Gelcap Dosage Form Receives Patent

A patent issued to Banner Pharmacaps (Highpoint, NC) tightens the competitive market for gelcap dosage forms. Banner's Soflet patent covers two end-product aspects: the gelatin composition of the shell and physical properties relating to tamper-resistance. The patent, explains Charles Cain, senior vice-president of legal and public affairs, "is independent of equipment or manufacturing processes." Patents issued to Banner in the mid-1990's already cover machinery and manufacturing processes for Soflet products.

Initial development of the gelcap design was in response to the need for tamper-evident dosage forms. Now a popular platform with a growing customer demand, gelatin dosage forms are especially useful for over-the-counter analgesics because of their attractiveness, swallowing ease, and odor-masking properties, prompting Banner to pursue more stringent product protection for their Soflet technology.

The major difference of the Soflet platform versus other known gelatin dosage forms, remarks Cain, is that "the caplets are gelatin-enrobed rather than dipped." The enrobing process involves the application of layers of elastic gelatin film to opposing sides of a solid tablet preform or core, which allows the film to bond tightly to the tablet. The layers are sealed together and extend around a specific location on the tablet to increase the visibility of tamper evidence.

Enrobing occurs at a low temperature and in a dry state versus the liquid gelatin baths used in the dipping process. According to Banner, low temperatures and a dry environment help the medicinal core tablets become less adversely affected by the enrobing process, aid in maintaining the integrity of the active ingredients, and eliminate the presence of air between the gelatin coating and the tablet core. The enrobing process can also be used to apply film layers other than gelatins, and enteric coatings also can be applied.

The gelatin films can be manufactured in various colors, producing single- or bicolored tablets, with bicoloring being an additional tamper-resistance feature.

Felicia Pride

PDA's ARC Gathers IT Creatures Great and Small

A work in progress since 2000, the Parenteral Drug Association's Audit Repository Center (ARC) is taking shape as a useful tool in the industry's move to higher levels of automation, information management, and total information technology integration and implementation.

As a prerequisite for validation under 21 *CFR* Part 11, companies providing computer products and services to the pharmaceutical industry, including commercial off-the-shelf (COTS) software, are required to undergo audits of their product development process. Although FDA has now indefinitely withdrawn its draft guidance document for 21 *CFR* Part 11, these audits are still required under the original underlying predicate rules of Part 11.

PDA established the ARC to help industry more efficiently and cost effectively meet this audit requirement, avoiding the cost and duplicate effort associated with carrying out multiple audits of a company's software development operations. As described by Harvey Greenawalt, ARC president, "Some suppliers were getting an inordinate number of audits, sometimes by two to three different divisions of the same company, and everyone could have a different set of criteria or emphasis on what was important." Instead, the ARC now offers a central, independent source of audit information on multiple software vendors that is accessible on request to client end-user companies.

The scope of an ARC audit can range from a complete enterprise resource planning (ERP) system to an embedded machine controller, involving a single auditor over a few days or an audit team over several weeks (see Table I). As

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FDA Shifts CBER/CDER Review Functions

By the end of June, FDA expects to complete a consolidation program that will move certain therapeutic product reviews from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). CDER's charter is to ensure the safety and effectiveness of pharmaceuticals, while CBER is responsible for ensuring the safety and efficacy of blood and blood products, vaccines, allergenics, and biological therapeutics.


Janet Woodcock

The objectives of the consolidation are efficiency of operations and consistency of reviews, especially in light of declining review funds. FDA has collected "significantly less" in fees than estimated as a result of a reduction in the number of new drug applications, according to FDA deputy commissioner Lester Crawford, DVM, PhD, speaking to the US House of Representatives in March 2002.

The consolidation also signals a market reality. "It's a recognition that the biotech industry is maturing. As it does, the regulatory structure around it must also mature," says Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research since 1994.

