guidance:

Program monitors and center compliance offices should be consulted prior to recommending regulatory action. FDA will consider regulatory action with respect to Part 11 when the electronic records or electronic signatures are unacceptable substitutes for paper records or handwritten signatures, and that therefore, requirements of the applicable regulations (e.g., CGMP and GLP regulations) are not met. Regulatory citations should reference such predicate regulations in addition to Part 11. The following is an example of a regulatory citation for a violation of the device quality system regulations.

> *Failure to establish and maintain procedures to control all documents that are required by 21 CFR 820.40, and failure to use authority checks to ensure that only authorized individuals can use the system and alter records, as required by 21 CFR 11.10(g). For example, engineering drawings for manufacturing equipment and devices are stored in AutoCAD form on a desktop computer. The storage device was not protected from unauthorized access and modification of the drawings.*

Issue date: 5/13/99



GLP – IN THE EUROPEAN COUNTRIES

Austria

The federal ministry of the environment, youth and the family, department I/3 is the GLP monitoring authority for all chemicals except medicinal products and veterinary drugs. The ministry of health and consumer protection is currently setting up a second GLP monitoring authority for these products.
Routine inspections take place every two to three years.
There is no bilateral agreement with third countries.
The GLP monitoring programme started in 1989 (industrial chemicals) and 1991 (pesticides).

Belgium

The ministry of public health and environment is in charge of the GLP monitoring authority, the **"Institut d'hygiène et d'épidémiologie"**, which is responsible for all chemical products.
The test facilities in the national monitoring programme work on a wide range of chemical products: industrial chemicals, medicinal products, veterinary drugs, phytopharmaceuticals, food additives and cosmetic products.
The laboratories are inspected every two to three years.
There are no bilateral agreements.
The GLP monitoring programme started in November 1988.

Denmark

The ministry of health and the ministry of trade and industry are in charge of the designation of the GLP monitoring authorities: the danish medicines agency (*Lægemiddelstyrelsen*) covers medicinal products and veterinary medicinal products. The danish agency for trade and industry (**DANAK**) (*Erhvervsfremme Styrelsen*) covers plant protection products, biocides, and food additives.
The inspections are carried out by the danish medicines agency and the danish agency for trade and industry (DANAK).
Routine inspections are carried out every two to three years.
There are no bilateral agreements.
The GLP monitoring programmes were launched on the 1st March 1989, but there has been a GLP inspection programme for chemicals since 1981.

Finland

The GLP monitoring authority is the **National product control agency for welfare and health**, which monitors directly test facilities carrying out environmental safety studies. The agency has delegated GLP-inspections for test facilities carrying out non-clinical safety studies on human health to the National agency for medicines.
There are no bilateral agreements with third countries.
The GLP inspection programme started in 1990.

France

The "Groupe interministériel des produits chimiques" (GIPC) is in charge of the GLP monitoring authority **Cofrac** for chemicals others than medicinal products, cosmetics and veterinary drugs. The Ministry of labour and social affairs is in charge of the GLP monitoring authority "Agence française de sécurité sanitaire des produits de santé" (AFSSAPS) for medicinal products and cosmetics. The Ministry of labour and social affairs together with the Ministry of agriculture and fisheries are responsible for the "Agence française de sécurité sanitaire des aliments", comprising the "Agence nationale du médicament vétérinaire", the GLP monitoring authority for veterinary drugs.
The test facilities in the three monitoring programmes work on a wide range of chemical products: new and existing chemicals, medicinal products, veterinary drugs, cosmetics, food additives, animal feed additives, pesticides.
Routine inspections are carried out in intervals of between 15 months (GIPC) and two years (AFSSAPS).
The GLP monitoring programme was started in 1984 for medicinal products, in 1999 for veterinary drugs, and in 1985 for other chemicals.

