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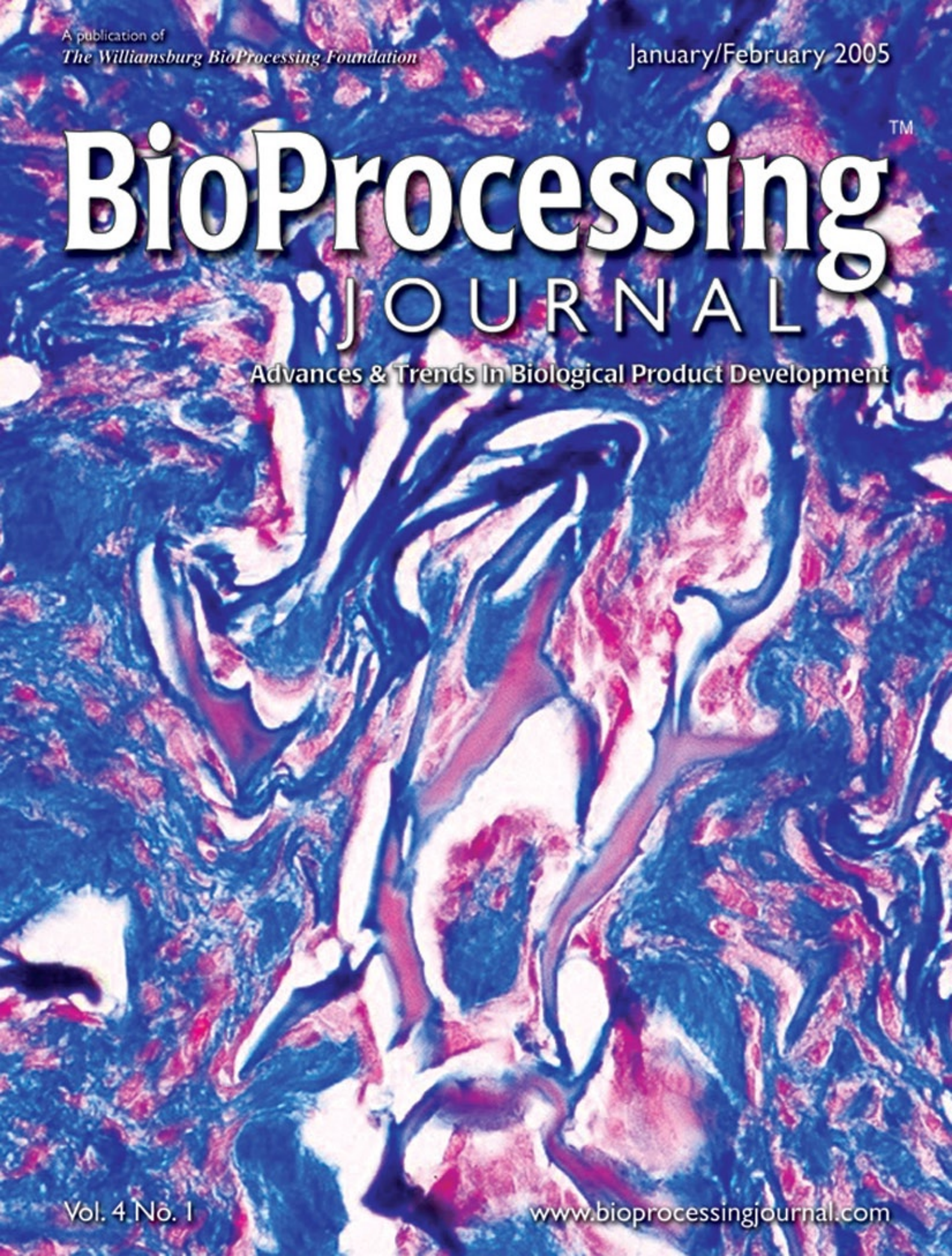

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Critical Path: *A Mindset for Better Product Development*

By KEITH L. CARSON

Illustration courtesy of Millipore Corporation.

Although biological products are being licensed at a fairly steady pace, the cost to develop each product can be incredibly high, and far too many products with very little chance of success are entering clinical trials.

The cost of developing a biological product is now estimated to be as high as $1.7 billion. This is truly a staggering figure that would seem to prevent all but the strongest company from attempting such a gamble. However, this number includes the cost of all the products that didn't make it through pre-clinical development, or which entered clinical trials and failed for any number of reasons.

If products could be assessed earlier as to their potential safety and efficacy, then the overall cost of product development could be cut dramatically. This is really the focus of the U.S. Food and Drug Administration's (FDA's) Critical Path Initiative, which was initially formulated and established in 2004 under the leadership of Mark McClellan, M.D., Ph.D., while he was the FDA Commissioner. Even though industry and academia have been working on better methods to predict and demonstrate safety and efficacy, this FDA initiative has the potential to galvanize and transport the necessary concepts into effective solutions.