Before taking on her current position, Woodcock was employed at CBER. Ironically, in the late 1980s, when she first joined FDA, the drug and biologics entities were one center rather than the two that exist today. Woodcock points out another irony: as a result of FDA's structure at that time, the first hormones were regulated as drugs. Growth in the biotech industry during the past 15 years appears enhanced by the number of new hormone therapies introduced, regulation notwithstanding.

"One-third of drugs in development today are biotech products," says Sara Radcliffe, assistant vice-president for biologics and biotechnology at the Pharmaceutical Research and Manufacturers of America (PhRMA, Washington, DC). "One-fifth of those launched worldwide are biotech products. That compares with only 7% in 1998 and only 0.5% in 1989."

Woodcock points out, however, that many of these biotech products are already regulated by CDER: "If you look at the number of approvals, the recombinant proteins and monoclonals are not a large group. There are many other products referred to as biotech: antisense molecules, Gleevac, the new polypeptide AIDS drug Fuseon, that are considered in the realm of biotech."

Radcliffe acknowledges the importance of the efficiency and consistency objectives of the CBER/CDER consolidation, but given the long development timelines for pharmaceutical and biotech products, says PhRMA is also concerned about commitments over time and about staff retention. "We have questions about how [the consolidation] will pan out one or two years from now," says Radcliffe. "Manufacturers at the investigational new drug (IND) and pre-IND stages now work with the CBER Office of Therapeutics Research and Review. But what happens with ongoing research programs, when manufacturers need advice and dialog? How will that transition be managed? It's important that those with an institutional memory remain for continuity, that the former CBER staff remain after they are merged into CDER."

PhRMA's concerns stem from the

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Chemical Libraries Aid Drug Screening Research

Boston University's chemistry department (Boston, MA) has been awarded a $10.7 million grant from the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) for the development of a center for chemical methodologies and library development (CMLD). The center's focus is aimed at asymmetric syntheses of complex, natural product-like scaffolds and molecules, and the development of novel combinatorial techniques that will help pharmaceutical researchers in their efforts to develop new drugs.

According to assistant professor of chemistry and pharmacology John A. Porco, who will direct the new CMLD, the chemical libraries are of great interest to pharmaceutical companies, as well as to biomedical science, as novel pharmacological tools. Pharmaceutical companies are limited in terms of what they can discover because of the small amount of diverse information available in chemical libraries. "The current lack of diverse libraries stifles innovation and limits the directions research can take," he said.

The libraries will provide the necessary resources to complement work in combinatorial chemistry that is conducted at major biotech and pharmaceutical firms. Along with Porco, BU researchers James Panek and John Snyder, both professors of chemistry, and Scott Schaus, an assistant professor, will contribute to the research projects the Center undertakes.

The NIH awarded one of their two Centers of Excellence grants to Boston University because of its strong collaboration of synthetic organic chemists. The grant stands as a commitment from NIH to support research in synthetic organic chemistry.

According to Porco, the BU CMLD will become an epicenter of chemical research and training and will provide molecules of unprecedented complexity for use in pharmaceutical and biological research.

Doreen Coppola

Table I: ARC audit categories.

Product/service type	Description
Building automation	Solutions for monitoring and controlling building and other environments
Factory automation	Solutions for distributed process control and warehouse automation
Shop-floor control	Solutions for supervisory control and data acquisition (SCADA)
Smart manufacturing equipment	Embedded machine control for sterilizers, fermenters, compressing machines, and so forth
Smart laboratory equipment	Embedded instrument control for HPLC, IR analyzers, X-ray analyzers, data loggers, and so forth
Manufacturing execution technology	Solutions for integrating FA, SFC, and SME above certain IT solutions for paperless manufacturing
IT business solutions	Solutions for automating diverse business processes and transaction. Products for MRP are placed here.
IT data and information managers	Off-the-shelf solutions to collect and manage data for diverse laboratory, research, and business operations. Example products would be laboratory, maintenance, personnel records, training, clinical data, and document management systems.
IT utilities and tools	Off-the-shelf solutions for data analysis and file managers
IT desktop solutions	Off-the-shelf productivity solutions that run on personal computers. Example products are word processors, spreadsheets, databases, unique data analytical tools, and statistical packages
IT network solutions	Networking hardware and software solutions.
Custom services IT solutions	Custom services for software programming to produce unique automated solutions for business processes.
Custom services real-time solutions	Custom services for software programming to produce unique automated solutions to control processes, devices and/or equipment. Examples would be PLC applications, robotics, and process control.
Custom services systems engineering	Custom services for providing turnkey systems solutions, which would include specifying, designing, procuring, constructing, and installing systems using any combination of products and custom programming services.