Germany

The Federal Ministry for environment, nature conservation and nuclear safety is in charge of the designation of the GLP monitoring authorities. There is one GLP monitoring authority in each *Land*. Their work is co-ordinated by the **"Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin"** (Federal Institute of consumer health protection and veterinary medicine).
The test facilities in the national monitoring programme work on a wide range of chemical products: industrial chemicals, medicinal products, veterinary drugs, food additives, animal feed additives, pesticides, explosives and cosmetics.
Routine inspections of test facilities are conducted on a regular basis. Test facilities have to apply for a renewed routine inspection at the latest four years after the last inspection. Additional inspections and study audits may be carried out on request.
There are four bilateral agreements (or memoranda of understanding) established with USA, Japan, Austria and Switzerland.
The GLP monitoring programme was launched on the 1st August 1990.

Greece

The Ministry of finance is in charge of the GLP monitoring authority, The General chemical State laboratory, which was initially responsible for all chemicals. By ministerial decision A7/10821/97 the **National drug organisation**, under the responsibility of the Ministry of health and social welfare, was appointed as the GLP monitoring authority for medicinal products and veterinary medicinal products, cosmetics, food additives and feed additives.
Test facilities in the national monitoring programme work mostly on plant protection products and medicinal products.
Study-audits are performed every year and routine inspections every second year.
There is no bilateral agreement signed.
The GLP monitoring programme was started in 1995.

Ireland

The Irish Department of enterprise, trade and employment is in charge of the designation of the GLP monitoring authority, "**The Irish national accreditation board**".
The products involved are the chemical substances as defined in directive 67/548/EEC.
Routine inspections are performed every second year.
The legislation was approved in January 1991, and the Irish authorities implemented the GLP monitoring programme in 1992.

Italy

The Ministry of health is in charge of the GLP monitoring authority, "**dipartimento Prevenzione**" (Department of prevention), which operates through an ad-hoc Committee comprising those departments of the Ministry of Health involved in GLP (Department of prevention, Department for pharmaceuticals and pharmaco-surveillance), Department of veterinary drugs and Department of food and nutrition) and the "Istituto superiore di sanità (National institute of health). Test facilities in the national monitoring programme mainly work on medicinal products, veterinary medicinal products, pesticides, food additives, cosmetics, and industrial chemicals.
Routine inspections are carried out every two years.
There is a bilateral agreement established with the USA (FDA) and a memorandum of understanding with Japan (Ministry of health) has been finalised but not signed (due to intervention by the EC)
The GLP monitoring programme was started in 1986.

Luxembourg

Luxembourg has transposed the directives 87/18/EEC and 88/320/EEC, but has no GLP compliance programme.

The Netherlands

The Ministry of health, welfare, and sport is in charge of the GLP monitoring authority, "**Inspectorate for health protection, commodities and veterinary public health, GLP department**".
The test facilities in the national monitoring programme work on a wide range of chemical products: industrial chemicals, medicinal products, veterinary drugs, and pesticides.
There are two bilateral agreements with the USA [Food and drug administration (FDA) and Environment protection agency (EPA)] and two memoranda of understanding with Japan (Ministries of international trade and industry, and Ministry of health and welfare - Pharmaceutical affairs bureau)
The GLP monitoring programme was started in march 1987.

Norway

The Ministry of trade and industry is in charge of the GLP monitoring authority "**Justervesenet**" (Norwegian metrology and accreditation service). The department for norwegian accreditation was appointed as monitoring authority for all chemicals in october 1993.
Routine inspections are carried out every two years.
No bilateral agreements have been concluded.
The GLP monitoring programme was started in 1994.

Portugal

The Ministry of health is in charge of the GLP monitoring authority "**Instituto da farmacia e do medicamento**" (Infarmed) (Institute for pharmacy and medicaments) for medicinal products, veterinary drugs

and cosmetics, the Ministry of economy is in charge of the GLP monitoring authority "Instituto portugues da qualidade" (IPQ) (Portuguese institute for quality) for other chemical products.
Routine inspections are carried out every two years.
There is no bilateral agreement signed.

The GLP monitoring programme started in 1993 for industrial chemicals and in 1994 for medicines.

