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Why Validation?

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INTRODUCTION

The origins of validation in the global healthcare industry can be traced to terminal sterilization process failures in the early 1970s. Individuals in the United States point to the LVP sterilization problems of Abbott and Baxter, while those in the U.K. cite the Davenport incident (1). Each incident was a result of a non-obvious fault coupled with the inherent limitations of the end-product sterility test. As a consequence of these events, non-sterile materials were released to the market, deaths occurred, and regulatory investigations were launched. The outcome of this was the introduction by the regulators of the concept of "Validation":

> Documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (2).

The initial reaction to this regulatory initiative was one of puzzlement; after all, only a limited number of firms had encountered difficulties, and all of the problems were seemingly associated with the sterilization of LVP containers. It took several years for firms across the industry to understand that the concerns related to process effectiveness were not limited to LVP solutions, and even longer to recognize that those concerns were not restricted to sterile products. Perhaps most unfortunate of all was the lack of enthusiasm on the part of industry in adopting this concept. From its earliest days, validation was identified as a new regulatory requirement to be added to the list of things that firms must do, with little consideration of its real implications. The first efforts reflected what can be termed the "scientific method" of observation of an activity, hypothesis/prediction of cause/effect relationship, and experimentation followed by new observations in the form of the experimental report. In the pharmaceutical validation model this has evolved into the validation protocol (hypothesis and prediction), field execution (experimentation), and summary report preparation (documented observations).

By 1980 when it was evident to all that validation was here to stay, pharmaceutical firms began to organize their activities more formally. Ad hoc teams and task forces that had started the efforts were replaced by permanent Validation Departments whose responsibilities and scope varied with the organization but whose purpose was to provide the necessary validation for a firm's products and processes. The individuals in these departments were the first to grapple with validation as their primary responsibility, and their methods, concepts, and practices have served to define validation ever since:

> *Validation*: Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes (3).

The first efforts at validation were rather crude and limited in their understanding of the full implications. For example, the first sterilization validations at most firms were performed without prior qualification of the equipment. Once validation had been established as a discipline and something more than a passing fad, methods for its execution became substantially more formalized and rigorous.

The validation community made significant strides in clarifying the various components of a sound validation program. Perhaps most important of all was the separation of activities into two major categories: Equipment Qualification and Process Qualification. The former (sometimes sub-divided into Installation and Operational Qualification) focused on the equipment in which the product was being processed. It is predominantly a documentation exercise in which details of the physical components of the system are recorded as definition of the equipment. Equipment operational capabilities are also established. Process Qualification (also known as Process Validation or Performance Qualification) confirms the acceptability of the product manufactured via the equipment, and relies heavily on the results of physical, chemical, and microbial tests of samples.

It was soon apparent that validation had to be more closely integrated into the mainstream of cGMP operations in order to maximize its effectiveness in larger organizations. A number of areas can be identified as pre-requisites for process or system validation. The origins of these elements can be identified in the cGMP requirements for drugs and devices (Table 1) (4).

With this understanding of its dependencies, validation is more easily assimilated into the overall cGMP environment rather than something apart from it. While a firm will likely continue to have a validation

Abbreviations used in this chapter: cGMP, current good manufacturing practice; FDA, Food and Drug Administration; GAMP, good automated manufacturing practice; LVP, large volume parenteral; PAT, process analytical technology; PMA, Pharmaceutical Manufacturers Association.

Table 1 Pre-Requisites for Validation

Process Development [21 CFR 820.30—Design Control]. The activities performed to define the process, product or system to be evaluated
Process Documentation [21 CFR 211 Subparts F—Production and Process Controls and J—Records and Reports]. The documentation (batch records, procedures, test methods, sampling plans) and processes (software) that define the operation of the equipment to attain the desired result
Equipment Qualification [21 CFR 211 Subparts C—Buildings and Facilities and D-Equipment]. The specifications, drawings, checklists and other data that support the physical equipment (hardware) utilized for the process
Calibration [21 CFR 211 Subparts D—Equipment]. The methods and controls that establish the accuracy of data
Analytical Methods [21 CFR 211 Subpart I—Laboratory Controls]. The means to evaluate the outcome of the process on the materials
Cleaning—[21 CFR 211.67 Equipment Cleaning and Maintenance]. A specialized process, the intent of which is to remove traces of the prior product from the equipment
Change Control—[21 CFR 211.100(b) Equipment Cleaning and Maintenance]. A formalized process control scheme that evaluates changes to documentation, materials, and equipment

department, it must be supported by the activities in other parts of the organization. For example, a poorly developed process performed using uncalibrated equipment to make a product that has no standard test methods could never be considered validated. All of the supportive elements must be properly operated in order to result in a compliant product, and one that can be validated. A later definition that addresses the larger scope of validation within the overall organization is:

