# *Auditing Procedures for Clinical Safety and Pharmacovigilance: Enhanced Compliance, Quality and Public Health*

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*“Success depends upon previous preparation, and without such preparation there is sure to be failure.”*

– Confucius (551-479, BCE)

*“I read the news today oh, boy…”*

– John Lennon and Paul McCartney, *A Day in the Life*

# FDA Inspections for Postmarketing Compliance

*Chapter 53 - Postmarketing Surveillance and Epidemiology: Human Drugs: Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations* (September 30, 1999)[1]

- Guidance to FDA field staff for enforcing Postmarketing Adverse Drug Experience (ADE) Reporting Regulations (21 CFR 310.305, 314.80 and 314.98)

[1]***www.fda.gov/cder/aers/chapter53.htm***

# Postmarketing Safety Reporting: U.S.

- ***21 CFR 310.305***
  - Records and reports concerning adverse drug experiences (ADEs) on marketed prescription drugs without New Drug Applications (NDAs)
- ***21 CFR 314.80***
  - Postmarketing reporting of ADEs on drugs with Applications
- ***21 CFR 314.98***
  - Postmarketing reports of ADEs (and recordkeeping) per 314.80 requirements on drugs with abbreviated NDAs (ANDAs)
- ***21 CFR 600.80***
  - Postmarketing reporting of biological product AEs

# Good Clinical Practice *vs* Premarketing Clinical Safety

- Important to distinguish between GCP and premarketing clinical safety audits
  - Focus/manner of performance differ significantly

***GCP Audit***

- Evaluation of range of trial-related activities/documents covered by GCP [see audit definition in ICH Topic E6 "*Guideline for Good Clinical Practice*"[2]]
- Customarily incorporates visits to site(s) where clinical trial itself being carried out

[2]***www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB***

# GCP *vs* Premarketing Clinical Safety

## *Premarketing Clinical Safety Audit perhaps best characterized as*

"systematic and independent examination of *safety*- related activities *[e.g., investigator reporting of serious adverse events (SAEs); SAE causality assessments performed by investigators and company safety personnel]* and documents *[e.g, completed SAE forms; submitted 15-day investigational new drug (IND) safety reports*; *annual reports]* to determine whether the trial *safety* data were recorded, analyzed and accurately reported according to the protocol, sponsor's…SOPs, and the applicable regulatory requirement(s)."[2]

***NB*: Italicized and bracketed words added by author**

# GCP *vs* Premarketing Clinical Safety

- Premarketing safety auditor generally doesn't visit clinical trial sites
  - Performs site visit(s) to office(s) where safety department personnel are located, and evaluates *their*
    - SOPs
    - Computerized system capabilities
    - Performance of case assessment
    - Other safety-related responsibilities
- Premarketing clinical safety auditing discussed here and as performed by safety/vigilance specialists does NOT refer to evaluation for compliance with GCP standards

# FDA Inspections for Postmarketing Compliance[1]

## *ADE Report Verification*

- Determine whether all reportable ADEs (in particular serious unlabeled ADEs) submitted to FDA
- Check company SOPs that describe ADE investigation, evaluation and submission, and determine adherence
- Check complaint files for any ADE complaints not submitted as an ADE to FDA
- Determine timely submission of both 15-day alert reports and periodic reports, per required regulatory reporting timeframes

# FDA Inspections for Postmarketing Compliance[1]

## *Standard Operating Procedures (SOPs)*

- *211.198*: Required written procedures for product complaints, including "provisions for determining whether a complaint represents a serious and unexpected ADE"
- *314.80(b); 310.305 (a); applicable under 314.98*: Any person subject to postmarketing ADE reporting requirements must develop written procedures for
  - Surveillance
  - Receipt
  - Evaluation
  - Reporting of postmarketing ADE information to FDA*

**same for postmarketing AEs w/biological products (600.80)*

# FDA Inspections for Postmarketing Compliance: SOPs

- Regulations do **not** specify what is required for written procedures
- Inspectional Guidance:
  - SOPs "should be adequate to ensure that ADEs are properly evaluated and are reported to the agency as required by regulations"[1]