Spain

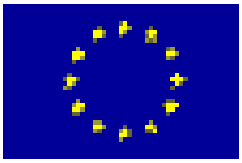
The Minstry of health and consumption, Directorate general of pharmacy and hygiene, is in charge of the GLP monitoring authority "**Agencia española del medicamento**" (Spanish agency for medicinal products) for medicinal products. For all other products, the Ministry of industry and energy and the Ministry of agriculture will be competent, but no monitoring programme is operating yet.
At the current stage, only medicinal products are covered by GLP monitoring.
No bilateral agreements exist.
The GLP monitoring programme was launched in may 1995.

Sweden

The Ministry of social affairs is in charge of the GLP monitoring authority "**Läkemedelsverket"** (Medical products agency, MPA) for pharmaceuticals, cosmetics and hygienic products and the Ministry of foreign affairs is in charge of the GLP monitoring authority *Styrelsen för ackreditering och teknisk kontroll* (Swedish board of accreditation and conformity assessment, SWEDAC) for other chemicals. Since 1998 there exists an agreement between the MPA and SWEDAC concerning GLP monitoring.
The routine inspections are carried out every year (SWEDAC) and every two years (MPA).
There are two memoranda of understanding with the USA (FDA) and Japan (Ministry of health and welfare) for pharmaceuticals.
The GLP monitoring programmes were started in 1979 (MPA) and 1991 (SWEDAC).

United Kingdom

The Department of health is in charge of the GLP monitoring authority, the "**United Kingdom GLP compliance monitoring authority**", which is a part of the Medicines control agency, and is responsible for all chemicals.
The test facilities in the national monitoring programme work on a wide range of chemical products: new and existing chemicals, medicinal products, veterinary drugs, cosmetics, food additives, animal feed additives, pesticides.
Routine inspections are carried out every two years.
There are bilateral agreements signed with USA (FDA and EPA, which have expired now) and memoranda of understanding with Japan (Ministry of health and welfare, Ministry of agriculture, fisheries and forestry and Ministry of international trade an industry).
The GLP monitoring programme was started in january 1983.



European Commission: LEGAL NOTICE on GOOD LABORATORY PRACTICE

GLPV Pt.4.2: Auslegung: Dispensoren und Pipetten (Kolbenhubpipetten) sind Geräte zur Erhebung von wichtigen Messdaten und sollten demzufolge GLP-konform gehandhabt werden.

Ein SOP über die Pipettenkontrolle sollte folgende Punkte zum Inhalt haben:

1. Typen und Modelle von Pipetten und Dispensoren
2. Benützung und Handhabung
3. Vorgehen bei der Kontrolle
4. Kontrollfrequenz und Dokumentation
5. Wartung und Reparaturen und deren Dokumentation

Pipetten-Kontrolle

Gravimetrische Kontrolle von Pipetten mit fixem oder variablen Volumen (z. B. Oxford, Eppendorf, Socorex, etc.) mit destilliertem Wasser:
Die Pipetten werden mit den Originalspitzen und destilliertem Wasser gefüllt auf einer analytischen Waage gewogen.

Beispiel:

	10 µl	**50µl**	**100µl**
Mean mg*	10.01	49.79	99.90
Std. Deviation	0.0123	0.0512	0.0350
Den. Corr.	1.0031	1.0031	1.0031
Mean µl	10.04	49.94	100.21
% Deviation	0.43	0.12	0.21

* Mittelwert von minimal 3 Wägungen

Hersteller Spezifikationen:

Accuracy range:	9.65 – 10.35	49.50 – 50.40	99.2 – 100.8
Precision (STD. Dev.)	0.10	0.12	0.15

Dazu sollte ein Logbuch geführt werden in welchem der Hersteller, das Modell mit Seriennummer, das Kalibrierungszertifikat vom Hersteller und die Laborkonditionen festgehalten sind.

