GCP Data Quality for Early Clinical Development

Edwin P. Rock1, Vernette J. Molloy2, and Jeffrey S. Humphrey3

Abstract

Good Clinical Practice (GCP) provides an internationally accepted standard to ensure subject safety and data quality in clinical trials. Much of GCP parallels ethical considerations that have accumulated in successive versions of the World Medical Association's Declaration of Helsinki. This document advocates for preservation of rights, safety, and well-being of human study participants. By contrast, GCP data quality provisions follow from evolution in the United States drug regulatory system during the 1960s. Evidence of fraudulent or otherwise biased data-gathering ultimately led to U.S. Food and Drug Administration (FDA) data integrity regulations that were subsequently embraced as GCP principles in the Declaration of Helsinki. This manuscript summarizes GCP data quality provisions and describes practices that clinical site investigators can adopt to comply with these principles and to prevent adverse audit findings in the event of a regulatory inspection. Clin Cancer Res; 16(6); 1756–63. ©2010 AACR.

The International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use was established in 1990 to rationalize approaches to medicines regulation among Europe, Japan, and the United States. Expert Working Groups have subsequently generated scores of advisory Guidelines on quality, safety, efficacy, and multidisciplinary topics. Guideline E6 on Good Clinical Practice (GCP) was approved by the ICH Steering Committee in May 1996 (Table 1). This document provides an internationally accepted standard of ethical and scientific quality for the design, conduct, recording, and reporting of clinical trials. Compliance with GCP provides assurance that study subject safety is protected and that trial data are credible.

Most GCP principles follow directly from ethics described in the Declaration of Helsinki, focusing on preservation of rights, safety, and well-being of study subjects. Academic investigators typically understand these principles well, consistent with GCP Principle 8 that requires documented training on these topics. Yet the importance and details of Principle 10 on data quality may be less well known. Clinical research data quality is important to clinical investigators for two reasons. First, data integrity fundamentals at the site level overlap closely with good medical record keeping, so the burden of compliance may be negligible if good quality medical records are already being kept. Second, data quality compliance either avoids or reduces problems during study monitoring and adverse audit findings from a regulatory inspection.

This article summarizes the history of GCP data integrity, the standards themselves, and principles to help academic investigators ensure that their research complies with both regulations and ethical expectations. The intent is to provide early phase clinical researchers with distilled information on generation and maintenance of high-quality source documents regardless of the extent of external monitoring. This article is not intended to be exhaustive. Investigators or academic institutions seeking to sponsor and develop their own study products should enlist qualified help and consider additional sources of information (1–4).

Data Quality Origins

Clinical research ethics have evolved incrementally, beginning with the 1947 Nuremberg Code, which emphasized the importance of voluntary consent and protection of subjects in medical experiments. Starting in 1964, successive versions of the World Medical Association’s Declaration of Helsinki have integrated emerging refinements, such as for informed consent, prospective research design, independent protocol review, confidentiality, and data integrity (5, 6). By contrast with GCP’s ethical antecedents, its data quality provisions follow from a key transition in drug assessment during the latter half of the 20th century. Therapeutic evaluation of new medicines evolved from individual physicians’ judgments on the basis of case reports to scientific evaluation based on statistically valid study designs (7). These events shifted the locus of power in drug development from largely autonomous industry participants to a science-based, government-controlled regulatory system. With this shift, demonstration of data integrity became an integral component of a medicine’s marketing authorization.
A key milestone in this evolution was passage in 1962 of the U.S. Federal Harris-Kefauver Amendments to the 1938 Food, Drug, and Cosmetic Act (FD&C; ref. 8). Details are provided in the Appendix. Soon after passage of the 1962 Harris-Kefauver Amendments, FDA implemented investigational new drug (IND) regulations. These rules are “in all phases of investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to