# FDA Inspections for Postmarketing Compliance: SOPs[1]

- Guidance recommendations for determining SOP adequacy (*NB*: not all-inclusive)
  - Designated office with final authority/responsibility for performing ADE regulation-mandated duties
    - Minimum qualifications of person(s) investigating/evaluating ADE reports
  - Description of how ADE reports are tracked, investigated and evaluated
  - Description of control procedures to ensure proper investigation (including detailed follow-up steps), evaluation and submission of all required ADE reports
  - Dated and signed by responsible company official

# FDA Proposed Rule: The "Tome"

***"Safety Reporting Requirements for Human Drug and Biological Products: Proposed Rule"***

***March 14, 2003***

Federal Register Volume 68, No. 50, 12405-12497[3]

– *Comment period closed October 14, 2003*

[3]***www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf***

# FDA Proposed Rule[3] and SOPs

***Proposed amendments to current postmarketing regulatory provisions for written procedures***

- Adding requirement to "maintain" beyond need to "develop"
  - Seen as clarification that records of written procedures must be maintained for FDA review
  - Review either upon agency request (proposed 310.305, 314.80, 600.80) or during inspections
  - Replace "adverse drug experiences" with "postmarketing safety information"

# Medical Devices and SOPs

- Compared to current and proposed drug/biologics regulations, applicable FDA Medical Device Reporting (MDR) regulations offer greater specification as to required written procedures
  - ***CFR 803.17:*** User facilities, importers and manufacturers "shall develop, maintain, and implement written MDR procedures" for:
    - "Internal systems that provide for:"
      - "Timely and effective identification, communication, and evaluation of events that may be subject to medical device reporting requirements;"
      - "Standardized review process/procedure for determining when an event meets the criteria for reporting under this part" of the regulation;
      - "Timely transmission of complete medical device reports to FDA and/or manufacturers;"[4]

# Medical Devices and SOPs

- ***CFR 803.17***: User facilities, importers and manufacturers "shall develop, maintain, and implement written MDR procedures" for:
  - "Documentation and recordkeeping requirements for:"
    - "Information that was evaluated to determine if an event was reportable;"
    - "All medical device reports and information submitted to FDA and manufacturers;"
    - "Any information that was evaluated for the purpose of preparing the submission of annual reports; and"
    - "Systems that ensure access to information that facilitates timely followup and inspection by FDA."[4]

[4]***www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm***

# FDA Inspections for Postmarketing Compliance[1]

## *Personnel Qualifications*

- *211.25*: Mandated that investigation and evaluation of ADEs be performed by "qualified personnel"
- "If serious deficiencies are found during the inspection, obtain copies of the procedures and determine personnel qualifications and staffing, especially if the firm utilizes computerized reporting."

# FDA Inspections for Postmarketing Compliance

## *Proposed Rule*[3]

- ***Active Query***: "health care professional (*e.g.*, physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training)" required to speak directly to initial SADR[SAR]/medication error reporter if outcome or minimum data set not determinable on first receipt by company
  - Entails (at minimum) "focused line of questioning" to ascertain "clinically relevant information"

# FDA Proposed Rule

## [*310.305, 314.80, 314.98, 600.80*][3]

### *Expedited Reporting: 15 calendar days*

- Information sufficient to consider changes in administration of product, based on appropriate medical judgment
  - Significant unexpected *in vitro*, animal or human (clinical; epidemiological) study safety findings or aggregate data from studies suggesting significant risk to humans (e.g., mutagenicity, teratogenicity or carcinogenicity)

# FDA Inspections for Postmarketing Compliance[1]

## *FDA-483, Inspectional Observations*

- Deviations from ADE regulations documented
  - Failure in submission of ADE reports
  - Failure to expeditiously investigate ADE
  - Information not accurate
  - Disclosure of available information incomplete
  - ***Lack of SOPs***
  - Failure of adherence to reporting requirements

*NB: While questions on medical judgment or evaluation should be discussed with company management, not to be included in FDA-483*

# FDA Inspections for Postmarketing Compliance[1]

## *Warning Letter*

- Considered when "significant deviations or violations exist and corrections may reasonably be expected by the firm's management"
  - Failure to submit reports for serious, unexpected ADEs
  - 15-day reports submitted in periodic report and not as separate 15-day report (applies to foreign & domestic data from scientific literature, postmarketing studies or spontaneous reports)

