

# BD Catapult

Propelling applications development in the areas of Biopharm Production, QA/QC & Environmental Monitoring

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## Rapid Enhancement of Antibody Production through DOE-Based Peptone Supplementation of an Optimized Base Medium

Cindy Hunt, BD Senior Scientist

AutoNutrient™ Media Design Service

It has been well documented that different production cell lines have unique nutritional requirements for maximum protein production. Through the BD AutoNutrient™ Media Design Service (AMDS), unique optimization procedures were utilized to achieve a 4-fold increase in antibody production from a CHO cell line in less than 18 months.

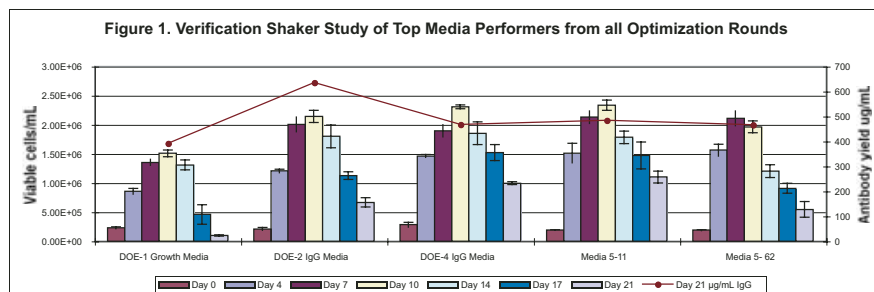
### Base Media Optimization

In order to identify an appropriate starting base medium, 33 proprietary chemically-defined library media were screened with the CHO cell line. Based on cell proliferation and antibody production, Medium 15 (M15) was identified as the best candidate for component optimization (data not shown).

A proprietary Design of Experiments (DOE) was used to optimize M15 through several rounds of component optimization. Based on proliferation and production, the best performing medium was used as the new starting base medium for the next round of component optimization. This was followed by a verification shaker study with the best performing medium from each round (Figure 1). Results indicated that the DOE-2 Medium had one of the greatest effects on cell proliferation and production.

### Peptone Supplementation

Using DOE-2 Medium, the CHO cell line was screened in a DOE against 6 animal-free peptones. The top 3 peptones at their best concentration were used for a scale-up study using another proprietary DOE (data not shown). Several peptone blends gave 2-fold increases in production as compared to the no peptone feed control.



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Blend 14 was selected as this contained the lowest total concentration of peptone.

### Feed Strategy

The CHO cells in DOE-2 Medium with Blend 14 were subjected to a proprietary DOE screen of peptones as feed supplements. Following identification of TC Yeastolate UF and Wheat 2A as the optimal peptone feed blend (data not shown), the feed timing and a double bolus feed on Days 3 and 7 as compared to a single bolus feed on either day was investigated (Figure 2). Results showed improvements in production by changing to a Day 3 and 7 feed as opposed to a single feed on Day 3 or 7.

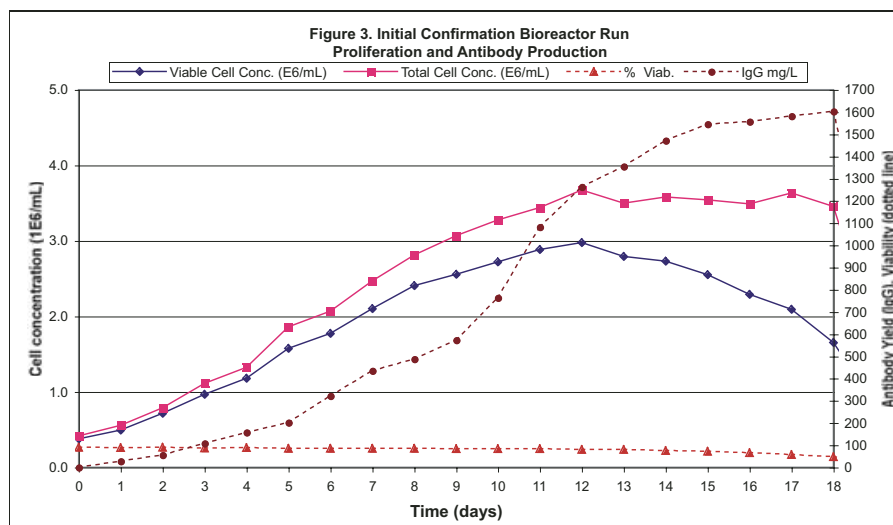
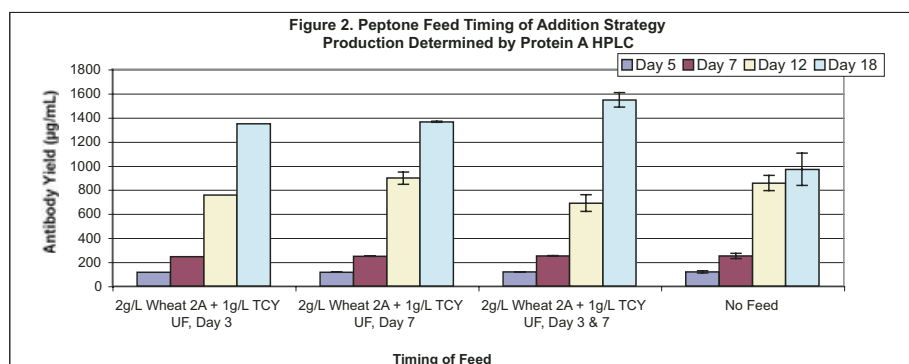
### Bioreactor Scale Up