In an effort to achieve the goals of this Initiative, FDA's Center for Biologics Evaluation and Research (CBER) held a workshop in Gaithersburg, Maryland on October 7.[1] A number of the comments and concepts presented in this article were proposed by the workshop participants.

When all is said and done, the primary concepts for improving product development boil down to improved, and possibly standardized testing methods and materials, plus better clinical trial design, more predictive safety and efficacy models, increased data sharing, and enhanced regulatory guidelines.

Methods Development

Analytical methods often become a contentious subject in the scheme of product development and testing. Some are covered by patents and others by years of personal investment in making the techniques appear to be the most powerful and predictive. Scientific careers can hinge on the acceptance or rejection of a method upon which many papers have been published.

However, there are huge benefits to be gained by establishing accepted, and possibly standardized, methods for product development and clinical evaluation. Regulators must now evaluate data on a vast range of product types for a wide variety of applications. But even when a similar product is being used to treat the same indication, different methods may make it impossible to compare the data for an investigational product to anything that has been previously evaluated.

While biological products are the most difficult to characterize, and their evaluation may require biological assays with large inherent variability, certainly some assays can be established as accepted standards for various product types. Such standardization would go a long way toward helping regulatory

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reviewers make reasonable comparisons among the data packages they receive for fairly similar products.

In addition, standardized methods would make data far more useable by industry and academia when they seek Investigational New Drug (IND) status for a product. If these methods produce very different results, then there would be reason to question the method itself, the standards being used, the training of the technicians, or even the product. Besides identity, purity, and quality issues, differences in homogeneity could be indicated, along with potential signs of immunogenicity.

Assay standardization could end up being fairly limited for newer product types especially with analytical technology rapidly changing. Yet such standardization would still provide significant value and should be the goal of each working group. In addition, such a standardized methods concept would not be intended to prevent better assays from being accepted as technologies evolve, but these new assays should only be adopted by the consensus of the major stakeholders.

Reference Materials and Standards

Certainly with many, if not most, assays, the results are only as meaningful as the reference materials or standards used to run them. Even with the biotech industry as far along as it is, very few high-quality reference materials have been established. Many of the reference materials now available for general use were not produced in a well-characterized manner, and their value is questionable.

Typically, every company and lab has produced its own reference materials for use in characterization and lot-release testing. While many of the industry-produced materials are well characterized and are being used in validated assays, there is often no way to compare the materials that are being used, or how they are affecting the results of the assay. This makes it essentially impossible for regulatory reviewers to compare the results of one company's assay with those from another product sponsor. When available for public consumption, these data are often meaningless to other firms or labs that are developing similar products.

Outside the realm of product testing, there is the even broader issue of testing raw materials. Once again, a very small percentage of the components used in biological product manufacturing have been sufficiently tied to an accepted standard. A tremendous amount of work will be required to establish what is needed for the most basic of components, let alone the more complex additives, including those that are animal derived.

Of the raw materials, none could be harder to tie down than the cells. Even when a full history is known for a cell line and a well-characterized bank has been produced, it is virtually impossible to compare one sponsor's cell bank to that of another. In cell-based product development, the products are expected to be heterogeneous, but it can be quite surprising just how heterogeneous cell banks can be for more advanced products such as recombinant proteins and antibodies. While product heterogeneity may be advantageous, and could even provide a crucial role in how the product works, the differences among the banks of the various product sponsors create additional concerns for the regulatory reviewers, and make data from similar products even harder to compare.

And then there are the products for which no cell line exists, such as autologous cell therapies that start with the patient's own cells. For such applications, there would still be aspects of the starting materials that could be comparable to some sort of reference.

Clinical Trial Design and Management

The focus of Critical Path thinking is to start with preclinical testing design. Here, models are needed to do a far better job of predicting product safety and efficacy earlier in the development process. Such models will require a more detailed understanding of the mechanism of action in the context of how entire biological systems work, and not just how cells behave in culture. New methods, standards, and biomarkers are needed to predict system and immunological responses, and significant improvements are needed in both *in vitro* and animal models for product safety, as well as the characterization and validation of surrogate clinical endpoints for product efficacy.

With more meaningful preclinical data, it is hoped that many products that would otherwise fail in clinical trials will be scrapped and not further waste sponsor resources. In addition, such process improvements would free patient populations, experienced clinicians, and regulatory reviewers for trials that would have a greater chance of success.

New technologies will have to be customized for use in these methodologies, and may include various applications of micro-fluidic, micro-array, and nanotechnology. Data mining and advanced data analysis techniques will be needed to better understand what to look for and what is actually significant, and statistical experimental design will have to become more rigorous and result in more meaningful results with smaller and more targeted patient populations.