Zusätzlich sollte noch Buch geführt werden über die Wartung und Reparaturen (ersetzte Dichtungen, O-Ringe, Reinigung des Kolbens, etc.).

QA - Global

Slovak Republic to become Member of the OECD

The Council of the OECD has agreed to invite the Slovak Republic to become the 30th Member of the Organisation. The examination of the terms of accession of the Slovak Republic to the OECD has now been completed, and the Council decided today that it will invite the Slovak Republic to accede to the Convention on the OECD on those terms.
The signature of the agreement setting out the terms of accession will take place at a date to be confirmed. The agreement will be signed by a representative of the Slovak Government and by the Secretary-General of the OECD, Mr. Donald J. Johnston.
Membership of the Slovak Republic in the OECD will be effective upon the deposit by the Slovak Republic of its instrument of accession to the OECD Convention with the French Government, depositary of the Convention. Until its accession, the Slovak Republic will be invited to participate as observer in the work of all the bodies of the OECD, in particular the Council.
Commenting on the Council decision, Mr. Johnston said: "This is a happy day for the OECD. We are completing the programme of Partners in Transition that OECD initiated in 1991 to assist Hungary, Poland, the Czech Republic and Slovakia to transform their economies into market-based systems so that they would be ready to join the OECD community. The government of the Slovak Republic has undertaken a bold programme of economic reform. I congratulate them. I am convinced these reforms will result in greater opportunities and prosperity for the Slovak people and their neighbours."

Requirements for GMP and GLP production of clinical grade molecular diagnostics and therapeutics.

The production, testing and quality control of all biological material used for human use has to follow procedures according current GMP/GLP guidelines. These guidelines have been established to protect patients from side effects resulting from impurities and contamination in the production process and ensure the identity, safety and purity of the product and the reproducibility of the production process.

Quality assurance and validation procedures will ensure the quality of all products, including:

- Testing for the presence of adventitious infectious agents
- Testing for replication-competent retroviruses
- Cell line authenticity
- Cell line cross-contamination
- Presence of the cell surface marker gene product

- Expression and function of the transduced gene products
- Viability of the cells after thawing
- Full supporting documentation

GCP: Auszug aus der GUIDELINE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS

Article 2.11: Application Of Good Laboratory Practices

It is important to ensure the quality and reliability of the studies. This is normally accomplished through the conduct of the studies according to GLP. Due to the unique design of some safety pharmacology studies it may not be feasible to conduct these in accordance with GLP. It has to be emphasized that data quality and integrity in safety pharmacology studies should be assured even in the absence of formal adherence to the GLP Principles. When studies are not conducted in accordance with GLP, study reconstruction should be assured through adequate documentation of study conduct, including archiving of data. Any study or study component not conducted according to GLP should be adequately justified and the potential impact on evaluation of the endpoint should be explained.
The safety pharmacology core battery is normally conducted under GLP. Follow-up and supplemental studies should be conducted in accordance with GLP to the greatest extent feasible. Safety pharmacology investigations can be part of toxicology studies; in such cases these studies would be conducted in accordance with GLP.
Primary pharmacodynamic studies do not need to be conducted according to GLP.
Secondary pharmacodynamic studies, where their objectives differ from safety pharmacology studies, do not need to be conducted according to GLP.
Safety pharmacology studies conducted as general screens in the absence of specific cause for concern do not need to be conducted according to GLP.

GLP IN INDIA: TOXICOLOGY

In India, increasing toxicological awareness and the associated challenges
faced by industry have been the key drivers for the implementation of international quality management systems, such as good laboratory practice (GLP), and industry has taken the initiative. Although GLP guidance was formulated in 1983, major progress was not made for a decade because of the lack of mobilization of adequate resources.
However, more recently, Indian Government agencies have taken action to ensure that laboratories are able to comply with GLP standards. In the authors ' facility, the implementation of GLP was undertaken with the as-sistance of the parent company and has been highly beneficial.