The bioreactor study evaluated how the conditions identified during the Feed Strategy development would translate into a stirred tank reactor. The run resulted in a maximum viable cell density of  $3 \times 10^6$  cells/mL on Day 12 with viabilities remaining above 75% for 14 days and a day 14 production level of 1.5 g/L (Figure 3). This bioreactor run showed that the medium and feed conditions are appropriate and scalable for this cell line.

### Conclusion

Base medium optimization required 8 months of development time and resulted in an approximate 2-fold increase in production from 343 mg/L to 580 mg/L. Identification of the optimal peptone supplementation scheme required 6 weeks and resulted in an additional 2-fold increase in production to 1.2 g/L. Feed strategy optimization using peptone blends required 8 weeks and further improved production to a final level of 1.5 g/L.

For more information about the BD AutoNutrient™ Media Design Service, please fill out and return the request for information card or visit our web site at [www.bd.com/ds](http://www.bd.com/ds).



## About the Author

**Cindy Hunt** is a Senior Scientist for BD Advanced Bioprocessing in Sparks, MD. Her main focus is managing technical projects in the development of customized media formulations for the AutoNutrient™ Media Design Service.

Cindy received her Master of Human Resource Management from Emmanuel College, Boston,

MA and a Bachelors of Science in Biology from Worcester Polytechnic Institute, Worcester, MA. Prior to joining BD, Cindy was a scientist for Cambrex, Walkersville, MD developing cell culture media and a scientist for Genetics Institute, Cambridge, MA developing bioassays.

# Biopharm Production

## BSE Risk Mitigation

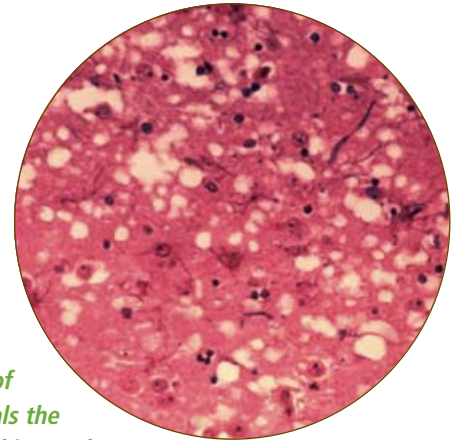
### Alternatives for Vaccine and Therapeutic Drug Manufacturers

Linda Kosterman

BD Marketing Manager

Over the past several years, concerns surrounding the use of components and culture media of animal origin in the manufacture of vaccines and therapeutic drugs have been steadily increasing. Specifically, the use of materials that are of bovine origin have been the topic of numerous regulatory guidelines and recommendations following the Bovine Spongiform Encephalopathy (BSE) epidemic in Great Britain. BSE, widely referred to as “mad cow” disease, is a progressive neurological disorder of cattle. It is an insidious disease whereby a cow could be infected for many years before being detected. Although there has been steady progress in the scientific community to understand the causative agent, mode of transmission, and development of a meaningful early diagnostic test, the world is still reliant on establishing preventative controls to try to reduce the chances of introducing the causative agent into final drug products and the human food chain.

In the absence of meaningful, early diagnostic tests that would assure manufacturers of BSE/TSE-free product, reliance on complying with worldwide regulatory guidelines is the only assurance of reducing risk. Rigorous regulations and guidelines have been put forth by several world governmental bodies that direct drug and vaccine manufacturers on the best practices in order to reduce the risk of introducing BSE/TSE into their final product.



*This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy. The presence of vacuoles, i.e. microscopic “holes” in the gray matter, gives the brain of BSE-affected cows a sponge-like appearance when tissue sections are examined in the lab.*

The European Union (EU) Note for Guidance<sup>1</sup> defines the bovine tissue risk according to the relationship to the brain and central nervous system of the cow. The categories are labeled as “Category A”, highest infectivity risk, (brain tissue), through “Category C,” no detectable risk, (casein would be a representative of this category). Likewise, regions of the world are categorized according to the likelihood that animals infected with BSE are present. These classifications are referred to as Geographical BSE Risk categories (GBR).<sup>1</sup>

- GBR I – Highly unlikely
- GBR II – Unlikely but not excluded
- GBR III – Likely, but not confirmed at a lower level
- GBR IV – Confirmed at a higher level defined as  $\geq 100$  cases/ 1 million adult cattle per year

Because there is no known diagnostic test to screen for the presence of BSE in culture media components derived from ruminants, the U.S. Food and Drug Administration (FDA) has made strong recommendations to manufacturers of biological products, including vaccine manufacturers, to assure the safety of their products for human and animal use. The manufacture of vaccines involves the cultivation of microorganisms or viruses in controlled conditions, through fermentation or cell culture production processes, in culture media, which provides the nutrients necessary for growth.