# FDA Inspections for Postmarketing Compliance[1]

## *Warning Letter*

- Inaccurate and/or incomplete 15-day reports
- 15-day reports not submitted on time
- Repeated or deliberate failure in maintenance or submission of periodic reports in compliance with reporting requirements

# FDA Inspections for Postmarketing Compliance[1]

## *Warning Letter*

- Failure to conduct “prompt and adequate” follow-up of outcome of serious, unexpected ADEs
- Failure to maintain ADE records or have written SOPs for investigating ADEs
- Failure to submit 15-day postmarketing study report “where there is a reasonable possibility that the drug caused the adverse drug experience”

# FDA Inspections for Postmarketing Compliance[1]

## *Injunction*

- Considered when follow-up inspection/investigation demonstrates ongoing pattern of major deviations despite previous FDA attempts to gain compliance
- May be warranted when
  - ***Repeated company failures to submit mandated serious ADEs OR***
  - ***Failure to act to ensure completeness and accuracy of required serious ADE reports***

# EU Inspections for Postmarketing Compliance

- 2001 EMEA *"Position Paper on Compliance with Pharmacovigilance Regulatory Obligations"*[5]
  - Marketing Authorisation Holder (MAH) needs to have "qualified person" responsible for pharmacovigilance (QPPV) within European Economic Area (EEA)
  - "establishment of a system for the collection, preparation and submission of expedited adverse drug reactions (ADRs) and periodic safety update reports to competent authorities"
  - Full guidance as to functions to be published in Volume IX of *The Rules Governing Medicinal Products In The EU*

[5]***www.emea.eu.int/pdfs/human/phvwp/161801en.pdf***

# EU Guidelines on Pharmacovigilance

- ***December 2005***: EC launched public consultation on Volume 9A, *Guidelines on Pharmacovigilance for Medicinal Products for Human Use*[6]
  - Certain sections missing, including Part 1, Section 2: *Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections*
- ***March 2006***: *Guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections (draft)*[7] for public consultation

[6]***http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/12-05/ draft_of_ volume_9a _12_2005.pdf***

[7]***http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/02_2006/v9_ compliance-guideline_pubcons_03-2006.pdf***

# EU Guidelines on Pharmacovigilance

## April 2007

***Final Volume 9A of The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use*[8]**

[8] *http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/ vol9A_ 2007-04.pdf*

*"In the fields of observation, chance favors only the mind that is prepared."*

– Louis Pasteur (1822-1895), quoted by Rene Vallery-Radot in *The Life of Pasteur*, 1927

*"In this bright future you can't forget your past..."*

– V. Ford, *No Woman, No Cry* [Bob Marley and the Wailers]

# EU Inspections for Postmarketing Compliance

- ***March 2006***: UK's Medicines and Healthcare products Regulatory Agency releases *MHRA Statutory Pharmacovigilance Inspection*[9] guidance
  - Presents information to help companies with preparation of Summary of Pharmacovigilance Systems (SPS)
- SPS used by MHRA's Pharmacovigilance Inspectorate to assist in planning and preparation for PV system inspections
- Document provides useful guidance as to material that will be reviewed during such an inspection

[9]***www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con2018030.pdf***

# MHRA SPS Guidance[9]

- Documents that may be requested prior to or during MHRA inspection include:
  - CVs, job descriptions and training records for interviewees
  - Organisation charts/organograms (with names, job titles)
  - Procedural documents (e.g. SOPs, working instructions, etc.)
  - Individual ADR cases files and CIOMS reports
  - PSURs
  - Contracts and agreements with third parties
  - Risk Management Plans
  - Meeting minutes
  - Line listings of ADR reports

# MHRA SPS Guidance[9]

- Following inspection, view SPS as living document, as up-to-date SPS will be requested by MHRA prior to routine re-inspection
  - Information contained within SPS may also be requested by inspectors from other EU agencies
- MHRA aims to allow companies at least 6 weeks to complete and return SPS (timeframe may be shorter)
  - Should be succinct and preferably no more than 25 pages (excluding appendices)
  - SPS should be submitted electronically (e-mail or CD-ROM) along with paper copy for each inspector
  - Wherever possible, simple plans, outline drawings and schematics can be used for illustration purposes