EPA: Taking GLP into the 21st Century

F.E. Liem and M.J. Lehr*
Key Words :

GLP* ; *US Environmental Protection Agency (EPA*); *OECD

The US Environmental Protection Agency (EPA) has been highly successful in implementing new programmes aimed at introducing and enforcing new Good Laboratory Practice (GLP) concepts, and this has resulted in an improvement in overall compliance. The EPA and foreign governments have begun working together to promote consistency in scientific data generated throughout the world, and the Organization of Economic Cooperation and Development (OECD), an intergovernmental organization consisting of 29 industrialized nations, has published consensus documents based on GLP standards.

The most common observations made by EPA inspectors in the last 3 years included violations with regard to organization and personnel, the protocol, and the conduct of the study.

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Implementing GCPs in Asia

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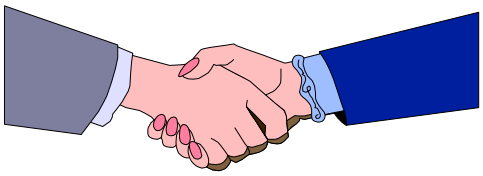
The implementation of International Conference on Harmonization (ICH)-Good Clinical Practice (GCP) standards in China, Taiwan, Thailand and Japan poses some unique challenges due to cultural influences, particularly in Japan. Auditing experiences were generally positive in all countries with auditing by a Western company being viewed as a positive and educational experience. Audit findings in the areas of informed consent, source documents, adverse event re-porting and monitoring are de-scribed.
It is critical for auditors to present a positive image at all times, even when confronted with blatancy.



Compliance Policy Guide
Sec. 100.900
International Memoranda of Understanding
(CPG≥ ≤7150.19)

SUBJECT:
This guide sets forth policy for initiating, developing, and monitoring agreements such as memoranda of understanding (MOU's) between the Food and Drug Administration (FDA) and foreign governments. The general principles herein may also be applicable to MOU's with international organizations.

BACKGROUND:
The FDA International Harmonization Task Force recommended in December 1992 that guidance be developed that describes the agency's objectives and promotes uniformity in developing MOU's with foreign government agencies. MOU's promote harmonization of laws, regulations, and enforcement activities. Further, MOU's, if negotiated and implemented properly, enhance FDA's ability to carry out its mission. Attachment A to this Compliance Policy Guide (CPG) sets forth the agency's criteria for setting priorities for international MOU's.
The three categories of MOU's described in the following paragraphs are merely examples. These categories are not mutually exclusive, and the concepts may be altered or combined as necessary. Because officials of sovereign nations have different approaches to regulation, FDA needs to maintain flexibility in its discussions with these officials.

Reciprocal Agreements with Countries Having the Same or Similar Systems
MOU's may provide for the mutual assessment of the comparability of specific FDA's programs or activities with those of a foreign regulatory authority. These MOU's are similar to mutual recognition agreements (MRA's), referred to in recent trade agreements, and include equivalence agreements. FDA MOU's that provide for the mutual assessment of the comparability of a foreign regulatory system or measure are suitable when it can be determined that FDA's controls and the foreign regulatory authority's controls are comparable and are designed to provide the same level of protection. Under one form of such agreements, mutual acceptance of data and information, such as analytical findings and inspection results, may ordinarily be considered adequate for regulatory decisions. The MOU's now in place for the exchange of results of good manufacturing practices and good laboratory practices inspections are examples. Under another form of such agreements, FDA and another country may agree that their regulatory systems governing certain products are the same or similar and are designed to provide the needed level of protection, enabling each country to consider reducing the rate of inspection or sampling of imports from the other country that would otherwise be necessary.

Certification of Import/Exports
MOU's may establish certification criteria for products regulated by FDA. Historically, these MOU's have concerned products exported to the United States with inherent or consistent quality or safety problems. However, they may also involve products with a good compliance history (see Attachment A of this CPG). They may identify controls to be employed by the exporting country to assure the validity and reliability of certification. Such agreements should be designed with the intent of reducing the FDA rate of inspection or sampling that would otherwise be necessary and with the intent of providing a basis for assurance that the consumer protection objectives of FDA are being met. Certification may be shown by marks on the product, container, or entry documents or by other paper or electronic communication. An MOU based on the controls to be employed and maintained

by the exporting country to ensure that articles exported comply with FDA laws and regulations may render such certifying marks, documents, or other communication unnecessary.