Many of these media formulations used for cultivation contain ingredients derived from animals and specifically cows. One of the many difficulties that vaccine manufacturers face is the possibility of introducing BSE transmissible agents

# Biopharm Production

## BSE Risk Mitigation

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into the manufacturing process and ultimately into the final vaccine product intended for human or animal therapeutic applications. Variant Creutzfeldt-Jacob Disease, a related disease, has been attributed to the consumption of products from BSE-infected cattle, among other possibilities.<sup>2</sup> It is based on this information that the FDA, along with the United States Department of Agriculture (USDA), have made very strong recommendations to vaccine and therapeutic drug manufacturers to take steps to reduce any potential risk of BSE introduction into their processes.

***The Center for Biologics Evaluation and Research (CBER) strongly recommends that manufacturers take whatever steps necessary to assure that materials derived from all species of ruminant animals born, raised or slaughtered in countries where BSE is known to exist, or countries where the USDA has been unable to assure the FDA that BSE does not exist, are not used in the manufacture of FDA-regulated products intended for administration to humans.***<sup>3</sup>

The vast majority of vaccine and therapeutic drug manufacturers are working to replace the animal-derived components of the culture media used in their production processes to grow cells or microorganisms to:

- Non-animal origin components and media
- Alternative reduced-risk animal tissue components (i.e., porcine-derived or minimal risk bovine categories), or
- Bovine-derived components from BSE risk-free regions of the world, (i.e., New Zealand or Australia)

BD has been working side-by-side with vaccine manufacturers in their efforts to reduce, minimize and eliminate the risk of BSE introduction by providing peptones and media of non-animal origin as well as bovine-sourced culture media supplements derived from GBR I regions of the world, specifically New Zealand and Australia, for the production phase of the vaccine or therapeutic drug manufacturing process. For many therapeutic drug/vaccine-manufacturing processes, the use of bovine-derived peptone supplements often delivers the optimum protein yield. Therefore, for these manufacturers, the most efficient way to meet risk-mitigation guidelines is to seek sourcing of these bovine tissues from BSE-free regions of the world. BD has been successful in partnering with these manufacturers to develop equivalent performing peptones that are sourced specifically from GBR I regions of the world. This allows continued final product importation into Japan and the EU as these products now adhere to the regional safety guidelines.



Likewise, BD has been successful in developing custom formulations and products for specific needs that allow for a total conversion to animal – free formulations and/or to alternative animal origin species tissues; i.e., porcine. Since 1998, BD has been providing non-animal origin components and media through the Select Alternative Protein Source (APS™) product line offering. These products are engineered and tested to deliver maximum performance without the risk of potential BSE introduction.

Over the past 12 – 18 months, BD has been successful in developing NZ/AU (New Zealand/Australia) derived peptones and media that show performance equivalence to the standard products, like Bacto™ Peptone, Proteose Peptone and PPLO Broth and customer-specified formulations through the BD Custom Program.

BD is well positioned to provide vaccine/therapeutic drug manufacturers with a variety of alternative options including non-animal components and media, alternative species components and media (i.e., porcine-derived), reduced risk category bovine components and media and GBR I sourced bovine-derived components and media to meet production demand and comply with worldwide regulations for the manufacture and distribution of vaccines and therapeutic drugs for human and animal applications.

For more information regarding BD animal free peptones, please fill out and return the request for information card or visit our web site at [www.bd.com/ds](http://www.bd.com/ds).

### References

1. "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/44110/01)."
2. Bovine Spongiform Encephalopathy (BSE). 4 Apr. 2002. <<http://www.fda.gov/cber/bse/bse/htm>>.
3. Letter to Manufacturers of Biological Products, April 19, 2000. 4 Apr. 2002. <<http://www.fda.gov/cber/ltr/bse041900.htm>>.

# $\beta$ -Lactamase I Potency Determination By Acidimetric Autotitration

Bunkim Chokshi, David Levinstim, and Thomas Kehoe

BD Department of QC Chemistry and Media Technology/Engineering

$\beta$ -lactamase (penicillinase) is a widely used industrial enzyme that hydrolyzes the cyclic amide  $\beta$ -lactam bond in penicillins and related compounds.  $\beta$ -lactamase is commonly used for sterility testing of antibiotic-containing products<sup>1</sup> and for determining microbial counts of materials containing penicillins.<sup>2</sup>  $\beta$ -lactamase is available from BD as Difco™ Penase and Difco™ Penase Concentrate.