**Table 1. Abridged principles of ICH good clinical practice**

<table>
<thead>
<tr>
<th>No.</th>
<th>Principle</th>
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<tbody>
<tr>
<td>1</td>
<td>Clinical trials should be conducted in accordance with the Declaration of Helsinki.</td>
</tr>
<tr>
<td>2</td>
<td>A trial should proceed only if the anticipated benefits justify the risks.</td>
</tr>
<tr>
<td>3</td>
<td>Rights, safety, and well-being of trial subjects prevail over interests of science.</td>
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<tr>
<td>4</td>
<td>Available nonclinical and clinical data should be adequate to support the trial.</td>
</tr>
<tr>
<td>5</td>
<td>Trials should be described in a clear, detailed, scientifically sound protocol.</td>
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<tr>
<td>6</td>
<td>Clinical trial protocols should undergo local independent ethical review.</td>
</tr>
<tr>
<td>7</td>
<td>Subjects should receive medical care from an appropriately qualified clinician.</td>
</tr>
<tr>
<td>8</td>
<td>Trial staff should be qualified by education, training, and experience.</td>
</tr>
<tr>
<td>9</td>
<td>Informed consent should be obtained from each subject prior to trial participation.</td>
</tr>
<tr>
<td>10</td>
<td>Trial information is recorded, handled, and stored to allow accurate reporting, interpretation and verification.</td>
</tr>
<tr>
<td>11</td>
<td>Subject confidentiality should be protected.</td>
</tr>
<tr>
<td>12</td>
<td>Investigational products are manufactured, handled, and stored using good manufacturing practice (GMP).</td>
</tr>
<tr>
<td>13</td>
<td>Systems and procedures to assure trial quality should be implemented.</td>
</tr>
</tbody>
</table>


**Table 2. Principal investigator responsibilities**

<table>
<thead>
<tr>
<th>No.</th>
<th>Responsibility</th>
<th>Components</th>
</tr>
</thead>
</table>
| 1   | Use good clinical judgment | • Do no harm  
• Review abnormal results  
• Decide if early study termination is needed |
| 2   | Confirm eligibility | • Review inclusion and exclusion criteria |
| 3   | Confirm informed consent | • Use an IRB-approved informed consent form  
• Conduct and/or supervise consent process |
| 4   | Adhere to protocol | • Address subject and staff compliance |
| 5   | Document adequately | • Compile key data to medical records |
| 6   | Manage data | • Ensure CRFs match medical records |
| 7   | Account for study product | • Maintain accurate, complete documentation of study product shipment, storage, dispensation, and administration |
| 8   | Manage documents | • Organize records to ease document retrieval |
| 9   | Manage staff | • Delegate responsibility where appropriate  
• Supervise |
| 10  | Communicate with IRB | • Obtain approval for study  
• Obtain approval of informed consent  
• Notify of serious adverse events  
• Notify of significant news, e.g., study hold |
| 11  | Maintain credentials | • Keep accurate, up-to-date, information-rich Curriculum vitae for each research clinician |

NOTE: Adapted from Mackintosh et al. (20).
help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety." (9). ICH GCP Principle 10 and data quality provisions extend directly from these regulations. Hence data integrity became integral to avoidance of biased results following from either undetected quality issues or outright fraud.

**Investigator Responsibilities and Source Documents**

Clinical study investigators are responsible for diverse tasks associated with the conduct of human drug trials (see Table 2). Regulations mandate that investigators maintain up-to-date records of investigator and subinvestigator qualifications to conduct the trial (10). These qualifications include education, training, and experience. Clinicians must be clinically qualified. Training may be from diverse sources, and there is no formal qualification. Although investigator certification by a private entity has become available, currently a majority of investigators hold no such certificate (11). Experience is similarly undefined, so rationale for the training method used should be included in records kept. The investigator must also maintain a list of qualified persons to whom trial-related duties have been delegated, as documented on the Delegation of Authority form (12). In addition, a written agreement between investigator and sponsor on financial aspects of the trial should be documented and retained at the clinical site in a location other than the study binder. Finally, protocol-specific training of study staff is required with documentation maintained in the site’s study binder.

Investigators are also ultimately responsible for creation and management of source documents at their site. These documents are retained at the study site to confirm existence of study subjects and to substantiate trial data integrity (13). Source documents include original records (or certified copies) containing source data, which is the raw data on clinical findings, observations, and other study activities needed for trial evaluation and/or reconstruction (14). Source data include what is written directly into the medical record, such as progress notes, as well as what is written into study-specific source document forms that are considered part of the medical record. Examples include but are not limited to the informed consent narrative, demographic information, medical history and physical exam notes, laboratory results, and information on study drug dispensation and accountability. Source documents thus serve both as the basis for a subject’s