Communications

Formalizing communication links facilitates the exchange of technical, scientific, and regulatory information. Technical cooperation leads to better understanding of safety and quality standards for products traded between the United States and other countries and promotes harmonization. Improved communications with foreign officials may improve FDA decision making and reduce resource expenditures for monitoring foreign made products.

POLICY:

It is the policy of FDA to pursue the development of MOU's that will further the agency's public health mission. FDA intends to enter into an MOU only with an agency of a foreign government or an international organization. The MOU should be designed to meet the following goals:

1. To enhance FDA's ability to ensure that regulated products are safe, effective, of good quality, and properly labeled;

2. To allow FDA to utilize its resources more effectively or efficiently, without compromising its ability to carry out its responsibilities; and

3. To improve communications between FDA and foreign officials concerning FDA regulated products. Further, before accepting the procedures and activities, including enforcement methods, of foreign governments as equivalent to its own, FDA will seek assurance that such activities provide the same level of product quality, safety and efficacy that is provided under the Federal Food, Drug, and Cosmetic Act (the act); the Fair Packaging and Labeling Act; the Public Health Service Act; and any other relevant law of the United States. FDA may find it necessary to confirm by on-site review or other appropriate means that the foreign government agency has the necessary authorities, product standards, capabilities, and infrastructure to successfully achieve the proposed terms of the MOU, and, therefore, that a determination of equivalence can be made. Where appropriate, FDA will publish proposed equivalence determination for comment.

FDA's criteria for deciding when to initiate consideration of developing MOU's are set forth in Attachment A of this CPG. FDA intends to review and update these criteria periodically.

Affected agency units will review the proposal for a new or revised MOU for consistency with the agency's international policy objectives and priorities before an FDA component begins substantive discussions with foreign officials about the MOU.

FDA auditing may be necessary to assure that the circumstances supporting the basis for an agreement continue to exist, whether or not the foreign government intends to conduct audits. The liaison office identified in the MOU is responsible for preparing a written evaluation. Participating FDA components will be queried by the responsible liaison office as to the overall effectiveness of the agreement, whether provisions should be added or deleted, and whether the MOU should be terminated.

Countersigned agreements are commonly referred to by FDA as "Memoranda of Understanding." However, some foreign governments have requested that such documents be titled as "Notes Verbal," "Arrangements," or "Mutual Recognition Agreements." Regardless of title, such agreements will be filed in chapter 56 of the Compliance Policy Guides Manual, and a notice of availability will be published in the FEDERAL REGISTER.

An "exchange of letters" should be used in lieu of a formal agreement when the actions contemplated require only a limited resource expenditure and do not rise to the significance of a formal agreement. For example, an exchange of letters could formalize an understanding that each agency will provide the other with documents that are available upon request to any member of the public. Each letter

should set out only the actions to be carried out by the agency signing the letter and not mutual considerations. Clearance of exchange of letters will be by the same process as used for MOU's except that, after clearance, the FDA letter may be signed by the appropriate Center or Office Director. Copies of the letters exchanged should be placed in the cooperative agreements portion of the Compliance Policy Guide Manual.

FDA's practice is to enter into MOU's for a period of 5 years. Each existing MOU should be evaluated at least once during the 5 year period of the agreement to determine whether the MOU should be modified, continued, or canceled. As part of the evaluation of an MOU, the agency may conduct independent or joint inspections or analyze imported products to evaluate the effectiveness of the MOU.

