Defining Your Product Profile and Maintaining Control Over It, Part 1

Session One of the WCBP CMC Strategy Forum, 19–20 July 2004

Heather Simmerman and Raymond P. Donnelly

A well-characterized biopharmaceutical product is defined during its development by identification and quantification, when at all possible, of both process-related and product-related impurities. The expanding repertoire and sensitivity of the latest analytical methodologies enable detection and measurement of process impurities and product variants at increasingly lower levels and in greater detail. Although a complete and well-defined product profile is understood to be the goal for a marketable biopharmaceutical, the extent of product characterization expected at earlier stages in development of a product is unclear. Expectations for permissible levels of residual processing components or product variants throughout the product development life cycle are also unestablished.

Several factors contribute to the difficulty in standardizing those requirements. Safety is a relative attribute depending on the dose, route and schedule of administration, and patient population — in addition to individual response patterns. Process capability to reduce unwanted components — and potential consequences of varying levels of impurities on product quality characteristics such as stability — highly depend on the structure(s) and nature of the active moieties. Such idiosyncratic variables have led to a "case-by-case" model for regulatory assessment of impurities to be specified and acceptable limits for control.

The absence of clear guidance contributes to uncertainty in the fitness of product development plans, potential misalignment of priorities, delay in regulatory review of filings as these questions are evaluated anew with each dossier, and inconsistent standards from product to product and sponsor to sponsor. Burgeoning clinical and market experience with biopharmaceuticals, especially with categories such as monoclonal antibodies (MAbs) and *Eschericia coli*–derived recombinant proteins, now affords sufficient data to suggest the possibility of setting upper limits for general acceptability of the most common impurities: host-cell proteins (HCPs), residual Protein A, and aggregate forms of the active molecule. Expanded use of in-process feedstream

WWW.PHOTOS.COM

analysis and improved process capabilities to validate reduction of certain impurities below detectable levels well upstream from bulk drug pools may obviate the need for routine specification of such impurities at the bulk drug stage. Establishment of appropriate standards for acceptable levels of process- and product-related impurities, along with strategies for removal and requirements for specification would facilitate efficient and cost-effective development, production, and availability of safe and beneficial new products.

The CMC Strategy Forum on Defining and Controlling Product Profiles: The sixth Well-Characterized Biotechnology Pharmaceutical (WCBP) Chemistry, Manufacturing,

PRODUCT FOCUS: ALL RECOMBINANT PROTEINS

PROCESS FOCUS: PROCESS DEVELOPMENT (PRODUCT CHARACTERIZATION)

WHO SHOULD READ: MANUFACTURING AND PROCESS DEVELOPMENT, PROJECT MANAGERS, REGULATORY AND ANALYTICAL PERSONNEL

KEYWORDS: HOST-CELL PROTEINS, MICROBIAL AND ANIMAL CELLS, PROCESS-RELATED IMPURITIES, IMMUNOASSAYS

LEVEL: INTERMEDIATE

and Controls (CMC) Strategy Forum was held 19–20 July 2004 at the Lister Hill Auditorium on the National Institutes of Health Campus in Bethesda, MD. Sponsorship of the event was provided by the California Separation Science Society (CaSSS; www.casss.org) as part of a series of discussions between industry and regulatory participants exploring current practices in analytical and bioprocess technologies for development and communication of consensus concepts. About 130 people participated in the workshop discussions, providing perspectives from US and European large and small biopharmaceutical companies, regulatory agencies, industry consultants, and academia.

The purpose of this two-day forum was to survey which methods are most useful in identifying and measuring process- and product-related impurities — and identify strategies and specifications to ensure a consistent product profile. The scope of discussion centered on bulk material production and processing and did not cover viral clearance issues or finished dosage form topics. The first day concentrated on process-related impurities (Part One of this article), whereas on day two the focus was shifted to product-related impurities (Part Two). Each day was divided into morning and afternoon sessions, with each day's morning session addressing general strategies for managing impurities and each afternoon session delving into specific strategies and techniques for a selected category of impurity. The afternoon session on day one probed how to demonstrate adequate and consistent removal of HCPs, and the afternoon session on day two explored characterization and specification strategies for product-related aggregates. On both days, forum attendees heard current perspectives from regulators, followed by case studies from industry speakers. Each half-day session then featured a workshop for open discussion.