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emphasized by Greenawalt, "companies 'fund' the audit, but we select and pay the auditors. This way, the funding company doesn't have influence over the auditing process. Whatever the auditors say is what's published."

The ARC audit methodology is defined in the PDA's "Technical Report 32" document issued in January 2000. Says Greenawalt, "TR-32 standardized the audit criteria into a comprehensive, thorough and evaluative approach. Users get a picture of the entire development process of the software that attests to its integrity. From this they can judge whether the product will meet their needs." With its first auditors qualified in February 2000, the ARC now holds around 28–29 completed audits with an additional 5–10 in progress and another 10 requested.

David Konciak, director of marketing and business development at Taratec (Bridgewater, NJ), sees the ARC as providing a service to the industry. As both a company frequently hired to conduct audits (some of its people have been through the PDA's ARC training), as well as a sometime recipient of customer audits, Taratec sees the process from both sides. "At a high level, I think it's a good thing that vendors are willing to step up and demonstrate their ability to handle a detailed audit," says Konciak. "It also helps industry by establishing a standardized approach to audits, providing a more level playing field."

Similarly, Keith Chambers, senior product evangelist at GE Fanuc Automation (Foxborough, MA), also sees value in the ARC concept, particularly for smaller pharmaceutical companies. "We've observed that larger drug companies will typically have a regular audit schedule involving specialized personnel, while smaller companies without the same kinds of resources, will tend to rely on forms and questionnaires." Chambers says they typically have about 10 vendor audits per year of their software process quality systems and also contract for self audit of their processes.

Dan Matlis, vice-president of business development at Stelex-TVG (Bensalem, PA), describes the ARC audit as "probably the most thorough, most detailed audit we've come across." As a supplier of automation systems and services, Matlis says they've been audited many times and see a definite benefit in being able to streamline the process.

The ARC isn't necessarily a panacea solution for all situations, however. Taratec's Konciak observes, "Although the ARC audit provides a good baseline, every pharmaceutical company has a somewhat different environment, with different hot points from a regulatory risk perspective." Konciak notes that some companies will choose to examine certain areas more than others. "Some companies use the ARC audit documents as a baseline for subsequent more specifically focused audits, or they may use them to make an initial cut from a list of systems or vendors."

Stelex-TVG's Matlis adds that although the ARC process is a good way of standardizing the way audits are conducted, "ARC provides a sort of regulatory compliance seal of approval, akin to a UL certification," it does not guarantee product satisfaction in all circumstances. "From a technology standpoint, there still needs to be an

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entire other level of standardization in the pharmaceutical industry in terms of software system interoperability and compatibility."

Part of a bigger picture

Clearly, the past perception of information technology as a luxury or non-essential business element of the pharmaceutical industry is no longer valid. GE Fanuc's Chambers points out that "IT has become a critical element of the total compliance process, partly driven by 21 *CFR* Part 11 and partly facilitated by it. It's very timely, because a lot of companies may not have looked at their software systems as a means of aiding in their total compliance task."

In this context, the ARC reflects a general need within the pharmaceutical industry for increased technology standardization.

Currently, the pharmaceutical industry is populated by a tremendous range of software products and sytems, produced by a large number of different vendors for a number of different purposes. The scope ranges from complete ERP and MES systems to subsystems or modules for document control or supply chain management, to individual machine controllers.

