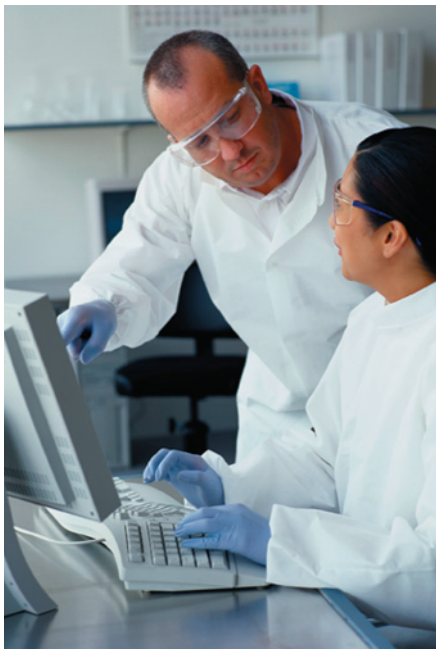

# Specifications and Manufacturing Change Control

## A Prototypic System for Electronic Document Tracking and Management

**Robert Zeid**

**The corporate fantasy where everyone knows all the systems all too often collides with a nightmare reality where all the systems are known by only a few. Any specification or manufacturing change that affects various departments can quickly become a bewildering morass of proposed, actual, and implemented changes — with few connections to actual lots and practices. Draw a line in the CMC "sand" where those changes actually began.**

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Although a change control program is required under the current good manufacturing practices (CGMPs) (specifically 21 CFR 211.100, subpart F and 21 CFR 610.9, subpart B), surprisingly little explicit guidance is available except for citations in warning letters and some excellent review articles (1–4). This paucity has given rise to a variety of industry approaches to managing change control, not all of them successful.

Supporting data requirements for process changes in classically synthesized drugs are outlined in the scale-up and postapproval changes (SUPAC) guidances, but no counterpart exists for biologics. That void is particularly difficult for biologics manufacturing because the regulatory requirements may not be interpreted the same way by CBER reviewers and Team Biologics inspectors, with significant potential effect on a marketed product. Inconsistent standards (or case-by-case approaches as with biologics), compounded by documentation poorly linked to production can dramatically increase the potential for releasing marketed lots manufactured by unapproved processes or process changes.

The comparability protocol guidance allows postapproval changes with abbreviated data packages, but the lack of a biologics SUPAC guidance complicates the amount of supporting data needed. That necessitates a very careful evaluation of each potential change and its anticipated regulatory reporting requirement (5). Even when changes are accurately predicted, comparability is demonstrated and the change approved, the adequacy of the studies may be questioned by regulatory authorities months or years later.

Additionally, biotech companies are generally smaller than their pharmaceutical drug counterparts. Often, insufficient staff is devoted to such areas, especially with fast track projects. A high rate of employee turnover combined with poor documentation practices spells disaster when trying to pull together development reports or justification for validation protocols in response to an FDA inspection query.

Biotech manufacturing change control across various departments can quickly become a bewildering morass of proposed, actual, and implemented changes — with few connections to actual lots and practices. Perhaps the most vital tenet of change control is to be able to draw a line in the chemistry, manufacturing, and controls (CMC) "sand" where changes actually affect testing and production. For optimal efficiency, a holistic approach would call for identifying key people or departments to serve as gatekeepers and chroniclers of change; then weave their results into a system that is readily transparent to the rest of the company.

### Life Cycle Flowchart

There are three reporting categories for controlled change: prior approval supplement (PAS), changes being effected (CBE-30), and annual report (AR). Figure 1 provides a brief overview of change control systems and how proposed changes evolve.

Additionally, change control status can be *proposed, FDA-approved, implemented,* or *superseded*. Usually a change control committee composed of representatives from key departments ensures a consistent review process and control of revised documents and procedures. However, the actual implementation of a change may be spurious or premature, as reflected in 483s

and warning letters. Such observations suggest that change control groups may not be extending the change control fully — to the implementation phase or harmonization with other procedures in the company.

**A familiar scenario.** A common complication in change control is regulatory approval status. After filing a proposed CBE-30 and receiving no response from FDA within 30–90 days, a company may assume the CBE-30 is valid and proceed to implement the change. However, months later when a Team Biologics observation arises, or an FDA reviewer submits comments well beyond the 30-day review clock, the validity of the CBE-30 may be challenged, and its regulatory status becomes a *de facto* PAS. Supporting data required from the sponsor is the same regardless of the initial regulatory filing status.