This month, we present the outcome of discussions on process-related impurities from the morning of day one. Part 2 in the September issue will focus in particular on host-cell proteins. In October and November, we will review results from discussions on product-related impurities from day two.

Session One: Process-Related Impurities

The main guidance for specification requirements of biotechnology products is ICH Q6B (**1**), which defines specifications as a list of tests, analytical procedures or methods, and appropriate acceptance criteria that specify numerical limits, ranges, or other criteria for results. These establish a set of criteria to which a drug substance should conform to be acceptable for its intended clinical use. Specifications constitute the critical quality standards proposed and justified by a manufacturer and approved by regulatory authorities. They are designed and selected as one element of an overall manufacturing control strategy that includes a validated manufacturing process and raw material, in-process, and stability testing.

Evaluation of process-related impurities as part of a well-defined manufacturing process provides assurance that such impurities do not compromise the quality or safety of the final product. For example, the ICH S6 guidance (**2**) cautions that there are risks of allergic reactions or other immunopathological effects associated with host-cell contaminants. Theoretical adverse effects arising from nucleic acid contaminants include integration into the host genome. In addition to cell substrate-derived impurities, other process-related impurities include those derived from cell culture (e.g., antibiotics and media components) and downstream processes (e.g., chemical additives and column leachables). The ability to quantitate such impurities accurately depends on the analytical technology used. The "Impurities" box lists impurities of special interest to regulators along with potential risks.

ICH Q6B provides general requirements for design and development of impurities specifications (**1**). Those requirements provide a framework for the decision tree shown in Figure 1, where they have been arranged as a list of five key factors to be considered: identity of the impurities, assay methods for the impurities, safety information regarding the impurities, process capability to remove the impurities, and overall impact of the impurities to the product quality. Forum participants discussed the questions and actions associated with addressing each factor to identify specific issues, approaches, and current practices used for evaluating process-related impurities and setting appropriate and acceptable limits for them. The decision tree does not rigidly prescribe a stepwise sequence; it is proposed as a tool to guide progressive and thorough development of a scientifically justified strategy that meets ICH requirements.

IDENTIFICATION OF IMPURITIES

Early in development of a product candidate, in mapping out a process an assessment should be made of potential impurities. The list should be based on raw materials used in the process, cell culture components present, cell substrate contaminants potentially shed, possible breakdown materials or leachables from chromatographic media or other production materials, and adventitious microbiological or environmental agents. A search must be conducted to detect all known potential impurities for determining which are actually present in what amounts, an exercise commonly performed as part of process characterization during early product development.

When developing a strategy for assessment and characterization of the impurities, most forum participants organize the list of potential impurities into two broad categories based on their nature as chemicals or inorganics (e.g., heavy metals) and biologicals or organics (e.g., protein, lipids, or carbohydrates). Those categories may guide selection of suitable analytical methods for

impurity detection and analysis, which depend on the physical attributes associated with each distinct class. For example, low–molecular-weight chemicals are relatively nonimmunogenic and therefore usually measured by HPLC methods, whereas protein impurities are often successfully evaluated by immunoassay. Certain classes of impurity, notably chemical solvents, may point toward existing sources of published information regarding their safety and toxicity (e.g., ICH Q3C for solvents) to aid in developing early risk profiles and prioritizing. Very few sponsors use a template approach, in which predetermined impurities or classes of impurities would always require a specification. Instead, forum participants agreed that the other four factors in the decision tree must be considered before deciding on a specification or alternative control strategy for a given impurity.

An approach practiced by most forum participants is to calculate the estimated level of an impurity that might be present based on the amount added to the process and subsequent dilution volumes or clearance factors associated with each process step. Such an initial estimation suggests the magnitude of sensitivity that will be required of an analytical method. The estimated levels can also give preliminary insight into which impurities will present the most challenge for reduction during process development.