As observed by Konciak, standardization will inevitably pave the way toward more complete, end-to-end solutions, both in terms of main process flow control, as well as how data is collected and stored. "Everyone's trying to get there, but pharmaceutical companies are also dealing with many more immediate and unique process challenges, and are still very much focused on closing their CGMP and Part 11 gaps."

GE Fanuc's Chambers points out that standardization efforts such as those through the ISPE's good automation manufacturing practices (GAMP) forum and the International Conference on Harmonization (ICH) already have proven beneficial. "Among its accomplishments, GAMP has helped the industry by simply providing a common baseline and language to build from. The same kind of benefit certainly comes in the move toward standardization of the audit process. The way different companies do this today can be all over the place."

Common software standards, interfaces, and development processes are in fact beginning to appear. As in other industries, these standards often develop by default as individual companies or products gain market dominance. Observes Greenawalt, "much of this is accomplished via partnering. For example, companies and products like SAP (Walldorf, Germany) sit on top of a group of other suppliers and partners."

Though the ARC is gaining in acceptance and appeal, many companies are still weighing their options. As described by Stelex-TVG's Matlis, "to this point, there's been some inertia in embracing the process." Matlis points out that the ARC audit is an extensive process requiring significant investment, and in the early stages, many vendors wondered whether there would be an adequate return. Now, however, Matlis says the ARC has reached "critical mass" where there are enough audits accomplished and end-user clients subscribing to the service to encourage vendors to take a second look.

Another consideration gaining weight is the additional value associated with having completed an ARC audit. As noted by Taratec's Konciak, "More than anything else, we, as well as some of our partners, are beginning to see ARC from a potentially beneficial marketing standpoint."

Ultimately, however, simple good business practice will be the final determinant. As pointed out by Greenawalt, Even discarding the FDA mandate, when you're spending hundreds of thousands, or even millions, of dollars on software, you want to know that it was properly developed."

John Haystead

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fundamental difference between biologics and pharmaceuticals. In contrast to most drugs that are chemically synthesized with known structure, biologics are derived from living sources. "Biologics are more variable than small-molecule drugs and require more case-by-case scrutiny," says Radcliffe. "That difference has to continue to be recognized [after the consolidation]. You can't approach biologics with a list mentality."

A more tangible area of concern is that CDER and CBER have different information-technology systems, says Radcliffe. Given the need for continuity over long development cycles, systems issues will need to be resolved.

So for PhRMA, the issue is not the consolidation per se, but rather its effect. "It's only a problem if it slows down reviews or makes them less effective," says Radcliffe. "FDA is aware of these issues and says it is addressing them. We [PhRMA] have offered our input and FDA is listening and considering it. We will continue to offer our views."

Despite the management difficulties that accompany the turning of a regulatory ocean liner, the single most impor-

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Consolidation specifics

The following product categories regulated by CBER will be regulated by CDER beginning in June (except as noted):

- Monoclonal antibodies
- Cytokines, growth factors, enzymes, interferons (including recombinant versions)
- Proteins intended for therapeutic use that are extracted from animals or microorganisms
- Therapeutic immunotherapies.

The following products, if presently at CBER, will remain at CBER:

- Monoclonal antibodies, cytokines, growth factors, or other proteins when used solely as an ex vivo constituent in a manufacturing process or when used solely as a reagent in the production of a product that is under the jurisdiction of CBER
- Viral-vectored gene insertions (i.e., "gene therapy")
- Products composed of human or animal cells or from physical parts of those cells.

Software Audit Trail Enhances Supply Chain Management

While some pharmaceutical manufacturers are taking a wait-and-see approach to FDA's recent re-evaluation of its electronic records and electronic signatures rule, others are taking aggressive steps toward complying with the agency's recommendation of maintaining audit trails. For some companies, these efforts have involved enhancing their supply chain planning and management systems with auditing capabilities. These systems track critical information such as date, time, and person whenever an adjustment is made during planning, manufacture, or distribution.