It is essential that sponsors be able to track the affected lots and provide additional data supporting the change. That may require product quarantine until the development studies are completed and reviewed; it may require a full recall, depending on the situation. In all, each sponsor must have an efficient system in place that allows for rapid identification of affected lots. If the sponsor lacks the tools to accurately identify lots made by an alternative procedure or test method, then inspection observations may be expanded to include those deficiencies.

## Database Organization

Responding quickly and accurately to FDA queries is frequently complicated by data sharing deficiencies. Large companies often have numerous databases with overlapping areas, but the actual sharing of data in a way that allows a facile evaluation across departmental disciplines is rare. Record systems and databases are typically department-specific (for example, regulatory, clinical, CMC). The functions of varying databases may complicate sharing and lead to departmental feuds. Figure 2 summarizes major database types.

The regulatory affairs department maintains submission databases with limited links to other departments for clinical and CMC data. CMC and production records are often completely separate from all other records, and analytical testing is a large yet discrete portion of that data. Sharing CMC-related data with non-CMC departmental groups is not always easy because most data are not electronically captured. Without a high level of integration, individual groups end up creating subset databases that only make sharing harder. Even when document control groups make information electronically available on the company intranet (for

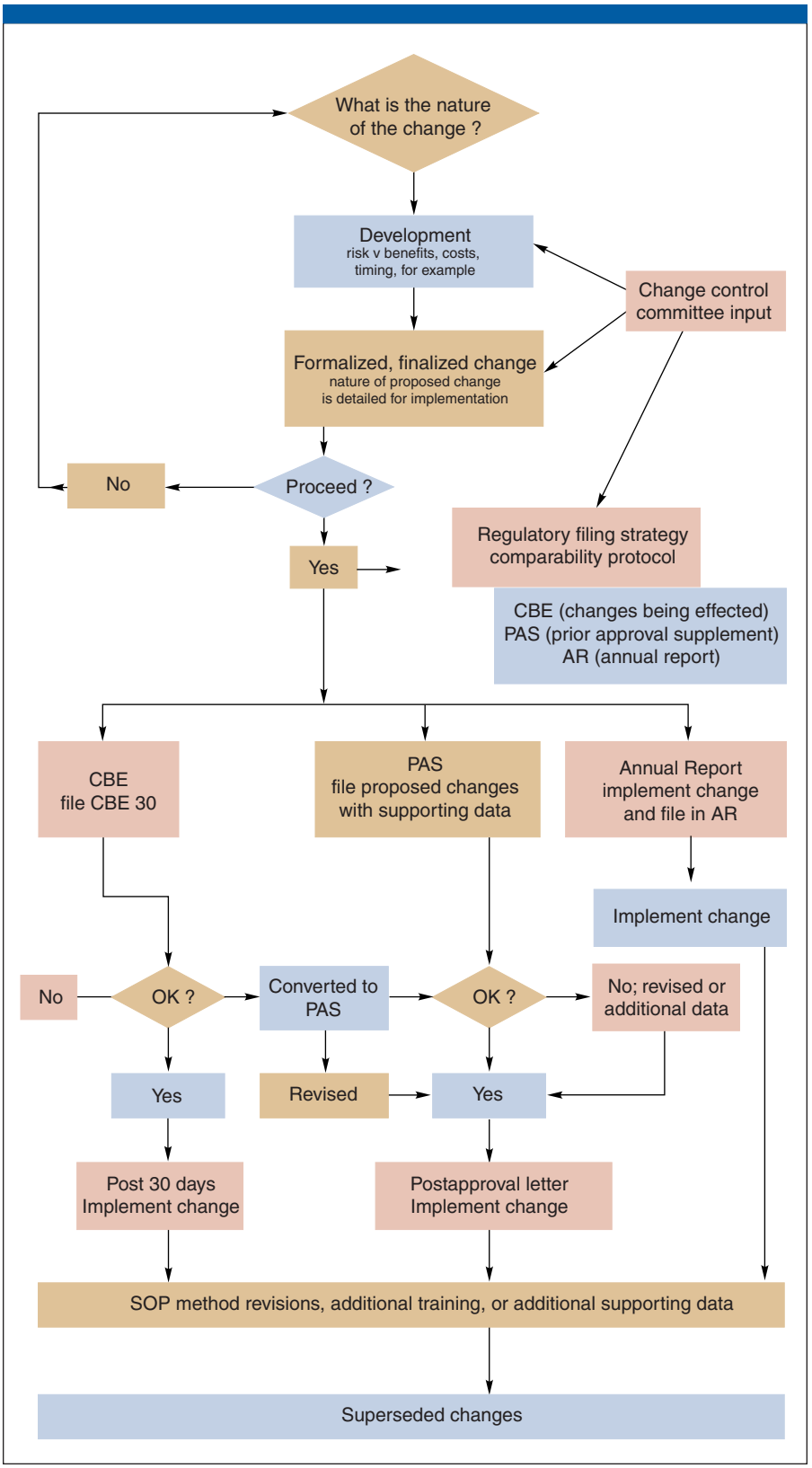


**Figure 1.** Change control life cycle

example, current specifications, change control database) it is rarely linked to actual production lots.