ANALYTICAL METHODS AND STANDARDS

In parallel with the development of a process to prepare bulk drug, analytical methods should be developed with sufficient accuracy and precision to measure and monitor process-related impurities at appropriate process points. Most sponsors begin developing proprietary methods at the IND stage for at least some impurities actually present, although commitment of significant resources to developing process-specific methods is typically outweighed by the certainty of changes in a process during development and scale-up. Use of commercially available kits is a commonly used strategy for some impurities (e.g., HCPs or transferrin). Suitability of a kit to detect and measure the particular impurities present in a specific process must be verified. Method qualification studies are especially critical for impurities with a heterogeneous profile (e.g., HCPs) that varies according to cell line and the specific steps in a process.

Another approach combines attributes of both the proprietary and commercial kit strategies in an in-house platform or generic method. About half of the forum audience uses this strategy, in which a proprietary method for a specific impurity or category of impurities (e.g., Protein A or HCPs) is developed and used to test multiple products from related or different processes. This approach allows rapid deployment of a method with a minimum development effort, and it permits comparison of impurity levels across products or processes.

When companies use a combination of commercial kits and in-house methods early in development, later development phases tend to focus more on establishing proprietary methods specifically tailored to accurately and reliably measure key impurities present in a bulk drug. The FDA recommends consultation with regulators early in development regarding strategy for selection and development of analytical methods, a common practice among forum particpants, to achieve a mutual understanding of the sensitivity required to demonstrate fitness for purpose.

Global standards and specifications for process-related impurities would, if available, guide development of appropriately sensitive assays. But a lack of standardized methods and absence of commercially available reference standards for impurities have hindered progress to these objectives. Except for DNA, which has a WHO specification (**3**), there are no internationally recognized specifications for process-related impurities. This has led to disparities among regulatory agencies in various global regions over reporting requirements and acceptable levels, often leading to different specifications and testing commitments across global filings for the same product.

Establishment of centralized laboratories qualified to perform standardized tests for common impurities (e.g., HCPs and culture media components) could provide a means for standardizing methods and assay materials. Such contract testing could be helpful for companies lacking the necessary expertise to develop complex antibody reagents, for example, or resources to establish in-house assay technologies. For many companies, however, the need for quick results to support expedited product development timelines might not be satisfied by a contract

laboratory. The heterogeneity and process-specific nature of some impurities and a persistent obligation to perform method qualification studies would also complicate a central, standardized laboratory approach.

Standards Are Needed: A large majority of forum participants, however, favor development of commercially available, certified reference standards that could be used with in-house methods to provide some standardization of assay responses across products, processes, and even companies. Participants broadly supported formation of a consortium to qualify and certify reference standard materials for commonly occurring impurities. It could include European and/or other global organizations with similar vested interests in establishing harmonized impurity standards. Use of standardized reference materials would enable collection of at least roughly standardized data for impurity levels in diverse products from many companies, in turn promoting development of global upper limits for these impurities.

Combined with platform or generic methods, the use of standardized reference materials and established acceptable upper limits for impurities could facilitate rapid development of a process suitable for preparation of Phase 1 clinical trial material. Phase-appropriate refinement of methods in response to process changes during development would be expected to ensure that actual impurities present are detected and accurately measured. A clear majority of forum participants retain and recommend retention of representative samples from the processes used during clinical development. Sufficient sample quantities are reserved to permit comparative testing as methods and processes evolve through development phases to demonstrate comparability and improvements in the quality of clinical and commercial materials. Ultimately, accuracy of impurity measurements and the determination of residual amounts of impurities in a bulk product are required for reliable