# MHRA SPS Guidance[9]

## *Appendices*

- Key personnel
- Company's product portfolio (licensed in UK)
- Studies
- Quality Management System
- *Regulatory reporting*: compliance statistics
- Third Party Agreements
  - Licensing partners (co-licensing; co-marketing; distribution; licensing-in; licensing-out)
  - Other service providers (e.g., contract organizations providing medical information or PV service)
- Product-related safety issues

# MHRA SPS Guidance[9]

## *Document requests to be submitted with SPS*

- "Procedural documents" (SOPs, working instructions, etc.) relating to these activities:
  - Case processing of spontaneous ADR reports
  - Case processing of clinical trial SAE reports
  - Follow-up of individual cases
  - Regulatory reporting of expedited reports to MHRA and EMEA
  - Monitoring of regulatory compliance with 7- and 15-day requirements
  - PSUR preparation and submission
  - Signal detection/trend analysis
  - Enquiry handling by medical information function in UK

*"At a cardiac arrest, the first procedure is to take your own pulse."*

– Samuel Shem, M.D, *The House of God*. New York: Richard Marek Publishers;1978:376

# Volume 9A[8]

- Sets out framework for implementation, in context of revised pharmaceutical legislation, of monitoring of compliance with PV obligations and inspections
- In same context, sets out information to be supplied in Marketing Authorisation Application (MAA) giving detailed description of PV system of MAH and proof that MAH has services of QPPV
- Guideline applicable for any medicinal product, whatever marketing authorisation procedure used
- Inspection process described focuses on Centrally Authorised Products (CAPs) -- however, principles may be generally applicable

# Volume 9A[8]

## *Detailed Description of PV System to Be Included in MAA*

- Where appropriate, detailed description of risk management system applicant will introduce also required
- Proof must be provided of QPPV services and necessary means for notification of AR occuring in EC or 3rd country
- Detailed description should comprise overview, with information on key elements
  - When aspects particular to product rather than main PV system, should be indicated in product-specific addendum

# Volume 9A:
## *Detailed Description of PV System*[8]

- Clear written procedures essential
- List provided of topics usually covered by written procedures
- PV system description should indicate which topics have associated written procedures in place
  - Should not list procedure titles, as one or more topics may have one or more procedures, depending on complexity and company organization
  - Ensure QC and review are appropriately addressed in various processes and reflected in relevant procedures

# Volume 9A:
## *Written Procedures*[8]

- Activities of QPPV and applicable back-up procedure in their absence
- Collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting of individual case safety reports (ICSRs)

# Volume 9A: *Written Procedures*[8]

- Reports of different type:
  - Organized data collection schemes (solicited), unsolicited, clinical trials, literature
  - Ensure capture of reports from different sources
    - EEA and third countries
    - Healthcare professionals
    - Sales and marketing personnel, and other MAH personnel
    - Licensing partners
    - Competent Authorities
    - Compassionate use
    - Patients
    - Other

# Volume 9A:
## *Written Procedures*[8]

- Follow-up of reports for missing information and information on progress and outcome of case(s)
- Detection of duplicate reports
- Expedited reporting
- Electronic reporting
- Periodic Safety Update Reports (PSURs)
  - Preparation, processing, quality control, review (including medical review) and reporting

# Volume 9A:
# *Written Procedures*[8]

***Global PV Activities Applying to All Products***

- Continuous monitoring of safety profile of authorized medical products (includes product-specific RM systems and PV planning)
  - Signal generation and review
  - Risk-benefit assessment
  - Reporting and communication notifying Competent Authorities and HCPs of changes to risk-benefit balance of products, etc.

# Volume 9A:
## *Written Procedures*[8]

- Interaction between safety issues and product defects
- Responses to requests for information from regulatory authorities
- Handling of urgent safety restrictions and safety variations
- Meeting commitments to Competent Authorities in relation to marketing authorization

# Volume 9A:
## *Written Procedures*[8]

- Global PV activities applying to all products:
  - Signal detection
  - Evaluation
  - Reporting
  - Communication, etc.
- Management/use of databases or other recording systems
- Internal audit of PV system
- Training
- Archiving