Capturing the volume of batch-specific data can be daunting, but it pales in comparison to the staggering amount of data produced over the course of a product development cycle or marketed product life-span (*Figures 3 and 4 online at www.biopharm-mag.com*). Without an effort to capture key data in real-time, a records retention policy can result in critical records being lost or destroyed before the related development reports or (belated) out of specification (OOS) investigations are finalized. Regulatory submissions may be hobbled by gaps in supporting data or the absence of a concrete rationale for certain development decisions.

Although change control is often associated with CMC changes, clinical examples are numerous, such as updates to protocols, informed consents, and investigator brochures. Updates or changes to eligibility criteria without similar changes to the database modules can complicate the integrated summary of safety (ISS) or integrated summary of efficacy (ISE). Preclinical studies may be poorly linked with finished product lots used in IND trials, hampering a comparison of varying impurity profiles for clinical trial material versus commercial lots. The consequence might be that little or no preclinical qualification of certain impurity levels are revealed in a BLA or NDA stability summary. Poor accountability of clinical trial material used for each protocol and study site can result in poor product traceability and affect stability or impurity conclusions. Poor stability of clinical trial material may not be identified or recalled per SOPs, resulting in use of OOS investigational material in pivotal studies. The result could disqualify patients or centers that received drug out-of-specification.

Although most company intranets make portions of such databases available, companies that use peer-to-peer networks or local area networks (LANs) instead of company intranets often have poor links to other sites. Such companies may not have captured sufficient historical data to evaluate the scope and time of change related to specific product lots. Finally, many companies, both large and small, consider the holistic integration of data too laborious and expensive to justify. Ironically, that choice may result in calculated risks that could entail a product recall or market delay which could be 20 to 100 times more costly.