Quality control testing of Difco Penase has historically been performed using the pH-STAT acidimetric method that quantifies  $\beta$ -lactamase I enzyme.<sup>1</sup> This method, first described by Hou and Poole,<sup>3</sup> measures the rate of hydrolysis directly by continuous titration with alkali in a pH-STAT titration. The enzymatic breakdown of the  $\beta$ -lactam bond catalyzed by penicillinase results in the production of a carboxylate molecule and one  $H^+$  ion with a decrease in pH. Historically this test has been performed manually. The main drawback of the manual titration is that it is laborious and difficult to match the fast enzyme-catalyzed reaction rate.<sup>1,2</sup>

BD Diagnostics has ongoing programs to continuously improve manufacturing and testing efficiencies in order to supply our customers with the highest quality microbiology products in a timely manner. Under this program of continuous improvement, BD is pleased to announce a change to the assay method for the measurement of penicillinase activity of Difco™ Penase products.

The change in assay method involves the measurement of penicillinase activity using an automated acidimetric titration method in place of the manual visual test. This automated method standardizes reading and interpretation of test

results, since this function is now performed by an instrument that will be read the same each and every time, as opposed to being left to human judgment and interpretation. This standardized reading and interpretation of results will provide improved efficiency and faster turnaround time of results versus the manual titration method.

The Difco Penase products were evaluated using the historical manual titration and the new automated titration methods.

The **manual titration** was conducted in a buffer-free environment in deionized water. pH was monitored externally using a flat surface pH probe. Titrant was dosed manually and titration volume was recorded at three minute intervals for 33 minutes or until 5 mL of NaOH was titrated. Penase potency was then calculated.



The **automated titration** was conducted in a buffered environment of 0.1 M phosphate buffer adjusted to pH 7.0 using NaOH or HCl. The reaction vessel was set to pH 7.0 using the same reagents before starting the assay. The automated titration was conducted on a Metrohm 799 GPT Titrino titrator (Metrohm, Ltd.) with a 10 mL dosing unit. pH was measured using a Metrohm Combined LL pH Glass Electrode (Metrohm, Ltd.). The assay was monitored and controlled via the Metrohm SCADA

(Supervisory Control and Data Acquisition) software package *tiamo*™ v. 1.1. (Metrohm, Ltd.) The titrator was set to dose at a rate of 50-500  $\mu$ L/min and to terminate at 33 minutes or after 5 mL dosed. Data points were recorded every 2 seconds. Enzyme potency was stoichiometrically calculated.

# QA/QC

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## Results

Several essential observations were made from the experiments conducted that were found to be critical to the accuracy of the enzyme potency determinations:

- When the manual acidimetric titration is conducted in a buffer-free environment, a noticeable drop in the rate of enzymatic activity (*hysteresis*) occurs. Conducting the assay in the buffered environment of the automated acidimetric titration stabilizes the enzyme, providing more accurate results.
- Conducting the assay in buffer pre-adjusted to pH 7.0 ensures that the rate of titration is not affected by a large starting pH deviation.
- Since the  $\beta$ -lactamase potency determination is reported as a volumetric rate, the actual assay value should be independent of the  $\beta$ -lactamase sample volume. In the buffer-free environment of the manual method, this was not the case. However, the normalized mean rate for assays conducted in buffer for the automated method was statistically the same.
- The first few minutes of the manual titration method demonstrated a much higher initial titration rate, with the rate decreasing over time, which was an effect due to several factors. When the same product was assayed in buffer with the automated titration method, the initial minutes skew the assay value, yet the overall titration rate remains constant thereafter (Figure 1).