*“You don’t need a weatherman to know which way the wind blows...”*

– Bob Dylan, *Subterranean Homesick Blues*

# FDA Inspections for Postmarketing Compliance

## *SOP Evaluation*

- In recent years pharmaceutical compliance inspection has evolved from simply confirming presence of SOPs to full evaluation of whether:
  - SOPs adequate to ensure compliance
  - Safety personnel have been trained on SOPs
  - Safety personnel are following SOPs

*"I shall not today attempt further to define the kinds of material...But I know it when I see it…"*

– U.S. Supreme Court Justice Potter Stewart (1915-1985), concurrence in *Jacobellis v. Ohio [June 22, 1964]*

# Lessons Learned: SOPs

- Based on performance of CSP-related audits internationally (including US, Canada and EU)
- Globally applicable
  - Aspects/deficiencies common across companies and medical products
  - Desired outcomes of clinical safety and postmarketing vigilance-related SOPs common across countries and regions

*“It all looks fine to the naked eye,*
*But it don’t really happen that way at all...”*

– Peter Townshend, *Naked Eye*

# Lessons Learned: SOPs

*SOPs should both outline procedures and drive performance of clinical safety and vigilance*

- SOPs outline how compliance with regulatory and company requirements is to be achieved
- Ongoing self-assessment and auditing of SOPs, and processes/procedures themselves, crucial to company safety, vigilance and risk management responsibilities
  - As time-sensitive documents, SOPs necessitate periodic review and updating based on new techniques, regulatory changes and company needs

# Lessons Learned: SOPs

*Differentiate AE report handling, evaluation, submission and tracking*

- Delineate responsible individuals/procedures for each
  - Ensure qualifications of personnel match functions performed
- Perform “walk-through” of processes, and assess for possible ways in which mistakes can occur
  - Evaluate processes for redundancies/Quality Assurance measures to minimize possibility of errors being missed

# Lessons Learned: SOPs

*Consider ALL possible sources of AE reports when drafting SOPs*

- Multiple sources of AE reports (internal and external)
  - Delineate mechanisms to ensure timely transmittal of reports to Safety department from ALL possible sources, e.g.,
    - Legal
    - Marketing (sales force)
    - Quality Assurance (product complaints)

***NB***: Ensure that ALL ongoing studies (including marketing) have mechanisms to capture/transmit AE reports to Safety department

# Lessons Learned: SOPs

*Coordination between Safety and QA departments maximizes ascertainment of AEs associated with product complaints*

- Two major routes for product complaints/AE reports including medication errors (*actual; potential*)
- Consistency between departmental practices and SOPs of necessity
  - Consider periodic checks to ensure appropriate triage of reports in both directions

# Lessons Learned: SOPs

*Delineate steps involved in investigation of AE reports*

- More detail provided as to assessment and follow-up to be performed based upon AE
  - Seriousness
  - Expectedness
  - Public health impact,

  the better
- Utilize current knowledge such as regulatory documents (including guidances and ICH guidelines), CIOMS recommendations and other appropriate literature

# Guidance for Industry: FDA

March 2001: *"Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines"* [draft][10]

- Upon Proposed Rule finalization, guidance will be updated with respect to new requirements and finalized to replace earlier guidances

August 1997: *"Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products -- Clarification of What to Report"*[10]

March 1992: *"Guideline for Postmarketing Reporting of Adverse Drug Experiences"*[10]

[10] ***www.fda.gov/medwatch/report/mfg.htm***

# Active Query and Case Follow-Up

- Consider proposed prioritization scale[11] to establish timeframes/procedures
  - *First*: Serious/unexpected (List C, *incl.* "special interest" cases)
    - Cases of "special interest" include events under active monitoring due to identified signal
  - *Second*: Serious/expected and non-serious/unexpected (List B)
  - *Third*: Non-serious/expected (List A)

Serious cases: should continue follow-up until outcome established or condition stabilized [*consistent with Proposed Rule*]

[11]***Report of CIOMS Working Group V. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2001***

# Assessing Postmarketing Safety Data

- FDA's risk minimization guidances[12] could be utilized, e.g.,
  - "*Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*" guidance[13]
    - Practical advice on identification and description of safety signals, including how to develop case series and use of observational studies to investigate signal
    - Applicable for incorporation into appropriate company practices and related documents

[12]***www.fda.gov/bbs/topics/news/2005/NEW01169.html***
[13]***www.fda.gov/cder/guidance/6359OCC.pdf***