**Table 3. Inspection findings from FDA Warning Letters, 2002 to 2009**

<table>
<thead>
<tr>
<th>No.</th>
<th>Audit finding</th>
<th>Example</th>
<th>Source document recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Incomplete medical history</td>
<td>Medical history does not support protocol-required documentation of failure of at least two prior chemotherapy regimens</td>
<td>Use progress note template to capture protocol-required histories in addition to standard clinic H&amp;P data.</td>
</tr>
<tr>
<td>2</td>
<td>Source documents are missing</td>
<td>Prior bone marrow biopsy results not verifiable</td>
<td>Incorporate pathology report from referring oncologist.</td>
</tr>
<tr>
<td>3</td>
<td>Conflicting source data</td>
<td>Transcribed laboratory results in medical record differ from values in reports</td>
<td>Use computer-generated laboratory reports.</td>
</tr>
<tr>
<td>4</td>
<td>Visits noted in CRF but not on source documents</td>
<td>Clinic chart does not capture study visits</td>
<td>Use clinic note template that is written, signed, and dated by qualified study staff.</td>
</tr>
<tr>
<td>5</td>
<td>Data entered directly onto CRF but not present in source documents</td>
<td>Study-specific tumor size measurements are absent from MR</td>
<td>Develop and use template to capture protocol-specific data.</td>
</tr>
<tr>
<td>6</td>
<td>Mismatch between source documents and CRF</td>
<td>Disease response notes do not conform to protocol-defined response criteria</td>
<td>Incorporate laboratory and radiology reports in study record; use template as needed.</td>
</tr>
<tr>
<td>7</td>
<td>Documents signed by personnel not listed on the study signature log</td>
<td>Delegation log not kept up to date</td>
<td>Maintain up-to-date Delegation of Authority Log.</td>
</tr>
</tbody>
</table>

Abbreviations: H&P, history and physical; MR, medical record.
future medical care and record of events that occurred during study participation.

Source documents exist in a hierarchy (primary versus secondary) on the basis of which one holds the first record of raw data. The first recorded value is generally presumed to be correct. Primary documents are generally more credible, including computer-generated laboratory reports; history and physical and progress notes; ER records; and medication administration records, among other documents. Secondary documents are a step removed from the first record of raw data, including transcribed flow sheets and laboratory values, discharge summaries, and SD template-generated data that was derived from original (primary) medical data. In general anyone involved in the subject's medical care may enter information. However, source documents must be signed by study personnel listed on a Delegation of Authority Form. FDA expects the investigator to show awareness of each subject's clinical status throughout trial participation. An investigator or listed designee should sign off on protocol-specified diagnostic test reports to confirm review by a person qualified to conduct the trial. Alternatively, the investigator or designee can indicate review of diagnostic tests on a progress note or source document template.

The Case Report Form, Monitoring, and Inspections

By contrast with source documents, the Case Report Form (CRF) is a study data collection tool that collates protocol-specific data and provides a condensed picture of each subject's involvement in the trial. GCP mandates that investigators ensure accuracy, completeness, legibility, and timeliness of data reported in CRFs, as well as consistency between CRFs and source documents (15). Although the CRF does not replace source documents, specific parts of the CRF may serve as a source document for data that are collected solely for study purposes. If present, such information will be clearly identified in the study protocol, is nonessential for clinical care, and is not routinely recorded in clinical practice. Examples include study-related self-rating assessments, visual analog scales, or repeated laboratory testing such as for phase 1 studies. CRF changes or corrections should include date, initials of the investigator or designee making the change, and explanation if necessary. Original entries should not be obscured; if information is redacted, fraud may be suspected. The investigator should endorse any CRF changes made by study staff and retain records of changes and corrections.

Study documents must be retained by the investigator until 2 years following the date of either the study drug's marketing approval or FDA is notified that clinical development of the study product has been discontinued (16). Investigators should “take measures” to prevent accidental or premature destruction of documents. The investigator must allow direct access to trial-related records on request of a study monitor, auditor, Institutional Review Board (IRB), or regulatory authority.

GCP (and FDA-mandated) clinical study monitoring verifies that (1) subject rights and well-being are protected; (2) reported trial data are accurate, complete, and verifiable from source documents; and (3) trial conduct complies with the protocol, GCP, and applicable regulatory requirements (17). However, the nature and extent of monitoring are flexible based on study circumstances. Study monitoring may entail CRF review, source document verification, drug accountability reconciliation, regulatory document review, and study staff interviews. Source document verification assesses whether CRF data match information in source documents and establishes whether source data are complete, attributable, legible, and accurate. All site facilities involved in the study may be evaluated in a site monitoring visit, such as the pharmacy, laboratories, and radiology record room.