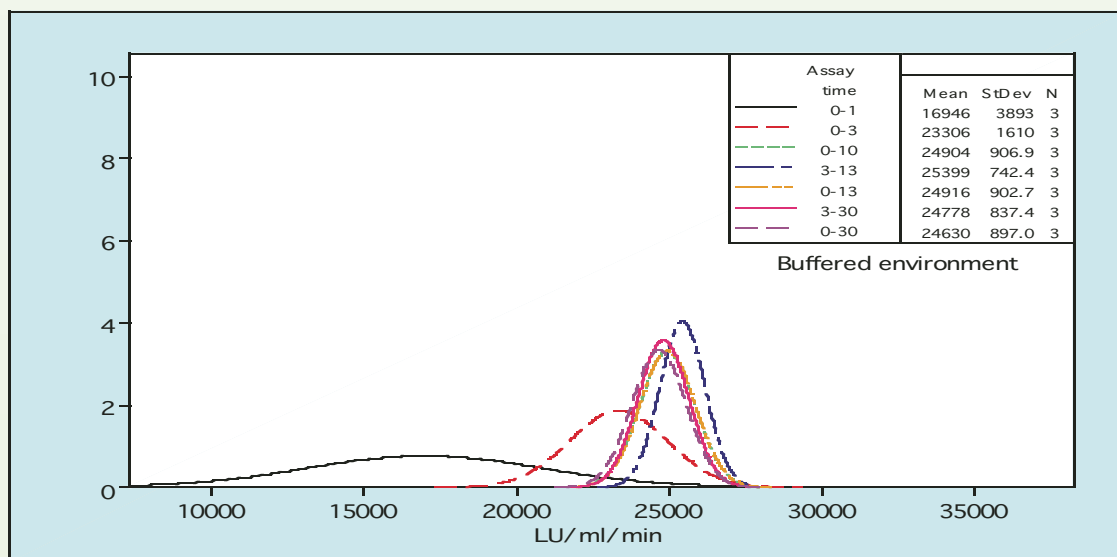
## Summary

BD Difco™ Penase and BD Difco™ Penase Concentrate potency can be accurately calculated via an acidimetric autotitration method. The autotitration method will overcome several factors observed in the manual titration method that can hinder potency determination. In addition, the new automated method provides a standardized measurement of penicillinase activity that is highly sensitive. Lastly, the autotitration method provides more consistent, reproducible and accurate determination of endpoints for calculation of penicillinase potency than the historical manual titration method.

## References

1. United States Pharmacopeia. 2006. Chapter 71, Sterility Tests, The United States Pharmacopeia 29-National Formulary 24, Second Supplement. Aug. 2006. <<http://www.uspnf.com>>.
2. United States Pharmacopeia. 2006. Chapter 61, Microbial Limits Test, The United States Pharmacopeia 29-National Formulary 24, Second Supplement. Aug. 2006. <<http://www.uspnf.com>>.
3. Hou, J.P., and J.W. Poole. 1972. Measurement of beta-lactamase activity and rate of inactivation of penicillins by a pH-stat alkalimetric titration method. *J. Pharm. Sci.* 61(10):1594-8.

Figure 1. Potency as a function of assay time when conducted in a buffered environment. The calculated potency approaches a constant value as the overall assay time increases past 3 minutes. Although the first minute and first three minutes are skewed, the overall assay rate is fairly consistent after the first three minutes.



# Environmental Monitoring

## BD Diagnostics and Moda Technology Partners Announce Marketing Agreement

Chet Shemanski

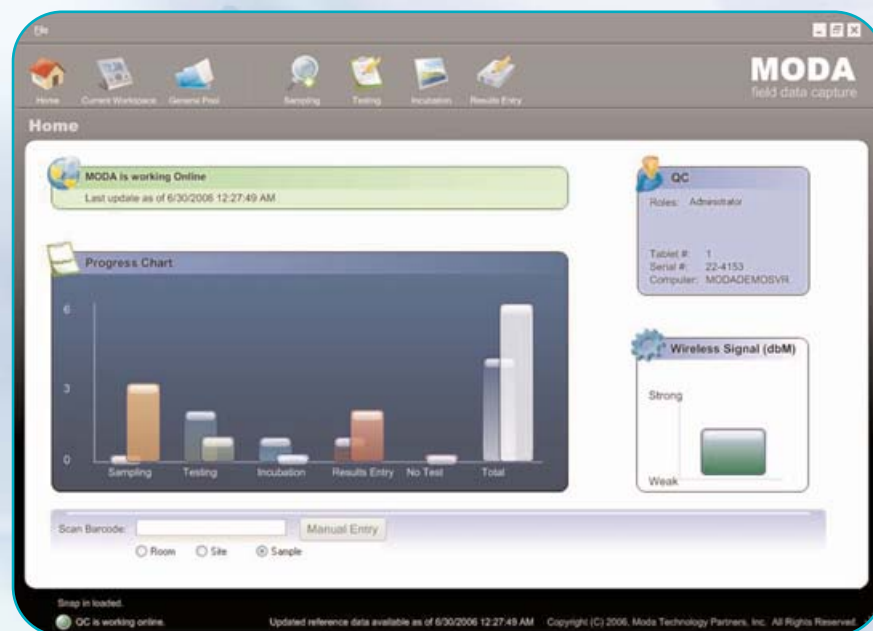
Vice President, Marketing and Business Development  
Moda Technology Partners

BD Diagnostics and Moda Technology Partners (Moda), a software company that provides mobile data acquisition solutions to the pharmaceutical manufacturing industry, announced the signing of a cooperative marketing agreement on June 27, 2006. The agreement was intended to effectively leverage the bar-coded sample collection media manufactured by BD Diagnostics and Moda's innovative environmental monitoring solution, **Moda-EM™**, to ensure product safety within biopharmaceutical manufacturing facilities.

Moda Technology Partners, headquartered in suburban Philadelphia, focuses on the growing need for effective automation and efficient regulatory compliance within pharmaceutical manufacturing. Moda's software systems leverage mobile computing technology to help their clients increase operational efficiency, improve quality, and reduce manufacturing costs.

Their initial product offering, Moda-EM™, is a comprehensive software solution that improves the efficiency of environmental monitoring operations while providing a regulatory compliant platform for the collection, management and reporting of environmental monitoring information. Moda-EM™ supports viable, non-viable, water, and personnel sampling and testing.