In addition, data reporting methods must become more standardized and do a better job of reporting adverse events and unfavorable data, as well as operate in a system that helps to minimize clinician bias while avoiding conflicts of interest for either academic researchers or industry consultants.

Sharing Data

Many individuals at CBER, plus others who participated in the recent CBER workshop, have expressed a desire to see product sponsors share more data during product development and clinical evaluations. Such data sharing would show sponsors what is working, and what FDA is responding to in a negative or positive manner.

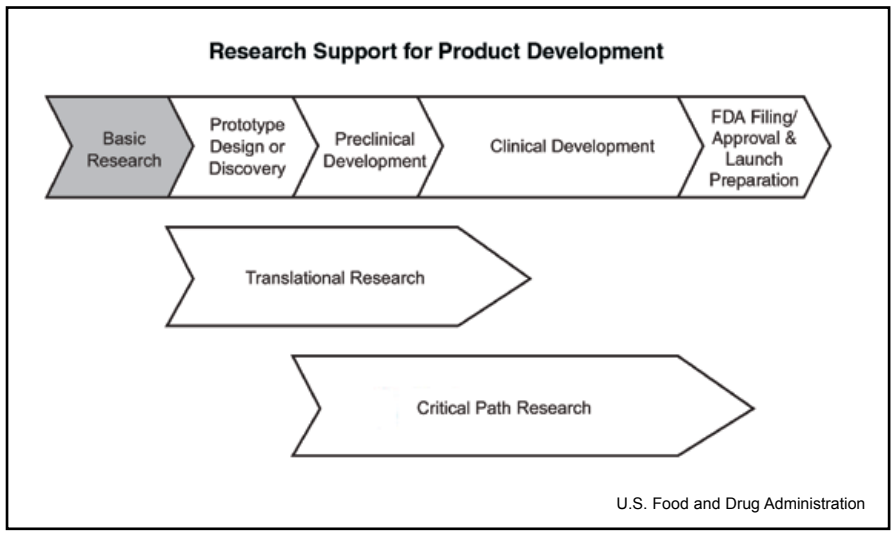
Of course, most companies consider such data to be confidential information that could give them an edge over their competition. The solution will be to show industry that there is more benefit to be gained from sharing such data than there is in keeping it confidential, and that seeing the data from another

company's products is more valuable than anything that could be lost by showing its own data.

When it comes to product data, the most informed and knowledgeable people are those at FDA who see all of the regulatory submissions. They know what has worked in prior submissions and what has not. They know that similar products have not been able to demonstrate certain claims and possibly why they failed. However, such data is confidential and could only be released by FDA in the most general manner, or for those products that become licensed. Therefore, FDA couldn't be relied on to help make much of the submission data and analysis available, no matter how valuable it could be.

Of course, product sponsors don't share all of their data with FDA. There appears to be a deep-seated distrust of how FDA would use additional product data, and what ramifications would befall the sponsor that provided such information. Certainly, the biggest fear is that FDA could see something that would make them take a product off the market, or at least require more clinical testing of a marketed product. Next is the fear that new data could support a requirement for lot-release testing, whereas the sponsor is only collecting the data to learn more about the product. Building trust in this area will be tough, but such additional product data could provide tremendous knowledge on how similar different products really are, and why they might perform in different ways when they reach the clinic. Armed with such data, FDA could make more informed decisions about products and help sponsors spot potential problems before they spend a lot more money. Unless this type of data is shared in some fashion, biological product development will suffer.

But where could such data be stored and shared? While FDA sees everything a sponsor is willing or asked to submit, it is my opinion that the agency does not have the resources to store and manage a vast amount of data. There are academic databases that have been specifically built for bioinformatics with web-based access. Such a database system could be contracted by an industry consortium to store and manage the data, and provide analysis routines through the user interface. In addition, there may be large private-sector databases that could serve this function.



Where Do We Go From Here?

Working Groups. What I have seen work quite well are the reference material projects that have involved working groups and FDA co-sponsorship agreements. The working groups are composed of representatives from industry and academic institutions. In addition, the co-sponsorship agreements allow FDA representatives to take part, and it puts an unbiased third party like WilBio in place to facilitate the process and make information available on its website. Such projects have resulted in the production of a well-characterized, wild-type adenovirus, and will soon produce an adeno-associated virus and a white paper on lentivirus reference materials.

In my experience, when there are many problems that have to be solved, it is best to identify the biggest problems and work on those first. But the importance of a particular problem is in the eye of the beholder, and both the problem list and priority order will be different for the various product types, applications, regulatory bodies, patient populations, and political environments that are involved.

Therefore, I recommend that product segments first be defined. Such segments will be dictated by the above factors, but also could be affected by other parameters that are less apparent. In general, a designated segment should be populated with individuals who have similar interests and issues, and are working on a certain type of product that is targeted at a common set of applications.