Figure 1: Decision tree for setting an acceptance criterion for a drug substance process-related impurity
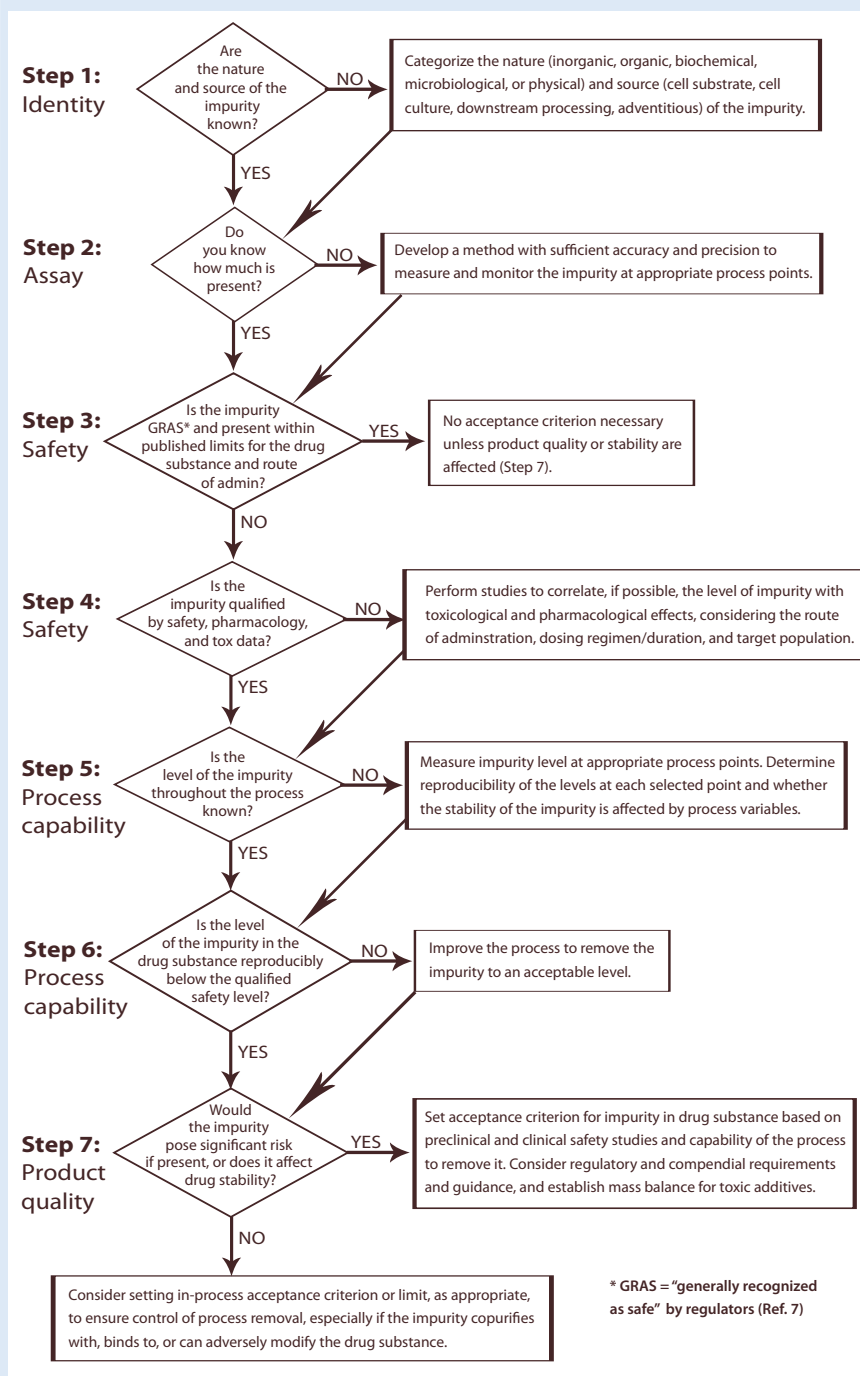
toxicological and safety evaluations.

SAFETY CONSIDERATIONS

Determining acceptable amounts of residual process-related impurities must be evaluated for patient safety. Following the concepts presented in the ICH Q3 and S6 guidelines, data must be obtained to demonstrate the biological safety of a given impurity or profile at the level(s) and in the manner presented to a patient. This

depends on the dose administered, the schedule and duration (acute or chronic) of dosing, and route of administration.

The target patient population can also have bearing on determination of an acceptable level of impurity. For example, pediatric, geriatric, or immunocompromised patients may have heightened sensitivity to a particular process-related impurity. Differences in population subgroup

sensitivities and intersubject variability in response have in most cases complicated establishment of a direct correlation between exposure levels and clinically observable effects. Latent adverse effects of chronic administration, including potentially more than one protein therapeutic at a time (e.g., patient under simultaneous treatment for cancer and rheumatoid arthritis), may be revealed only with very large and diverse patient populations. These issues — and the potential for future development of product with additional indications in different patient populations, as well as off-label uses — prompts a regulatory recommendation to reduce impurities to levels as low as reasonably possible.