# Caveats

- ***Agency Guidances***: While FDA guidances "represent the Agency's current thinking on a particular subject"[14], neither they nor any other regulatory agency's guidances supercede existing regulations
  - FDA: "an alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both"[14]
- ***ICH Guidelines*** have no regulatory force until incorporated into domestic regulations or other appropriate measures[15]
- ***CIOMS*** is international, non-governmental forum[16] – while recommendations of working groups have been incorporated into national regulations, not regulatory body and no formal regulatory status

[14]***www.fda.gov/cder/guidance/index.htm***
[15]***www.ich.org/cache/compo/276-254-1.html***
[16]***www.cioms.ch/frame_what_is_cioms.htm***

# Lessons Learned: SOPs

***Provide enough detail to minimize ambiguity or confusion as to individual responsibilities***

- Processes should be sufficiently clear so that upon SOP/other procedural document review
  - Qualified designee can fulfill responsibilities in absence of personnel usually assigned to task
  - Outside evaluator (auditor; inspector) can readily understand processes
- SOPs/other procedural documents should NOT need to be interpreted

# Lessons Learned: SOPs

- Delineate specific time limits for actions to be performed
  - ***Calendar days*** invariant; ***business days*** are not
    - Calendar days generally preferred - business days can be used if consistent/compliant with regulatory timeframes
    - Anticipate “worst case scenario” (e.g., AE report receipt before extended national holiday)
  - Do NOT establish timeframes so stringent that needless non-compliance with SOPs likely to occur
    - Consider need for reports to be complete as possible for international transmission and regulatory submission

# Lessons Learned: SOPs

*Use flowcharts or other graphical displays (to degree possible) to illustrate steps in text*

- Examples include decisional steps taken in case triage, evaluation, follow-up and report submission
  - Timeframes chosen in service of complying with
    - Local (national) regulatory reporting requirements
    - International regulatory reporting requirements (company multinational)
    - Company requirements

  should be clearly specified to reinforce text and facilitate review
- Keep as simple as possible

# Lessons Learned: SOPs

*If entities (e.g., process; form; procedural step) used in clinical safety and vigilance functions are not denoted in SOPs, THEY DO NOT EXIST*

- SOPs should accurately reflect how AE reports are handled, assessed, submitted and tracked, thus anything used in service should be noted
  - If question as to inclusion of entity in SOPs, strongly question/ consider whether it should continue to be utilized

# Lessons Learned: SOPs

*If an SOP is inadequate, training of personnel based on the SOP will be inadequate*

***("Fruit of the Poisonous Tree")***

- Staff training on SOPs deficient with respect to detail, clarity, completeness, regulatory requirements or other important aspects will be compromised
- SOPs should be crafted with consideration as to their utility as both procedural AND training documents

# Lessons Learned: SOPs

*If company multinational, local and global SOPs must be consistent*

- *Global SOPs* should provide clear timeframes for transmission/distribution of AE information
  - Enable local affiliates to meet regulatory requirements for submission of foreign reports
- *Local SOPs* should provide clear timeframes for steps taken to fulfill local (national) regulatory requirements
  - Ensure timely global distribution of appropriate local AE reports to meet other national/international regulatory requirements

# Lessons Learned: SOPs

*ALL SOPs involving functions of clinical safety and vigilance must be consistent*

- *Internal*: Safety department SOPs, e.g.,
  - Timeframes for actions
  - Job titles/qualifications
  - Application of current relevant regulations
- *External*: Applicable SOPs of departments who work with Safety (e.g., QA; Clinical Research; Regulatory)
  - Points of contact/information sharing
  - Consider joint review/sign-off

# Lessons Learned: SOPs

## *Special Considerations*

- Work Practices/Guidances/Operating Instructions, *et al.*
  - Consider subject to inspection/review
  - Be sure as to necessity
  - Need to be consistent with SOPs, with defined relationship
  - Periodic review?
- Document control
  - Maintain all AE records, including "raw data" (Warning Letter interpreted paper upon which AE information obtained by phone was written and entered into database as such)

