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)

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

1www.fda.gov/cder/aers/chapter53.htm

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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

²www.ich.org/MediaServer.jserv?@_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).”

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
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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

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**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)

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• 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”

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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

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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, 12405-12497³

– Comment period closed October 14, 2003

³www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf
FDA Proposed Rule³ 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;”

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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.”

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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.”
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Proposed Rule

• **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)
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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

**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)
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*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

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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”
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**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
  - Failure to act to ensure completeness and accuracy of required serious ADE reports

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EU Inspections for Postmarketing Compliance

• 2001 EMEA “Position Paper on Compliance with Pharmacovigilance Regulatory Obligations”
  – 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

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


\(^7\)http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/02_2006/v9_compliance-guideline_pubcons_03-2006.pdf
EU Guidelines on Pharmacovigilance

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“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](http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con2018030.pdf)
MHRA SPS Guidance

• 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

- 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

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

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MHRA SPS Guidance

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.”

Volume 9A

- 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

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 occurring 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

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Volume 9A:
Detailed Description of PV System

- 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

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Volume 9A: Written Procedures

• 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

• 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

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Volume 9A: Written Procedures

- 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

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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

- 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

- 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

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“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]

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


March 1992: “Guideline for Postmarketing Reporting of Adverse Drug Experiences”

10 [www.fda.gov/medwatch/report/mfg.htm]
Active Query and Case Follow-Up

• Consider proposed prioritization scale\textsuperscript{11} to establish timeframes/procedures
  
  – \textit{First}: Serious/unexpected (List C, \textit{incl.} “special interest” cases)
    
    • Cases of “special interest” include events under active monitoring due to identified signal
  
  – \textit{Second}: Serious/expected and non-serious/unexpected (List B)
  
  – \textit{Third}: Non-serious/expected (List A)

  \underline{Serious cases:} should continue follow-up until outcome established or condition stabilized [\textit{consistent with Proposed Rule}]

\textsuperscript{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\textsuperscript{12} could be utilized, e.g.,

  – “Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment” guidance\textsuperscript{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

\textsuperscript{12}www.fda.gov/bbs/topics/news/2005/NEW01169.html
\textsuperscript{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](http://www.fda.gov/cder/guidance/index.htm)


\(^{16}\) [www.cioms.ch/frame_what_is_cioms.htm](http://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

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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

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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

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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

  – 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

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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

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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

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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

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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

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“What we’re saying today is that you’re either part of the solution or you’re part of the problem.”