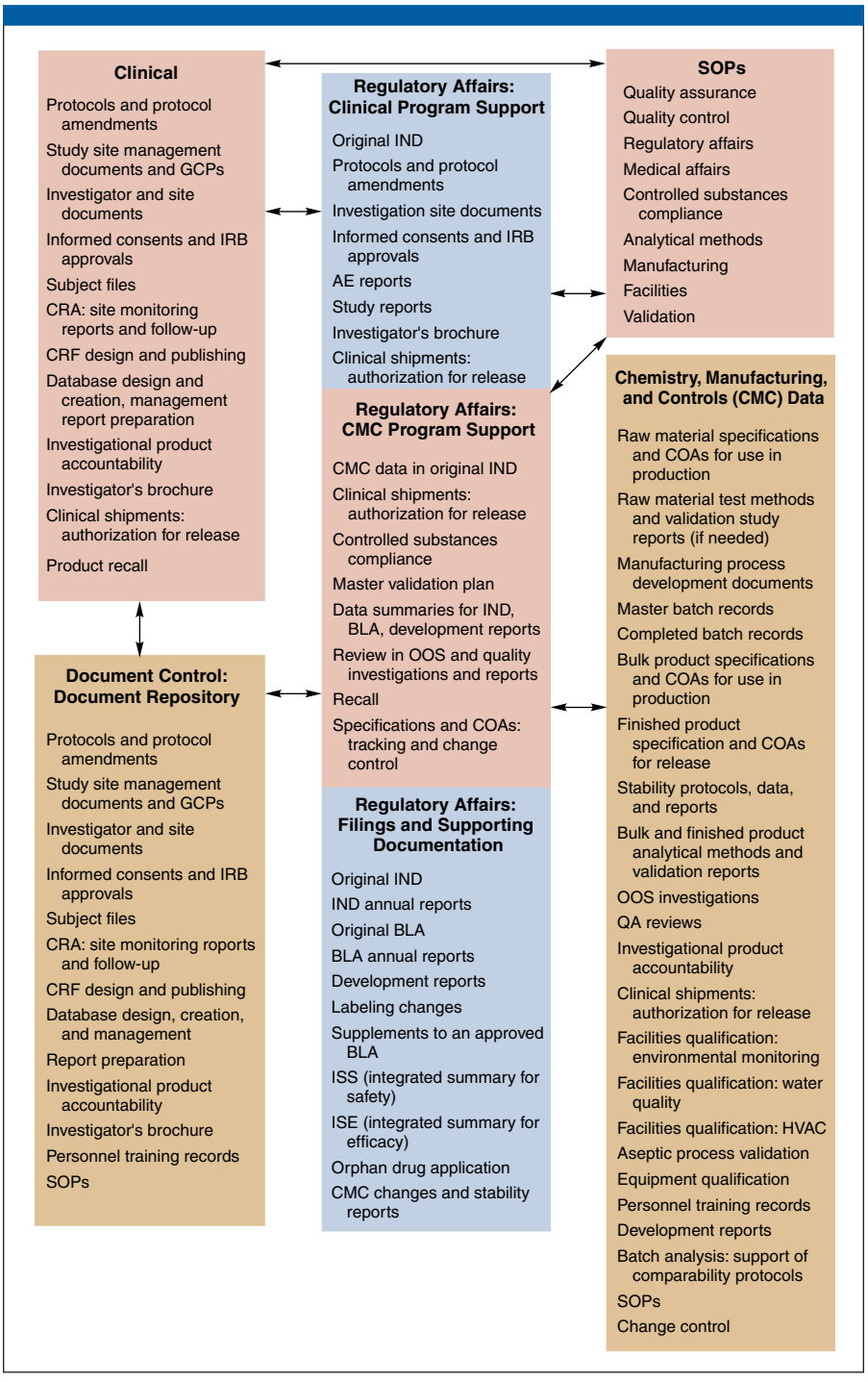


**Figure 2.** Overview of databases

## Data Relationships

How could anyone possibly organize such a bewildering array of data, captured over time, for easy access and traceability back to its original documentation? Would production records alone suffice? What about analytical test data? Even the most thorough batch records can never completely capture all the relevant facility and analytical testing features that could affect an investigation. It is vital to create an intranet with a production flow chart that captures the complex interplay among data, facilities, testing, and policy for production documentation (Figure 5).