Moda-EM™ provides direct, tangible return-on-investment by reducing the time required to execute environmental monitoring protocols and by reducing the error rates inherent with paper-based recording and batch data entry. It also reduces the risk of regulatory non-compliance through the use of



automated workflows that mirror a company's environmental monitoring standard operating procedures (SOPs).

The solution consists of the following Moda software modules, integrated hardware components and implementation services to provide a complete turnkey solution:

**Moda-FDC™** Field Data Capture - module leverages wireless computing technology to provide a mobile platform for collecting, labeling (via barcode) and tracking environmental monitoring samples. An automated workflow engine drives the location-based sampling regimens which, in turn, improves productivity and ensures compliance with standard operating procedures. Moda-FDC™ software is bundled with a rugged tablet PC, barcode reader, barcode printer, badge reader and a stainless steel cart that can be used to store and transport sampling media and an auxiliary battery pack.

The entire configuration (PC, peripherals and cart) can be sanitized using standard chemical disinfectants without harming the devices. Moda-FDC™ includes proprietary "severability" functionality that allows sampling technicians to continue working despite any potential disruption in wireless network connectivity. Once connectivity is restored, Moda-FDC™ automatically synchronizes all cached information with the Moda-EIM™.

**Moda-EIM™** Enterprise Information Management server – a 21 CFR Part 11 data repository that serves as the complete system of record for all environmental monitoring information. It also provides functionality to support the incubation, testing and results entry for environmental monitoring samples. Moda-EIM™ includes decision support and business intelligence functionality via a supervisory dashboard and a

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# Environmental Monitoring

## BD Diagnostics and Moda Technology Partners Announce Marketing Agreement

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data reporting and trending package designed to meet both operational and regulatory needs.

**Moda-VIP™** Visual Intelligence Portal – extends the business intelligence platform to provide visualization of environmental monitoring information. Moda VIP™ integrates the comprehensive inventory of environmental monitoring information stored within the Moda-EIM™ repository with electronic blue prints of the manufacturing facility to help site supervisors identify and arrest potential environmental excursions before they occur. By using the drill-down and time-lapse features of Moda-VIP™ in conjunction with its flexible data sorting and filtering capabilities, the time required to collect, aggregate and report information is significantly reduced. Moda-VIP™ can also integrate data from other external applications such as Building Management Systems or Equipment Maintenance Systems to provide an even more comprehensive view into the manufacturing environment.

Moda-EM™ is a highly configurable solution that can be adapted to meet specific environmental monitoring SOP requirements. Using XML configuration files, the data capture modules can be tailored to an organization's specific information management requirements. Additionally, the Moda-Admin™ module provides the ability to define and maintain the system parameters that govern environmental monitoring programs. These parameters include facilities, sites, test types, equipment,

media, and organisms. It also allows a facility to define sampling, incubation and testing schedules which drive the automated workflows.

Moda's optimized implementation methodology has been designed to get the system configured, validated and into production quickly and with minimal risk. The Moda-EM™ solution can be deployed in approximately six calendar months. This schedule is dependent on many factors including the availability of client personnel to participate in specification workshops, the time required to finalize requirements and the readiness of the organization to accept the system into the operating environment.

BD Diagnostics manufactures several product lines that may be used with the Moda-EM system. BBL™ Sterile Pack Plated Media for critical environments are gamma irradiated and validated for performance and sterility according to the Association for the Advancement of Medical Instrumentation (AAMI)

guidelines. The product is available in many formulations and plate types including RODAC™ (Replicate Organism Detection and Counting) plates for personnel and surface sampling, settling plates for active and passive air sampling, Finger Dab™ plates for sampling of gloved hands and contact plates.

BBL™ Isolator Pack Plated Media are also gamma-irradiated but designed for use in isolator systems. The multi-wrap packaging protects media from vaporized hydrogen peroxide exposure. BBL Isolator Pack plated media are available in a variety of media types and plate formulas as well.

BD™ Sterile Pack Bottles are terminally sterilized inside of autoclavable double-bags, resulting in a bottle exterior that is free from environmental contaminants and particulate matter. BD™ Sterile Pack Swabs are the first, double-wrapped, gamma-irradiated, ready-to-use sterile swabs for surface sampling, and are packaged with a rinse solution-filled tube.



For more information regarding BBL™ Sterile Pack Prepared Plated Media, BBL™ Isolator Pack Plated Media, BD™ Sterile Pack Bottles or BD™ Sterile Pack Swabs, please fill out and return the request for information card, or contact your local BD Sales Representative.

Additional information about the Moda-EM™ System is available at [www.modatp.com](http://www.modatp.com)

# Regulatory Corner

## Regulatory Documents Available 24/7 on Internet

In an effort to provide BD customers with the latest, state-of-the-art web site, we have updated our 24/7 on-line access to regulatory documents, such as Certificates of Analysis, Compliance, Conformance, Sterility, Analysis/Origin (Animal) or Quality and Material Safety Data Sheets. Several factors determine which types of certificates are available for a given product, so all documents may not be available for every product.