> Validation is a defined program which, in combination with routine production methods and quality control techniques, provides documented assurance that a system is performing as intended and/or that a product conforms to its predetermined specifications (5).

APPLICATION OF VALIDATION

Beginning with its first association with LVPs in the early 1970s, the application of validation spread quickly to other sterilization processes. It was also applied for the validation of other pharmaceutical processes, albeit with mixed success. In sterilization and, to a slightly lesser extent, in processes supporting the production of sterile products using aseptic processing, there is little difficulty applying validation concepts. The apparent reasons for this are the common and predominantly quantitative criteria for acceptance of the quality attributes of sterile products. Building consensus on validation of sterile products has been achievedbut not without debate. There are numerous excellent guidance documents outlining validation expectations on the various sterilization processes, as well as numerous publications from individuals and suppliers. The only relatively deficient areas in sterile product validation are elements unrelated to sterility, e.g., endotoxin and particulate matter.

Validation of non-sterile products and their related processes is less certain. Despite the obvious importance of cleaning procedures, cleaning validation was not publicly discussed until the early 1990s. To this day there is still confusion regarding the requirements for validation of this important process. The difficulties with validation are even more complicated for pharmaceutical dosage forms. There are no widely accepted validation requirements for the important quality attributes of drug products. While the key elements are known (dissolution, content uniformity, and potency), there are no objective standards upon which to define a validation program. The compendial standards of the various pharmacopeia are poorly suited to validation. The small sample size and absolute nature of the acceptance criteria are extremely problematic for direct application to large scale commercial production. After more than 30 years, the absence of universal criteria for dosage forms is unfortunate and problematic.

Applying validation requirements to water and other utility systems is somewhat easier than for pharmaceutical products. Equipment qualification of utility systems is relatively easy to perform, and samples of the supplied utility (water, steam, environmentally controlled air, compressed gas, solvent, etc.) taken across the system can directly support the acceptability of the preparation, storage (where present), and delivery system. Classified and other controlled environments have proven relatively easy to validate. Their physical elements readily lend themselves to equipment qualification, and sampling affords confirmation of their operational capabilities directly.

Biotechnology first came of age in the late 1980s into a regulatory environment that expected validation of important processes. Since the first biotech products were injectable drugs, it was quite natural for these firms to validate their processes from the onset. As a consequence, cell culture and purification processes of all types have always been subject to validation expectations. There is a substantial body of validation knowledge on these processes available. In marked contrast, the bulk pharmaceutical chemical segment of the industry has been relatively slow to embrace validation concepts. While the rigorous environmental expectations associated with many dosage forms and virtually all biotechnology processes are not present, the important considerations of impurity levels, byproduct levels, racemic mixtures, crystal morphology and trace solvents all suggest that there are important quality attributes to be controlled (and thus validated) as well.

Computerized systems became subject to validation requirements when they were first applied for cGMP functions in the 1980s. For ease of understanding, the parallels between computerized systems and physical systems are utilized. The computer hardware can be qualified like the process equipment to which it is often connected, while computer software has some similarities to the operating procedures utilized to operate the equipment. This approach may be an over-simplification of the required activities for the software, but it provides some clarity to the uninitiated. Computerized system validation is still a subject of substantial interest, but is no longer the misunderstood behemoth task it appeared to be when first encountered. The early efforts of PMA's Computerized Systems Validation Committee and the later development of GAMP have reduced the uncertainty associated with the use of computerized systems substantially (6).