FDA inspects clinical sites to verify data submitted, respond to a complaint, or investigate classes of drugs on the basis of public health issues (18). Inspections are regularly done of the highest enrolling sites in studies supporting a marketing authorization. By contrast, early phase sites are rarely inspected. Following inspection, FDA personnel prepare an Establishment Inspection Report and in addition issue a Form FDA 483 (Inspectional Observations) to the investigator when deviations from regulations are observed. Ultimately the appropriate FDA Center may send a letter to the investigator noting no significant deviations, an “untitled letter” identifying deviations for which voluntary corrective action is sufficient, or a Warning Letter that identifies serious deviations, requests prompt corrective action, and mandates a formal written response. If the investigator submits false information in any required report or repeatedly or deliberately fails to comply with regulations, the FDA may disqualify that person from receiving investigational products in the future. Good source documents decrease the occurrence of data queries, negative audit findings, and site regulatory violations.

Data Quality Challenges and Solutions

Inaccurate, missing, improperly corrected, or conflicting source documentation are a constant risk in clinical trials. Yet knowledgeable, motivated independent investigators can collect good quality source documents, even without monitoring. The most effective means to address data quality issues is preventive via planning prior to and at study site start-up. Effective planning can generate source document templates that facilitate timely, appropriate collection of correct source data. Such templates may allow inclusion of additional comments to account for unplanned or unexpected events. Appropriate chart layout eases generation and maintenance of good source documents. Separate sections for progress notes, consults, and reports facilitate subsequent review for both patient care and source document verification.
Simple, clear procedures for entering sequential observations and making insertions or corrections reduce problematic audit findings. Finally, a competent and motivated on-site study coordinator can make a crucial difference by addressing gaps in source document preparation and investigator sign-offs.

Several data quality issues arise regularly in site inspections. Table 3 provides information from publicly disclosed FDA Warning Letter findings on data quality. Noncompliant trial documents and inadequate or absent source documents are avoidable with appropriate planning and follow through (19). Typical data quality issues include the following:

1. Trial documents may omit required information or be missing entirely. Examples of missing or inaccurate information include elements of informed consent, Form 1572 inaccuracies about where subjects are seen (such as different satellite oncology clinics), investigator Curriculum vitae without date, institutional affiliation, or licensure information, and/or evidence that a site was officially, properly closed.

2. Medical histories and adverse event recording may be inaccurate or incomplete on the CRF (for example, missing prior chemotherapy or radiation regimens) in spite of accurate source documents. One way to mitigate this problem is to ensure that source documents include a clear subject history and adverse event information that includes onset, severity, potentially confounding clinical observations, and concomitant medications. Alternatively, investigators and study coordinators may document adverse events on a source document template specifically generated for the trial. Data on these templates are culled from the medical record and interviews with the subject. However, adverse events may also be noted in parts of the medical record written by other health providers, which are not included on the adverse event source document template. Once identified, these adverse events should be added to the source document adverse event template (if used) and provided to the investigator for review; i.e., for determination of causality and severity.

**Table 4. Clinical trial study documents**

<table>
<thead>
<tr>
<th>No.</th>
<th>Document type</th>
<th>Examples</th>
</tr>
</thead>
</table>
| 1   | Regulatory          | • FDA Form 1572  
• Dated Curriculum vitae for each investigator  
• Medical license  
• Study protocol and/or amendments, signed by investigator  
• IRB approval(s) of protocol and/or amendments  
• IRB approval(s) of informed consent form  
• List of IRB members and affiliations  
• Sponsor (or FDA) notification(s) of serious adverse events  
• IRB notification(s) of serious adverse events  
• IRB notifications of trial progress, study closure, etc.  
• Laboratory normal ranges  
• Laboratory certifications  
• Delegation of Authority Form  
• Study Staff Signature Sheet |
| 2   | Product Accountability | • Shipment and receipt records  
• Inventory and dispensing log  
• Reconciliation log  
• Freezer temperature chart (if applicable) |
| 3   | Other Documentation | • Investigator Brochure(s), including out-of-date versions  
• Monitoring reports and sign-in log  
• Investigator correspondence  
• Enrollment log  
• Investigator-Institutional Agreement  
• Insurance-Indemnification Record  
• Financial Disclosure Form  
• IND Safety Reports  
• Documentation of protocol training  
• Documentation of investigator training |
3. Source document verification may reveal no source documentation to support CRF data, for example, to confirm eligibility that a subject had received at least one first-line chemotherapy regimen prior to enrollment in the study. An FDA investigator's conclusion may be that if something isn't recorded, then it wasn't done. The solution is to create source data documenting the subject's prior chemotherapy regimens on source document templates or in free text on standard clinic data sheets that are signed and dated in chronological order. Faxed or copied presudy physician notes or chemotherapy sheets should be signed to indicate investigator or designee review and retained as source documents.