Before evaluation of human responses to a Phase 1 clinical product profile is begun, nonclinical data supporting safety of the drug constituents must be obtained. Toxicity studies in animal models are essential (**2**), although the relevance of those data in predicting human safety may be diminished by species-specificity differences. Published sources of information may provide guidance regarding levels of substances generally regarded as safe up to specified levels, through a history of use as buffers, solvents, or excipients in already approved products (**4–5**); as a normal physiological constituent of blood (**6**); or as substances used as food additives (**7**), which would be qualified for oral administration only. Known toxicities and threshold levels for toxic effects of many chemicals are also online at http://toxnet.nlm.nih.gov, at www.epa.gov/ebtpages/polltoxicsubstances.html , and at www.envtox.ucdavis.edu/TDC/DocCenter/default.html).

Other existing data specifically regarding process-related impurities can be found in the set of drug substance specifications for approved biopharmaceutical drug products. A database of such specifications (not identifiable by product or company) would be useful in providing perspective and context if it included test methods used and acceptance criteria, along with selected product information such as cell line, dosing, and administration details. Development of ICH guidelines on

residual solvents linked to a database of toxicological results for solvent types or categories with exposure limits and dosage levels actually administered in a survey of synthetic chemical APIs and corresponding drug products. Recently, confidential surveys of existing data (data mining) and collaborative work plans between industry, regulators, and academic resources have been initiated by the Product Quality Research Institute (www.pqri.org) to establish science-based pharmaceutical standards. Forum participants were interested in using such an approach to establish a database for biopharmaceutical product information.

Relevance of existing data to the targeting of acceptable impurity levels in new products would need to take into account the similarity of the products and overall product profiles because presence of a given impurity in combination with others and the specific active moiety could produce different effects. The importance of an overall product profile in safety assessments is predicated on the ability of a manufacturing process to simultaneously remove a suite of impurities to varying degrees at each step. Focusing on the levels of impurities with known safety issues as signal impurities could provide a gauge for assessing the overall acceptability of a multicomponent profile and provide an appropriate driver for process development.

PROCESS CAPABILITIES

There is a certain elegance in reducing impurity levels to the lowest level achievable and measurable, but that comes at a high price. Resources and time for process development must be factored in, with consequent delay in market availability of potentially life-preserving drugs for unmet medical needs. There is also the risk (and cost) of failed batches unable to meet over stringent limits that are not meaningful to patient safety, thus jeopardizing supply of essential products. From a public health perspective, establishing a standard for impurity removal based on the best available process capability (lowest level achieved) could inhibit new

market entries without regard to clinically relevant threshold levels. In the absence of established, acceptable upper limits for impurities, sponsors must establish their own internal control targets and appraise their processes for meeting them.

Process Development: Most forum participants follow a process development program consisting of three stages: characterization, qualification, and validation. Early in development, clinical trial material is made by a process using defined parameters providing some information on the natural variability of its performance. Extensive testing is performed for known and potential impurities, both at in-process stages and in the end product. In other typical laboratory-scale studies, process operating parameters are purposely varied to assess their impact on performance and product quality, helping to determine the robustness of removing process-related impurities. Few companies have predetermined points in their processes by which clearance of impurities should occur. Characterization efforts, which may include pilot-plant consistency runs, confirm the process development work and provide a basis for defining clinical-phase limits of acceptable ranges and determining critical process parameters. Although the concepts of failure mode analysis are applied during process development by many companies to identify critical and noncritical process parameters, systematic and quantitative risk-based approaches are not yet implemented to manage process development.

The transition from process characterization to qualification appears for most companies to coincide with the production of Phase 3 clinical material. This may be done at pilot or commercial scale, but a clear majority of forum participants indicated the importance of using the intended commercial process to link qualification of the impurity profile of product with clinical outcomes during pivotal trials. For some companies, the qualification exercise is associated with initial scale-up runs at commercial scale to demonstrate comparable performance with the pilot-scale

process. In either case, process validation is performed at the commercial facility to show reproducibility, and the resulting data are used to finalize a control strategy: what end-product specifications and in-process controls will be set and what tests may be eliminated from routine performance.