DEVELOPMENT GUIDANCE:

Developing an MOU with a foreign government requires coordination between the sponsoring center or office, the Office of Regulatory Affairs (ORA), the International Affairs Staff/Office of Health Affairs (IAS/OHA), and the Office of Policy (OP). Generally, there are three phases in the process as described below:

Stage I--Exploring Feasibility

1. The sponsoring Center or Office makes a preliminary assessment whether the proposed MOU is in line with FDA policy goals. If the sponsoring Center or Office believes that the MOU should be pursued, the Center or Office informs ORA (HFC-10) in writing and explain why it believes that the MOU should be pursued.
2. The initiating agency component provides a general description of the agreement it wishes to develop, e.g., mutual recognition of a quality assurance program, product certification, information exchange, etc.
3. The parties exchange information on laws, standards, and other requirements for subject products, inspection and sampling abilities, and analytical methodology, as appropriate.
4. On-site review of facilities, operations, and controls may be arranged.
5. If the foreign government appears not to be, and in FDA's opinion is not, capable of developing an adequate infrastructure to carry out the intended program, the sponsoring agency component will explain FDA's position in writing and suspend further action until FDA's concerns are adequately addressed. The letter addressing this issue should be reviewed by OP and IAS/OHA.

Stage II--Determining Effectiveness

1. If discussions are to continue, IAS/OHA should be notified so that appropriate notification to the Department of State (DOS) can be made.
2. The parties may consider an informal trial to gain confidence in the planned agreement. A draft MOU may be prepared along with a protocol that may provide a basis for the trial. Together these documents may include:

A. A complete description of the trial program.
B. Information regarding roles and capabilities of involved government and private organizations.
C. Certificate issuance and use procedure, if any.
D. Audit frequency and measures to be applied.
E. Description of training or information needs.

3. Whether or not there is a trial, FDA may conduct as appropriate independent or joint inspections with the foreign government, or analyze imported products to evaluate the effectiveness of the program.

Stage III--Finalizing an MOU

1. The MOU should be prepared for clearance after the substance of the MOU has been finalized, including after rulemaking, where appropriate.
2. If appropriate, instructions for auditing the agreement should be issued to field offices by the sponsoring center or office, through ORA.

ATTACHMENT A

FOOD AND DRUG ADMINISTRATION
CRITERIA FOR MEMORANDA OF UNDERSTANDING

In deciding whether to begin discussions that could lead to the development of an MOU, an agency component should consider the factors that are listed below:

Health Benefits (Including Risk Reduction) Associated With Products or Programs

FDA should consider the benefits to public health (particularly for the United States population) when it sets priorities for its international activities.

Products Imported into the United States

FDA should place a higher priority on international activities that are directed toward improving the quality, safety, or efficacy of products offered to consumers in the United States For example, FDA should give a low priority to investing resources in developing a memorandum of understanding with a foreign country that covers a product where there is little likelihood of significant exports to the United States or significant risk to the public.

History of Compliance Problems

FDA should place a higher priority on international activities directed toward remedying product defects that have been demonstrated to be previous compliance problems or where there is a demonstrated scientific basis for increased surveillance.

Comparative Costs of Alternative Programs

FDA should pursue international programs and activities that provide the greatest benefit in relation to the resources required to administer them. For example, the costs of developing, implementing, and monitoring an agreement should be weighed against the costs of higher sampling levels to obtain the same degree of confidence in rates of compliance in the absence of an agreement.

Regulatory Burden on Industry

FDA should consider the regulatory burden on industry that could be diminished by harmonization efforts. However, these activities need to be compatible with FDA's primary public health mission, the act, and other laws and regulations that FDA enforces.

U.S. Foreign Policy Objectives and Priorities of Other U.S. Government Agencies

FDA should be knowledgeable of U.S. foreign policy objectives and international programs and policies of other U.S. Government agencies and appropriately balance these interests with those of FDA's primary mission.