4. Start and stop times of study drug may be found in the CRF but not found in source documents. For example, the protocol may require that an anti-emetic be given along with study chemotherapy. However, the standard at some oncology clinics is not to document dosing times of such standard medications. Clinical investigators or their designees should confirm drug administration, including documentation of each drug, its administration time, route, and amount given.

Table 4 provides an example checklist of study documents to be maintained (20).

Discussion

Tension has been noted between clinical versus public health ethics (21). Clinical ethics focuses on individual patient interests in the context of the physician-patient relationship. By contrast, public health ethics emphasizes measures to monitor and improve the health of populations. Similarly tension exists between advancement of medical science and regulatory credibility. In the United States, for example, the National Cancer Institute supports education, training, and research on cancer and its treatment. By contrast, the Food and Drug Administration is a law enforcement agency whose purpose is to protect public health, including from marketing of drugs on the basis of inaccurate data or fraudulent safety and efficacy claims. Data integrity issues are born of public health ethics.

Although data quality is fundamental to drug regulation, regulatory authorities may allow a marketing authorization despite marginal data quality in the New Drug Application (NDA) submission. The initial 1995 accelerated approval of doxil (pegylated liposomal doxorubicin), summarized in the Appendix, provides a noteworthy example (22). As the basis for doxil's approval, FDA rejected the sponsor's own analysis and presentation in favor of the FDA reviewer's direct evaluation of source documents. Regulatory flexibility becomes most apparent when a drug under consideration shows activity in treatment of a disease with high unmet medical need. In such instances regulators have substantial discretion to balance the sometimes contrary demands of clinical and public health ethics. Photofrin (see Appendix) and doxil highlight that source documents, including from early phase investigations, may be vital in supporting early approval of new drug products that meet serious unmet medical needs.

Appendix: Maturation of the U.S. Drug Regulatory System

Before 1962 there were scant controls on testing and marketing of medicines in the United States. The 1906 Pure Food and Drug Act (PFD&A) was passed as a response to cure-all claims for impure, adulterated, or otherwise valueless medicines and established a requirement for truthfulness in medicine labeling. In 1930 the Food and Drug Administration (FDA) was formed as a government agency to regulate content and safety of consumer drugs and food. The 1938 Federal Food, Drug, and Cosmetic Act (FD&C) was passed after a public health tragedy involving an elixir of sulfonamidamide with diethylene glycol, which increased solubility of the antibiotic and generated a sweet taste. No animal or clinical testing was done, and more than 100 people died after using the formulation (1). FD&C implemented premarketing safety review of new drugs. Yet FDA's powers remained circumscribed. Approval could be refused if submitted safety reports "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" (2). However, whereas a single reviewer could approve a new drug, the reviewer's rejection of an application could be and often was overruled by a supervisor. FDA had no control over investigational drug testing and limited ability to integrate analysis of drug effectiveness into review.

Starting in 1959, U.S. Senator Estes Kefauver conducted a series of controversial Congressional hearings to examine pharmaceutical industry practices (3). Testimony revealed a prevalent business practice of branding new formulations of generic drugs then marketing the product on the basis of unsubstantiated claims of superior efficacy. Kefauver's efforts went on for years and in the setting of intense industry resistance might have come to nothing.

Thalidomide Provokes Outrage

Although the sedative thalidomide was never approved for sale in the United States, FDA reviewer Frances Kelsey's resistance to approval had been unusual (4). After seeing a journal letter describing peripheral neuropathy in patients taking thalidomide, Kelsey and a colleague surmised that nerve damage caused by the drug might lead to birth defects. She requested evidence from the sponsor that the drug was safe in pregnancy. No such evidence existed. In 1962 reports surfaced from Europe and Canada of an epidemic of thousands of babies with
phocomelia following use of thalidomide by their mothers during pregnancy. Successive news releases revealed that thalidomide's sponsor had distributed the drug in the United States to more than 1,200 physicians for "investigational" purposes in at least 2.5 million labeled tablets, as well as tens of thousands of unlabeled tablets, liquids, and powders (5). Furthermore, records and reporting of thalidomide's distribution and use within the United States were substantially incomplete (1). Less than half the doctors dispensing the drug had any record of how much of the drug they either received or distributed. This public health tragedy precipitated passage of the 1962 Harris-Kefauver Amendments to FD&C.