# Ongoing Assessment of AE Report-Related Functions

- Should exist on several levels:
  - Levels of review/QA in day-to-day AE report-related functions
  - Spot checks of functions
    - Remedial action taken based on results
  - Training of personnel, both on periodic and *ad hoc* basis
    - Documentation critical
  - Auditing of processes/procedures by personnel external to department
    - Remedial actions taken, followed-up and documented

*“Luck is the residue of design.”*

– Branch Rickey (1881-1965), Member of Baseball Hall of Fame [attributed]

# Ongoing Assessment of AE Report-Related Functions

- Training/documentation of training does not only apply to designated safety personnel, but to ALL company employees/contractors who might be recipients of AE reports
  - Essentially all employees/contractors, including security personnel and sales force
  - Systematic training of monitors, investigators and other clinical trial/study personnel of essence

# Enhancement of Vigilance Through Ongoing Assessment

- If procedures designed to ensure timely assessment, processing and submission of AE reports in place and working effectively
  - Higher quality data becomes available
  - Appropriate resources can be applied to AEs of special concern
- Establishment of satisfactory regulatory compliance enables focus to be on vigilance and risk management

# Warning Letters and SOP Deficiencies

- Procedures not developed as required by 314.80(b), 314.98(a), and 310.305(a) - specific lack of procedures for
  - Follow-up investigations
  - Adequate completion of FDA Form 3500A
  - Maintenance of records to ensure timely submission of expedited (15-day) reports
  - Evaluation of AE data for serious outcome and event expectedness

# Warning Letters and SOP Deficiencies

- Among deficiencies in compliance with 314.80(b) in other recent Warning Letters:
  - Lack of inclusion of procedures to ensure
    - Prompt investigation of 15-day reports
    - Submission of follow-up reports within 15 days of new information receipt
    - Maintenance of records of unsuccessful attempts to obtain further information
  - Lack of adequate procedures for information exchange with another contracted firm
  - Lack of procedures for medical evaluation of AEs

# Warning Letters and SOP Deficiencies

- None of the written procedures
  - Outlined steps related to surveillance/receipt of postmarketing ADE reports (oral or written) by marketing/distributing firm contracted to perform initial ADE report collection
  - Included procedures on how company performs surveillance/tracks reports handled by contracted firm
  - Included procedures on how ADE reports were to be received from contracted firm
- Inadequate written procedures
  - Wrong applicable regulation cited
  - Stated document retention policy out of compliance with regulatory recordkeeping requirements

# Warning Letters and SOP Deficiencies

- Among IRB deficiencies in recent Warning Letters:
  - Failure to maintain and follow adequate written procedures for conducting initial and continuing review of research [56.108(a) and 56.115(a)]
  - Written procedures for initial review did not adequately reflect regulatory requirements for obtaining informed consent [56.108(a)(1)].
  - Failure to prepare, maintain, and follow adequate written procedures for conducting initial and continuing review of research [56.108(a) and (b); 56.115(a)(6)]
  - Failure to have written procedure in place to ensure prompt reporting to FDA of any unanticipated problems involving risks to human subjects or others [56.108(b)(1)]

# Summary

- Use regulatory agency transparency in postmarketing safety compliance to company's advantage
  - *"Forewarned forearmed"*
    - Miguel de Cervantes (1547-1616), *Don Quixote de la Mancha, part II, book III, chapter 10, page 502 [1605-1615]*
- SOPs are compliance AND educational documents
- Processes/procedures should be as detailed and clear as possible (avoid ambiguity or need to interpret)
- Timeframes should be spelled out explicitly

# Summary

- Assessment of processes/procedures should be ongoing and multifaceted
- Coordination between relevant departments critical
- Think locally AND globally
- Training, training, training
- Consistency, consistency, consistency
- Good postmarketing AE report compliance enhances medical product vigilance and risk management

# Future Directions

## *Perceived need for*

- Greater guidance from regulatory agencies as to SOPs
- Establishing formal venues for clinical safety/ postmarketing vigilance auditing and inspectional personnel to
  - Share experiences
  - Highlight areas in which enhanced clarification, examination and harmonization would be of significant benefit
- Relevant literature

*"What we're saying today is that you're either part of the solution or you're part of the problem."*

– Eldridge Cleaver (b. 1935), speech in San Francisco, 1968; cited in *Eldridge Cleaver, Post Prison Writings and Speeches (ed. R. Scheer), 1969*