Once these product segments are established, I suggest that a working group be set up for each one. The members of each working group can be recruited through various means, but membership must be open to any individual who has a real interest and involvement in the product segment, and who can make a real contribution. Note that some issues, such as bioethics and patient rights, may require a separate working group that will concentrate on less technical aspects of the Critical Path Initiative.

The key to any effective working group is having key members who drive its activities. Since industry typically has the most to gain from such an endeavor, it is vital that an industry representative take a leading position and serve as the chairperson for the group. If possible, an academic representative should become a co-chair, and someone from FDA and the facilitating organization (e.g., WilBio) would serve on an executive committee.

Once established, a working group can meet via email exchanges, internet chat rooms, teleconferences, or face-to-face discussions during an established technical conference at which

the product segment is typically supported. The first task would be to define the problems associated with making product development more efficient, and to place the problems in the order of priority.

Toward the top of any such problem list should be methods, reference materials, data sharing, and regulatory guidelines. However, some groups may have issues that are even more pressing.

Then, the really hard work of solving these problems would begin, and it would take dedication and persistence by all working group members to see measurable results. Participation would require a long-term commitment from both the group members and the organizations that pay their salaries.

Raw Materials and Contract Services. I also recommend that a separate working group be formed to work on raw material standards and testing methods, and yet another group should handle issues specifically related to contract manufacturing and other contract services. As the demand for both raw materials and contract services continues to grow, the key issues must be defined and advanced by individuals who are most capable of addressing them.

For example, representatives from the leading cell culture media supply companies should be sharing testing methods and data for a wide range of raw materials. While the U.S. Pharmacopeia (USP) has addressed many of the more basic components, the vast majority of cell culture raw materials have not been linked to standards, and the testing methods vary such that much of the characterization data on these substances cannot be readily compared A database is then needed to store characterization data on the key components, and a standardized certificate of analysis could be adopted that would show the same test parameters for a particular component. The work published from this effort could also lead to more rapid and reliable testing methods for biological product identity, purity, and quality.

Reference Materials. Each working group would define the critical reference materials that are needed for the group's specific application and product type. Projects along the lines of that used for the Adenoviral Reference Material could then be adopted to produce an adequate supply of the material needed, and this material could then be used to validate a sponsor's internal reference materials and assays.

Cell Lines and Substrates. As stated earlier, cell lines can contribute much of the inconsistency that is seen among similar products. Therefore, there are very good arguments for establishing standard cell lines that would be used for all product manufacturing. Taken from an established repository, such cells would be used to develop master and working cell banks. With more standardized media components, cell characterization techniques, and freezing methods, much of the product variation from cell line differences could be eliminated.

Methods. Each working group would establish a list of key issues that are affected by variations in testing methods. Wherever possible, standardized methods could be adopted for various product assays, or could serve as platforms for improvement. If reference materials were available, then the data from these assays would be even more comparable for similar products.

Guidelines. All of the working groups could then generate a report, or white paper, that describes their key issues, priorities, objectives, and proposed solutions. As an FDA representative would be involved in each working group, regulatory input would be such that the white paper could serve as the basis for regulatory guidelines. While certainly not an official regulatory document, product sponsors could follow the guidance of this document when no other FDA guidance exists.

Data Sharing. Along with the other working group efforts, participants would have to agree on what data they would be willing to share, and how it would be made available. As more data is shared on product characterization and clinical trial results, it is hoped that the resulting benefits would become obvious, and decisions would be made to share even more data. At the same time, FDA representatives in each working group would have to earn the trust of the members and assure them that their openness would not create even higher regulatory hurdles.

With more shared data, plus standardized materials and methods, the entire biological products industry should realize lower development costs, and FDA would be able to do a far better job of understanding and regulating the products they see. The end result will be a more successful industry and lower product costs that could be passed on to consumers.

More Information, Plus Comments and Questions

A considerable amount of information on the Critical Path Initiative has been amassed on the FDA website, and includes an excellent White Paper entitled *Challenge and Opportunity on the Critical Path to New Medical Products.* To view this white paper, go to *(http://www.fda.gov/oc/initiatives/criticalpath/)*. In addition, CBER has posted slides from its workshop that was held October 7, 2004, in Gaithersburg, Maryland *(see http://www.fda.gov/cber/summaries.htm and scroll down to 10/7/2004).*[1]

CBER is accepting comments on these slides and suggestions on any Critical Path issue at the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852, or at *www.fda.gov/dockets/ecomments*. Please identify all comments with docket number 2004N-0366, and submit two copies unless submitting as an individual.

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1. *From Concept to Consumer: Center for Biologics Evaluation and Research Working with Stakeholders on Scientific Opportunities for Facilitating the Development of Vaccines, Blood and Blood Products, and Cellular, Tissue and Gene Therapies.* October 7, 2004. http://www.fda.gov/cber/summaries.htm.

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