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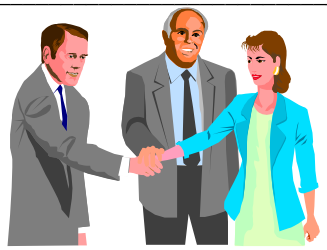


CALENDARIUM

26./27.09.00 DGGF: Jahrestagung mit Präsentationen
D-Lahnstein bei Koblenz

3./4.10.2000 BARQA: Two Day Course: Auditing
Madingleyhall, Cambridge (GRB)

18./19.10.2000 isomehr.:"Statistische Methoden Zur Validierung von Prüfverfahren"
Hotel Mercure Kongress, D-66115 Saarbrücken

26.10.2000 SPAQA: Diskussionsrunde mit Behördenvertretern
bei Hoffmann La Roche in Basel

14.-16.11.2000 isomehr.:"QMB Forum 2000" : moderne Technologien, Kommunikationstraining, Motivation, Workshops und Praxistraining
Hotel Mercure Kongress, D-66115 Saarbrücken

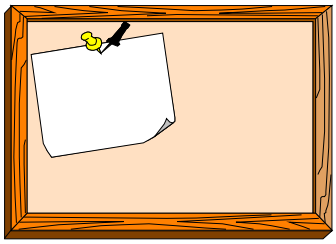
15.-17.11.2000 BARQA: 15th International Congress/23 th Annual Meeting : "Harmonisation"
Sheraton Hotel, Edinburgh, Schottland

30. 11. 2000 PTS-Training Service, Dr. R. Schnettler, Arnsberg:
" Praxistraining Computervalidierung"
Maritim Hotel, D-Würzburg

30.11./1.12.2000 Concept Heidelberg: "Inspektorentraining" Praxisworkshop für Fortgeschrittene
Maritim Rhein-Main Hotel, D- Darmstadt

1.-3.12. 2000 PTS-Training Service Dr. R. Schnettler, Arnsberg:
"5. GMP-Konferenz"
Maritim Airport Hotel, D-Hannover

5.-6.12. 2000 The Application of GLP Principles to Field Studies
UK (Contact BARQA)



SCHULUNG / AUSBILDUNG:

Anglia University:

Ein Diplom in Research Quality Assurance kann an der Anglia University in Chelmsford (UK) erworben werden. Die Ausbildung erstreckt sich in arbeitsbezogenen Forschungsprojekten aus Gebieten wie Qualitätsstandards und Management, Gute Praktiken in Sicherheits-und Wirksamkeitsprüfungen für die pharmazeutische, agrochemische und chemische Forschung und Entwicklung.

Die Ausbildung geht über 12 bis 18 Monate und die Kosten belaufen sich auf ca. £ 2600 plus VAT. Detaillierte Auskunft und Programme erteilt:

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Center for Professional Advancement:

Das Ausbildungscenter erteilt Schulung in GLP, GCP und ISO-Normen in 3 Tages- Kursen zu ca. $ 1500. Information über:

The Center for Professional Advancement
Oudezijds Voorburgwal 316A
1012 GM Amsterdam, Holland

Tel. 0031 20 638 28 06
Fax 0031 20 620 21 36

Wichtige Bookmarks fürs Internet:

CH-GLP: http:// www.glp.admin.ch
BARQA http:// www. barqa.com
BGVV: http:// www. bgvv.de
DGGF: http:// www. dggf.de
EU: http://europa.eu.int./index-de.htm
DIA: http:// www. DIAHOME.ORG
FDA: http:// www. fda.gov

EPA: http:// www. epa.gov
JSQA: http:// www. jsqa.com/english/home-e.htm
OECD: http:// www. oecd.org./ehs/glp.htm
SQA: http:// www. sqa.org
Dr. Paul Lepore: http:// www.glpguru.com
Klinkner & Partner : http:// www.klinkner.de/seminartermine.html
Center for Professional Advancement: http://www.cfpa.com
ICH: URL: www.pharmweb.net/pwmirror pw9 ifpma /ich5.html
Concept Heidelberg : http:// www.gmp-navigator.com
Wiley: http://www.interscience.wiley.com

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Deutsche GLP-Bundesstelle: Prof. Dr. H.W. Hembeck