One useful concept taken from the validation of computerized systems as it evolved was the "life cycle model" (7). Originally utilized for computer software, it was later applied to the entire computerized system. It suggests that considerations of system qualification, maintenance and improvement be incorporated at the onset of the design process. Its utility for computerized systems is substantial; however it may have even greater functionality for pharmaceutical processes. In the early 1990s, the FDA launched an initiative related to the demonstration of consistency of processes and data from clinical lots through to commercial manufacture (8). They mandated the conduct of Pre-Approval Inspections to affirm that commercial materials had their basis in the pivotal clinical trial materials. The utility of the "life cycle model" in this context is clear. Its application to pharmaceutical development, scale-up, and commercial production allows for a coordination of supportive information in the same manner as software and computerized systems validation. A landmark publication in this area was Kenneth Chapman's paper entitled "The PAR Approach to Process Validation" (9). It addressed the developmental influence on the ability to successfully validate commercial operations, a message that has been somewhat forgotten until just recently. Ajaz Hussain, then of the FDA, voiced concerns relative to the lack of process knowledge on the part of many pharmaceutical firms (10). That the FDA believed that such a missive was necessary supports the lack of appreciation for Chapman's earlier effort:

> The goal of development is to identify the process variables necessary to ensure the consistent production of a product or intermediate (11).

Application of the "life cycle model" to pharmaceutical operations addresses the compliance and quality expectations of the industry in an appropriate manner and should be a near universal goal.

Another regulatory development of some importance is that of PAT (12). The concept was well articulated by Dr Hussain while he was with the FDA. To many in the industry, PAT seems like an advance of some magnitude that could seemingly replace validation. To those well versed in automation, PAT is nothing more than the extension of long-standing control practices into pharmaceutical batch production. Engineers familiar with process control will recognize PAT as the installation of feedback control relying on sensors in the process equipment. This is by no means startling, except to those unfamiliar with control loops. PAT has its utility and will improve the quality of products produced by it—of this there can be little doubt. It will not, however, replace validation. In order to use a PAT system, the designer must assure that the installed sensor accurately reflects the process conditions throughout the batch otherwise it will provide no benefit. The need for that assurance means that the PAT system, rather than replacing validation, will actually have to be validated itself!

WHY VALIDATION

First, and certainly foremost, among the reasons for validation is that it is a regulatory requirement for virtually every process in the global health care industry—for pharmaceuticals, biologics, and medical devices. Regulatory agencies across the world expect firms to validate their processes. The continuing trend toward harmonization of requirements will eventually result in a common level of expectation for validations worldwide.

Table 2 Benefits of Validation

Increased throughput
Reduction in rejections and reworks
Reduction in utility costs
Avoidance of capital expenditures
Fewer complaints about process related failures
Reduced testingin process and finished goods
More rapid and accurate investigations into process deviations
More rapid and reliable startup of new equipment
Easier scale-up from development work
Easier maintenance of the equipment
Improved employee awareness of processes
More rapid automation

Utility for validation beyond compliance is certainly available. The emphasis placed on compliance as a rationale has reduced the visibility of the other advantages a firm gleans from having a sound validation program. Some years ago this author identified a number of tangible and intangible benefits of validation realized at his employer at the time (Table 2) (13). In the intervening years, there has been repeated affirmation of those expectations at other firms, large and small. Regrettably, there has been little quantification of these benefits. The predominance of compliance-based validation initiatives generally restricts objective discussion of cost implications for any initiative. But once a process/product is properly validated, it would seem that reduced sample size and intervals could be easily justified, and thus provide a measurable return on the validation effort. Aside from utility systems, this is hardly ever realized and represents one of the major failings relative to the implementation of validation in our industry.

Validation and validation-like activities are found in a number of industries, regulated and unregulated. Banking, aviation, software, microelectronics, nuclear power, among others all incorporate practices closely resembling validation of health care product production. That such verification activities for products, processes, and systems have utility in other areas should not be surprising. The health care industrys fixation on compliance has perhaps blinded us to the real value of validation practices.

CONCLUSION

Validation is here to stay; it has become an integral part of regulatory requirements and everyday life in the global health care environment. There are millions of pages of validation documentation across the world. The presence of such a mountain of information is not justification for its continued existence. Its presence affords a level of confidence in the quality of products for human health. The extent that the risk to the patient is reduced by a validation effort (or any other activity impacting product quality) will ultimately determine its continued utility. If risk-based thinking is adopted across the industry, as

it appears it might be, then certain validations will be become more rigorous, others less so, and others unchanged. If the considerations associated with the implementation of validation for a process become financially driven, there may be additional opportunities. Validation for its own sake seems unlikely for the foreseeable future.

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