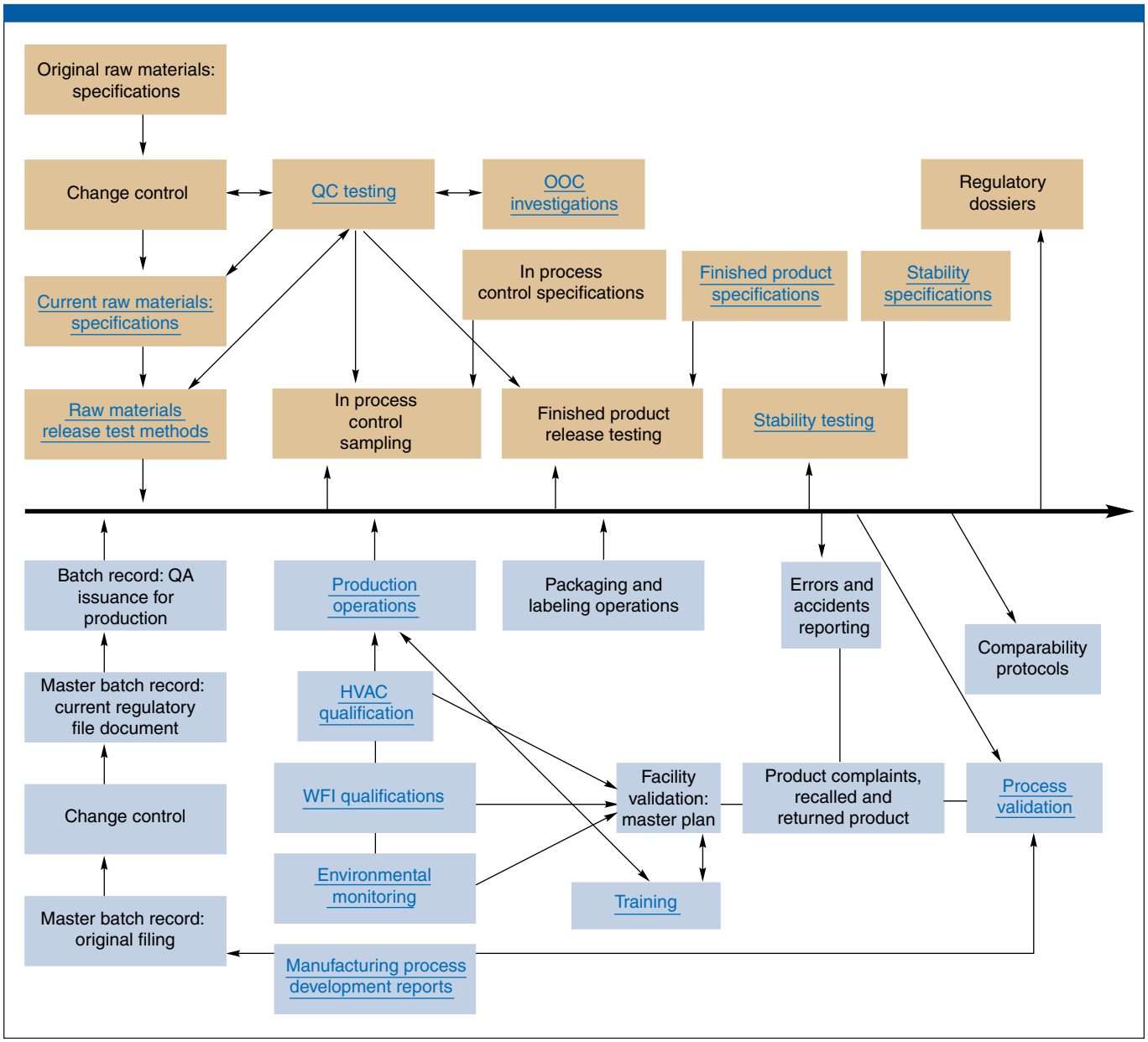


**Figure 5.** A production flow chart should capture the complex interplay among data, facilities, testing, and policy.

If a **production flow chart** can be hyperlinked back to other databases for specifics, it is possible to establish a network of product-specific or lot-specific databases as in Figure 6 on page 44. Such "cradle-to-grave" accountability is critical for rapid product lot identification for raw material accountability, batch record version, specification version, and product recall; errors and accidents, and other OOS investigations; rapid accountability of lots on stability; rapid identification of lots used for comparability studies or process validation studies; the relationship of lots to water for injection (WFI), HVAC, and environmental monitoring status; and better control of lots for change control issues.

For example, a hyperlink to raw material specifications and COAs used in production could lead back to a table that captured the raw material name, specification number, and batches of raw materials used in production and released according to that specification (Table 1, next page). Other tables would include master batch records (Table 2), bulk specifications and COAs for release (Table 3), or finished product specifications and COAs for release (Table 4). *(Tables 2–4 can be found online at www.biopharm-mag.com.)*

Depending on the company needs and resources, some hyperlinks from the intranet might be to a summary tabular listing of all changes associated with a particular product. Other approaches could include a snapshot for each production lot with a hyperlink to scanned documents such as production records, test data results, or OOS investigation findings (see examples online at www.biopharm-mag.com).