The Harris-Kefauver amendments instituted two key changes in U.S. drug regulation. First, FDA was granted regulatory oversight over investigational drug research; new regulations followed quickly. Second, premarketing demonstration of new drugs' effectiveness for their intended use became mandatory. This requirement underscored a problem with drugs on the market when the legislation passed. About 2,820 different drugs made by 2,340 companies were approved between 1938 and 1962 on the basis of safety alone, not efficacy (1). Thus in 1966 FDA contracted with the National Academy of Sciences (NAS) via its study arm the National Research Council to do the Drug Efficacy Study (DES) of these products. The DES examined evidence for efficacy of these drugs and categorized each as effective, probably effective, possibly effective, or ineffective. More than half were reported to be ineffective on either some or all claims made in the drug label. Two years later, FDA began to implement NAS recommendations on these drugs in the Drug Efficacy Study Implementation (DESI), a program that continued for decades (6). The DESI program quickly resulted in market removal of numerous drugs. Lawsuits followed. One noteworthy case involved Panalba, a fixed-dose combination antibiotic containing tetracycline and novobiocin. The drug was commercially successful, and its sponsor balked at removing it from the market. In March 1969 an FDA inspector found in the manufacturer's own files previously undisclosed studies showing that novobiocin antagonized tetracycline's antibiotic effects. FDA's authority to ban Panalba was ultimately upheld by the U.S. Supreme Court (7).

As a consequence of DESI, FDA in 1970 implemented new regulations that defined "adequate and well-controlled" clinical studies (8). These rules can be summarized as follows (9).

1. There is a clear statement of objectives and analyses.
2. The design allows a quantitative comparison with a control group.
3. Subjects have the disease to be treated or risk of disease to be prevented.
4. The treatment assignment method minimizes bias.
5. Subject and observer bias are minimized.
6. Methods of assessment are well defined and reliable.
7. Analysis is adequate to assess the effects of the drug.

The characteristics of adequate and well-controlled studies identify biases that may confound interpretation of clinical trial results. Importantly, these principles allow drug approvals on the basis of clinical benefit shown in single-arm trials in which the quantitative comparison assumes no effect in a historical control group. For example, the initial marketing authorization in 1995 of Photofrin (porfirmer sodium) for palliation of obstructing esophageal cancer was based on a single-arm study in 17 patients (10). Porfirmer's example illustrates that early phase investigators studying drugs to treat cancers with a high unmet need can generate pivotal support for a new drug's approval.

**Data Quality and Risk-benefit Equipoise: The Story of Doxil and Kaposi's Sarcoma**

Doxil's sponsor in the mid-1990s submitted a New Drug Application (NDA) for the drug's use as second-line treatment of AIDS-related Kaposi's sarcoma after failure of prior combination chemotherapy due either to disease progression or unacceptable toxicity. At that time there were no known therapeutic alternatives for patients after first-line therapy. Also it wasn't yet clear that highly active antiretroviral therapy would transform the epidemiology and natural history of AIDS-related Kaposi's sarcoma.

The doxil NDA presented a number of challenging regulatory issues. First, the single clinical study submitted in support of approval was a nonrandomized study that was originally intended as a compassionate use protocol to absorb subjects that enrolled to either of two separate pivotal clinical studies. Second, standards for evaluation of AIDS-related Kaposi's sarcoma were not yet mature, and the study's primary efficacy analysis was based on retrospectively defined criteria of tumor response. Finally, eligibility standards, particularly the requirement for refractoriness or intolerance to first-line therapy, were inconsistently applied.

In the NDA's single pivotal study of 173 subjects, only 77 had case report forms that seemed to meet eligibility criteria of refractoriness or intolerance to prior combination chemotherapy (11). However, even for these subjects case reports submitted by the drug's sponsor were inadequate to document prior therapy. Thus case report forms and the study database were effectively rendered moot. Rather, FDA ultimately based its review on analysis of source documents (medical charts) from 71 of these 77 subjects for whom records were available. This analysis documented eligibility, prior therapy, and reasons for stopping it, and measures of patient condition and response. Six patients were identified whose charts contained source documents that showed data supportive of at least probable benefit from doxil therapy. Prominent data gaps in source documents included duration since prior treatment with doxorubicin, prior doxorubicin dose, and which responding patients had previously received doxorubicin.

Investigators should not assume that FDA will again base a marketing authorization on such flawed and
incomplete data. Nonetheless, doxil’s 1995 accelerated approval provides a noteworthy example of data quality deficiencies so severe that the sponsor’s own study database was rejected in favor of source document analysis to support regulatory review and approval.

Appendix References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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