Thorough understanding of process capabilities and appropriate control limits for impurities can enable postapproval process changes by providing a meaningful gauge to assess comparability of pre- and postchange products. Responding to process deviations and excursions can be expedited if characterization studies show the robustness of the process to maintain impurities within acceptable ranges — and when margins between the target and proven acceptable range are wide and well-defined. A large majority of forum participants retain samples from toxicology, clinical, and other key batches for reference comparison when changes are made to processes, methods, or facilities — and for use as control samples during deviation investigations.

IMPURITIES AFFECT PRODUCT QUALITY

Process control of impurities is key to product quality. Within the framework of a total quality strategy to ensure product consistency, one of several approaches may be selected to control a given impurity: a specification may be established for routine lot-to-lot testing of the end product; a limit may be set for routine lot-to-lot testing of in-process samples without setting an end product specification; or consistent elimination of an impurity may be demonstrated by process characterization and validation, obviating the need for routine in-process or end-product testing. Nearly all companies represented at the forum have successfully used a strategy of process validation or in-process monitoring in lieu of end-product specification testing for selected impurities. This strategy has achieved regulatory acceptance when adequately justified with sufficient data. Through Phase 3 clinical trials, virtually all sponsors conduct end-product testing

for the impurities known to be present, delaying until the market filing any proposals for deleting those end product specifications for which process validation has demonstrated impurity removal. Because of a limited data set available at the time of filing, postapproval review and potential modulation of acceptance criteria for end-product specifications and in-process limits can be expected to encompass the normal process variables encountered over time in the finalized acceptance criteria.

Selection of a suitable quality control strategy depends on holistic consideration of all relevant factors: e.g., critical quality attributes of the protein product, impurity sources in the process, ability of analytical methods to detect that impurity from in-process or end product samples, and the margin between process capability and the safe level of the impurity. If an impurity is introduced late in a process, if it can adversely affect a critical product attribute (e.g., stability), if it presents a safety risk, or if there is marginal capability for process clearance, then a specification should be set for that impurity's presence in the drug substance. Conversely, if the new impurity is inert, if its source is early in the process, and if clearance capability is very high and consistent, then process validation is a viable approach to demonstrating control. When one impurity can act as a sentinel for detecting incipient deviations from manufacturing consistency, and the associated assay is simple and quick to perform, then setting an in-process limit for that impurity at appropriate process points can provide an effective means for monitoring cGMP compliance and control to ensure product quality.

In the September issue, part two of this four-part article will examine the challenges of monitoring and controlling host-cell protein impurities (Session Two). Part three in October will cover the topic of product-related impurities (Session Three), and in November the article will conclude with a focused discussion on aggregation (Session Four).

REFERENCES

1 ICH. Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. *Federal Register* 64, 18 August 1999: 44928; www.ich.org/MediaServer.jser?@_ID=432&@_MODE=GLB.

2 ICH. S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. *Federal Register* 62(222), 18 November 1997: 61515; www.ich.org/MediaServer.jser?@_ID=503&@_MODE=GLB.

3 WHO Expert Committee on Biological Standardization. Highlights of the 46th Meeting, October 1996. *WHO Epidemiological Record* 72 (20) 16 May 1997: 143–145; www.who.int/docstore/wer/pdf/1997/wer7220.pdf.

4 Nema S, Washkuhn R, Brendel R. Excipients and Their Use in Injectable Products. *PDA J. Pharmaceut. Sci. Technol.* 51(4) July–August 1997: 166–171.

5 Powell M, Nguyen T, Baloian L. Compendium of Excipients for Parenteral Formulations. *PDA J. Pharmaceut. Sci. Technol.* 52 (5) September–October 1998: 238–311.

6 Kasper DL, et al. Appendix: Laboratory Values of Clinical Importance. *Harrison's Principles of Internal Medicine* (16th Edition). McGraw-Hill, Inc., New York, NY, July 2004.

7 Substances Generally Recognized As Safe. *Code of Federal Regulations* Part 182, Title 21, Volume 3, revised 1 April 2004; www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=182&showFR=1. ⊕

Heather Simmerman, PhD, is associate director of corporate quality compliance for Amgen, Inc., Thousand Oaks, CA. Raymond P. Donnelly, PhD, is with the division of therapeutic proteins in the Office of Biotechnology Products at FDA's Center for Drug Evaluation and Research. Other panelists in this session were Greg Blank, PhD (Genentech, Inc.) and Lynn Conley, PhD (Biogen Idec).