By using a combination of Microsoft (MS) Word and Excel, with Adobe Acrobat software, you can create or edit pages appropriately and post them on a secure intranet. You can also insert hyperlinks from the production flow charts to Microsoft Access databases (which may be the best application, because that software allows

**Table 1.** Raw material specifications and COAs for use in production

| Raw Material (RM) Name | Specification Number | List of RM Lot Numbers Used (Vendor COA #) |
|---|---|---|
| Mannitol, USP | 2735-001 | WB-QR89-501 (JBL-004-001-XYZ)<br>WZ-SR64-399 (JBL-011-013-HEY) |
| Mannitol, USP | 2735-002 | BZ-QR89-501 (JBL-0214-0301-XGZ)<br>AA-SR75-359 (JBL-014-019-HOY) |
| Mannitol, USP | 2735-003 | QQ-ABC89-501 (JBL-023-0101-XBZ)<br>DD-ER64-3599 (JBL-0511-07-HYL) |
| Mannitol, USP | 2735-004 | WEB-QR89-511 (JBL–006-009-LLL)<br>PPP-SR324-465 (JBL–123-013-ABC) |
| Glycerin, USP | 15642-001 | WB-QR89-501 (JBL-004-001-XYZ)<br>WZ-SR64-399 (JBL-011-013-HEY) |
| Glycerin, USP | 15642-002 | BZ-QR89-501 (JBL-0214-0301-XGZ)<br>AA-SR75-359 (JBL-014-019-HOY)<br>PPP-SR324-465 (JBL-123-013-ABC)<br>WEB-QR89-511 (JBL-006-009-LLL) |
| Glycerin, USP | 15642-003 | QQ-ABC89-501 (JBL-023-0101-XBZ<br>DD-ER64-3599 (JBL-0511-07-HYL) |

easier searching and sorting of affected lots than do Word and Excel) in accordance with 21 CFR Part 11, electronic records.

Layers of hyperlinks within the source documents could allow stratified searching. For example, a production flow chart link to facilities HVAC qualification could lead to a smaller separate database of HVAC validation, water validation, and environmental monitoring summaries broken out by affected lots. Such broad separation would allow easier determination of facility upgrades and associated validation issues for production runs.

### Cues and Reminders

Properly executed, an intranet system will allow a holistic approach to the marriage of document control with electronic checks and balances.

**Some key considerations**. Your change control committee should have read/write access to the change control database (for example, MS Access). Link the change control database to critical specification and manufacturing processes for immediate evaluation of every lot made. The documentation history should be readily available for every lot made and should be easy to generate for key component specs, testing reports, bulk and finished product specs, and stability. Revised documents with approved change controls should be signed off by the change control committee. Weave a change control reporting mechanism (for example, AR, CBE, or PAS) into the revision history for all specifications, process documents, and other critical manufacturing areas. The change control database should have automatic searches, cues, or reminders about version control when adding documents with similar root directory names. Electronically flag critical documents still pending approval using for example **UNAPPROVED: DO NOT IMPLEMENT** in flashing text. Evaluate critical document changes for links to other areas such as training, testing, and so forth to ensure the implementation of the change does not conflict with procedures that now reflect a superseded process.

System failures (poor links between development engines, for example) can have disastrous consequences. For instance, incomplete analytical method validation before the manufacture of biotech lots for an NDA or stability lots for a BLA can complicate the utility of data. Similarly, technology transfer for analytical methods may not be complete before the manufacture or release testing of NDA, BLA, or ANDA demonstration lots. IND lots may be accidentally tested according to the marketed product specifications rather than the wider IND product specifications leading to OOS investigations. Other system failures could include release and sale of a marketed product made by unapproved changes, implementation of new procedures with inadequate training in place, release and sale of a marketed product with incorrect