To access a Certificate on line, follow these easy steps:

- 1 Go to [www.bdregdocs.com](http://www.bdregdocs.com)
- 2 To search for a particular certificate, enter the BD catalog number and corresponding lot number located on the container label and click "Search."
- 3 Click on the PDF link in "Search Results" to download the certificate to your computer or printer.



### Information Provided on BD Certificate of Analysis/Certificate of Origin (COA/COO)

#### Header

- On the left side is the business name and address
- On the right side is the type of Certificate, for example "Certificate of Analysis"

#### Identification Block

- The name of the product, as defined in the BD computer system. It is limited to 40 characters and might not exactly match the name on the product label.
- Product Catalog number
- Batch Number
- Dates
  - Certificate Creation Date
  - Manufacture Date, if applicable
  - Expiration Date, if applicable

#### Attribute Test Data

- A listing of QC testing and associated test specifications performed on each batch of product.
- Each batch must meet this specification in order to be approved for use.
- Attribute data varies with the product. For media products, testing typically includes growth performance, appearance, etc.
- Testing is performed to substantiate the label claims made by using Test Instructions, which define the Quality Control release criteria for each product batch.
- In addition, BD also has supporting Standard Operating Procedures (SOPs) and Stability Protocols (SPs).

#### Variable Test Data, If Applicable

- Variable Data is listed in table format.
- Column headings include Characteristic, Unit, Value, Low Limit and High Limit.
- Examples of variable data are pH, Bulk Lot Number, and Loss on Drying.

#### Animal Origin Data, If Applicable

- Animal Origin Data is listed in table format.
- Column headings include Animal Source, Country of Origin, and Tissue Category (BIC, SIC and ABC).
- Table will list batch-specific animal sources depending on the lots of raw material used in the product batch.
- Individual batch source countries could vary depending on the raw material lots used in that batch.
- Any special comments concerning animal origin will appear in a paragraph just after the table.
- Refer to the Animal Origin Position Statement which can be obtained on our web site. It is located just to the left on the Certificate of Analysis Document Search screen.

#### Closing Paragraph

- Includes batch/lot number, Quality Systems and, if applicable information on animal origin data listed on the COA/COO.

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# BD Change Notification Options

Susan Keinath  
BD Quality Engineer

Due to issues surrounding BSE (Bovine Spongiform Encephalopathy), it is current practice for regulatory agencies to require manufacturers using raw materials of animal origin to document items such as country of origin of the raw material, what type of tissue is used, or what species of animal is used. In addition, current regulatory compliance requires companies to keep track of changes to their raw materials that could impact their products. BD Diagnostics provides two change notification systems to help customers meet their regulatory compliance needs.

The **Standard Change Notification Program (SCNP)** provides notification of certain changes to all of BD Diagnostics products. Examples of these changes are listed in Table 1 below. Please note that “Direct Customer Notification” will be sent to the shipping address. If BD products are obtained through distributors, it will be up to the distributor to forward the change notification to the end user. The SCNP is a “passive” system where, in most cases, the change is observed when the customer receives our products and associated documents.

**Table 1. Standard Change Notification Program**

Type of Change	Notification Method
Company Name Change	Distributor Notification for Distributed Products
	Direct Customer Notification for Direct Ship Products
	Product Label, Certificate of Analysis, Certificate of Origin
Product Name Change	Distributor Notification for Distributed Products
	Direct Customer Notification for Direct Ship Products
	Product Label, Certificate of Analysis, Certificate of Origin
Assigned Catalog Number Change	Distributor Notification for Distributed Products
	Direct Customer Notification for Direct Ship Products
	Product Label, Certificate of Analysis, Certificate of Origin
Deletion of Product	Distributor Notification for Distributed Products
	Direct Customer Notification for Direct Ship Products
Change in Supply Method	Direct Customer Notification for Direct Ship Products
Addition or deletion of a Generic Class of ingredient	Product Label
Change to Finished Product Appearance or Performance Specifications (label claims unaffected)	Product Insert, where applicable
	Certificate of Analysis
Change to Product Intended Use, Appearance or Performance (label claims affected)	Product Insert, where applicable
	Certificate of Analysis
	Product Label
Storage Temperature or Condition Change	Product Label
	Product Insert, where applicable
Significant Reduction in Product Shelf-life	Expiration date on Product Label
Significant Change in Packaging Dimensions	Distributor Notification for Distributed Products
	Direct Customer Notification for Direct Ship Products
Addition of Animal Material to Formerly Non-Animal Product	Certificate of Origin available at BD website address <a href="http://www.bdregdocs.com">www.bdregdocs.com</a>
Retrospective Animal Origin Information from BD Suppliers	Updated Certificate of Origin available at the BD website address <a href="http://www.bdregdocs.com">www.bdregdocs.com</a>



## BD Change Notification Options Continued from page 10

The **Automated Change Notification Program (ACNP)** was designed for customers who require notification of changes above and beyond those listed in the SCNP to meet regulatory compliance. This system is available for culture media products; i.e., Dehydrated Culture Media, Prepared Plate, Tube and Bottle media, and some miscellaneous laboratory

reagents. The ACNP will provide customers as much notice as possible prior to implementation of the change made by BD Diagnostics. This service is provided at no charge to our customers. See Table 2 below for changes covered in the ACNP.