To this end, software maker Manugistics has expanded its software to incorporate a new configurable Web-based architecture. The architecture enables pharma companies to not only manage complex channel networks but also track secure information through each step of the supply chain.

Jeff Anderson, director of life sciences solutions, says much of the industry's need has centered around controlling inventory costs while meeting consumer need and taking into account product shelf life. It involves determining "the right amount to make, where to make it, where to store it, and how to most efficiently get it to the customer when their looking for it," he says. The software incorporates a common security model that underlies all the applications on the platform with optimization engines running under the applications. "The engines make all the intelligent decisions and recommendations and are supplemented by what we call collaborative services."

Collaborative services allow the platforms to share information over the Web. The combined entity is integrated into [a company's] existing systems, whether they be legacy systems, major ERP package systems, or manufacturing execution systems at the shop-floor level.

Although the challenge in implementing such a system involves investing the initial time, cost, and additional level of detail, the payoff may be "an overall smoother integration and implementation," said Andersen. In addition, says Karen Johannes, group vice-president of client support and corporate quality, implementing this level of auditing and tracking detail into supply chain planning provides the documented evidence should FDA decide to expand 21 *CFR* Part 11 to cover all processes that could potentially affect quality or purity.

"There's a wide range there," says Johannes. "There are companies that have viewed 21 *CFR* Part 11 as transactional based. But we have some clients that have been audited by FDA recently, or know that FDA is looking at them very closely, and they are much more inclined to interpret 21 *CFR* Part 11 as inclusive of their planning systems and have chosen not to wait."

Maribel Rios

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tant aspect of the consolidation, according to Woodcock, is "no disruptions in the review process. That's why we're doing the consolidation in steps. We want market reviews to go smoothly, without delays." She adds that, for manufacturers, procedures remain the same at CDER as they were at CBER. In addition, "We're not changing the physical location of files. The new-drug part of CDER [which will absorb many of the CBER employees] has plans to move in 2005; we'll finalize the integration then."

Like PhRMA, the Biotechnology Industry Organization (BIO, Washington, DC) is "sympathetic to the idea of bringing consistency and predictability" to a complex regulatory process, says Gillian R. Woollett, MA, DPhil, vice-president for science and regulatory affairs. "We see the value to industry. But regarding the pooling of best practices between the centers, we'll have to watch and wait. We like to be involved in determining best practices," says Woollett.

Woollett refers to the best practices objective of the consolidation spelled out in an October 2002 memo from the leadership of the CBER–CDER product consolidation working group that stated, "implementing [the consolidation] decision is predicated on merging the best practices—both scientific and procedural—of both centers with respect to review of these products. By organizing the drug development and review process around the disease being treated, informed by specific product and technology expertise, the agency decision process … can be made even more patient-centered and science-based."

The consolidation program itself began in September 2002 when deputy commissioner Crawford announced the plan. The decision for the transfer "was made after a lengthy process of fact finding and deliberation. The Office of the Commissioner hired consultants in the fall of 2001 to conduct an assessment of the drug review process to identify best practices and make recommendations for improving those processes," Crawford wrote to employees.

Fueling the consolidation decision was the goal of achieving consistency of reviews across FDA divisions. This goal was stated by industry representatives during the renegotiation of the Prescription Drug User Fee Act. Performance goals were set and are monitored. "I decided that the therapeutic biologic review could be handled with less duplication of effort and greater consistency if it was integrated into similar drug review functions that reside in CDER," wrote Crawford to employees.

Although there is no formal process by which BIO or any non-FDA group can participate in the consolidation process, Woollett says BIO "is willing to make the effort. We have ongoing discussions. We hope to be constructive."

Woodcock said in early April that the consolidation is on schedule. Today, CDER is 1900 employees strong, some 1300 of whom are involved in the review processes. CBER employs 1030 personnel. The consolidation involves the move of about 200 employees to CDER from CBER, some 130 of whom currently work at the CBER Office of Therapeutics Review and Research.

George Miller