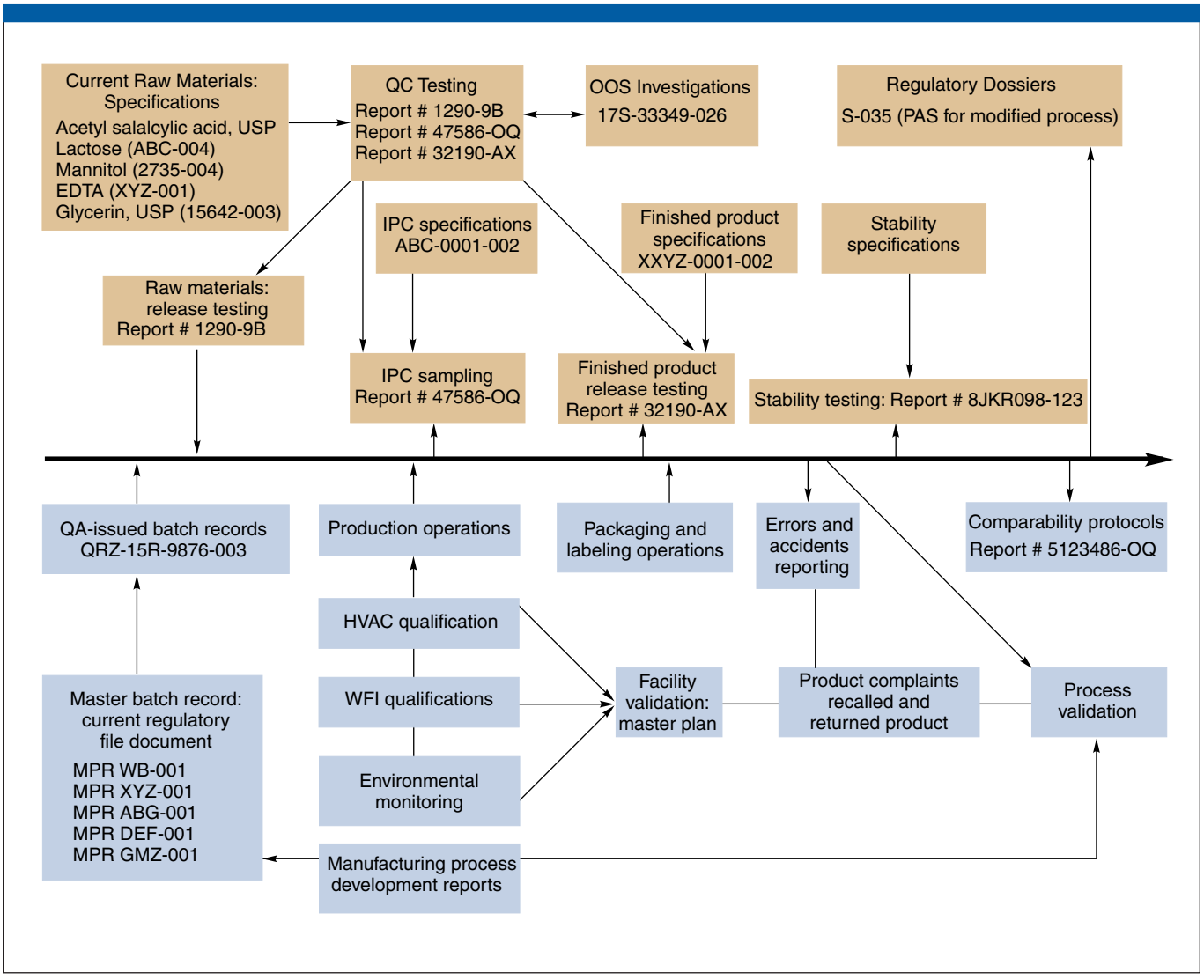


**Figure 6.** Document mapping

labeling, or scale-up to manufacturing without appropriate process validation (such as expanded powder-filling operations).

## Points to Consider

Implementing an electronic document management system early in the product life cycle can be useful for a number of tracking issues, but its greatest impact may be on change control. It is transparent and, if kept up to date, can be used by everyone in the company who has access, keeping departmental feuding and personality differences to a minimum. Accountability is high because change control failures can be readily ascertained and corrected.

Change control is a vitally important area because a Team Biologics inspection is a system-wide evaluation of procedures and documentation related to each production lot. Future FDA inspection teams will no doubt continue their focus on quality integration throughout production and testing. An electronic tracking system that allows easy document management of lot-specific specifications and manufacturing change controls over time will help identify problem areas and prevent product recalls.

The ultimate product is a transparent document management system on a company intranet that allows rapid, real-time assessment of specification and manufacturing change controls, regulatory filing status, and implementation. The investment in personnel and software to create that product is only a fraction of the cost for a routine recall, a delay in preapproval inspection, or a delay to market.

## References

(1) *Code of Federal Regulations, Food and Drugs,* Title 21, Part 211.100, subpart F and 21 CFR 610.9, subpart B (U.S. Government Printing Office, Washington, DC).
(2) C.M. Kennedy, "Managing Equipment and Procedural Change Control," *BioPharm* 8(3), 34–37 (1995).
(3) C. Deitz, "Developmental Change Control," *Pharm. Technol.* 22(9), 78–86 (1998).
(4) B. Immel, "Passionate About Change Control," *BioPharm* 9(9), 55–57 (1996).
(5) Center for Biologics Evaluation and Research, *Guidance for the Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* (FDA, Rockville, MD, April 1996). **BP**