**Table 2. Automated Change Notification Program**

Change Category	Change Description
<b>Business</b>	<b>Company Name Change</b>
Product Identification	Product Name Change
	Assigned Catalog Number Change
	Lot Number Identification Method Change
Product Access	Intention to Delete Product
	Change in How Customer Gets Product - through a distributor or direct (limited to U.S. customers)
<b>Raw Materials</b>	<b>Raw Material Change where BD Finished Product Performance and /or Appearance Affected</b>
Product Design/Specs	Specification Change (i.e., Visible to User or Affecting Published Specifications; Requires Change to Label, Package Insert and/or Certificate)
	Temperature and/or Condition Change in Specifications Relative to Product Storage, Transport or Use
	Significant Change in Product Shelf-life (i.e., +/- 25% Change or More)
	Change in Product Sterility Assurance Level (SAL) <sup>x</sup>
	Change in Packaging Size, Shape, or Type of Material Used
Animal Origin	Addition of Animal Materials to Formerly Non-Animal Product
	Change in Animal Species Used
	Change in Animal Tissue Codes Used
	Change to the Set of Countries of Animal Origin Used
Manufacture Location	Move to a Different BD Facility
	Initiation or Discontinuation of Use of a Subcontractor/OEM Supplier as Manufacturer
	Change in Subcontractor Used for Only Part of Manufacturing Process (e.g., contract sterilizer)
	Temporary Use of an Alternate BD Facility of Manufacture
	Move to Different Location Within Existing Facility, with Different Processes and/or Environmental Controls
Manufacturing Process	Use of a New and Different Manufacturing Process
	Significant Change in One or More Processing Specifications in an Existing Manufacturing Process

BD takes seriously the responsibility for providing customers information to meet their regulatory compliance needs. BD Diagnostics is certified to ISO 9001:2000 Quality Management Systems. BD facilities are registered with the United States Food and Drug Administration (FDA) and are regulated by the FDA's Quality System Regulations (QSRs).

For more information on enrollment in the Automated Change Notification Program, contact your local BD Sales Representative.

# Regulatory Documents Available 24/7 on Internet

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## Additional Information Located on BD Web Site

### Material Safety Data Sheets (MSDS)

- To search for a particular MSDS, enter the BD catalog number located on the container label and click "Search."
- Click on the PDF link in "Search Results" to download the MSDS to your computer or printer.

### Position Statements

#### Animal Origin Position Statement

- This document lists BD Diagnostics, Diagnostic Systems policy and practices with respect to

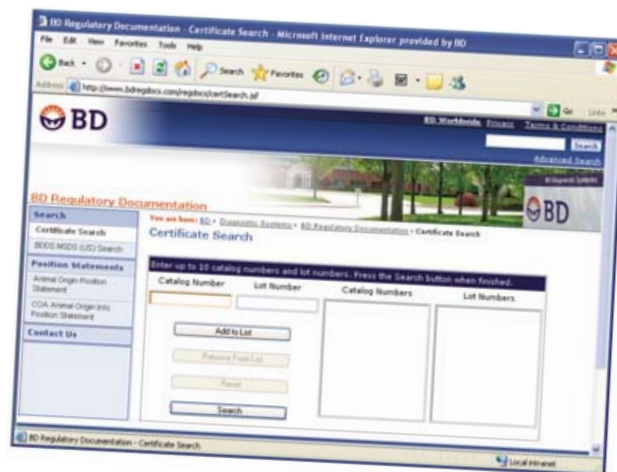
sourcing and handling materials of animal origin.

#### COA Animal Origin Information Position Statement

- This document contains more detailed information about the animal origin data listed on the COA/COO.

### Contact Us

- Provides a list of email contacts for Technical Services.



For more information regarding BD Regulatory Documents, please fill out and return the request for information card.

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Contributions or suggestions on topics of interest for future editions of the newsletter are welcome. Please send comments, suggestions or articles by mail to the attention of Sharon Miller, Mail Code 632, by fax to 248.888.8382, or by e-mail to [Sharon\\_Miller@bd.com](mailto:Sharon_Miller@bd.com). Send address changes and mailing list additions to the attention of Marketing Communications at Mail Code 634.

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## CALENDAR OF EVENTS

- February 28 – March 2, 2007  
IBC Antibody Production & Development  
Carlsbad, CA
- March 19-23  
2007 PDA Annual Meeting  
Las Vegas, NV
- April 19-20  
Food Safety World Conference  
Washington, D.C.
- April 23-27  
Waterside Conference  
San Juan, Puerto Rico
- May 21-23  
ASM – 107th General Meeting  
Toronto, Canada