TVM

TVM Regulatory Resource Bulletin

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TVM Workshop for Portfolio Companies: Holding Effective Meetings & Teleconferences with FDA in Today's Environment
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The Role of the TVM Regulatory Resource Bulletin

The TVM Regulatory Bulletin is an issue driven publication focusing on the particular regulatory needs of TVM portfolio companies and their executives. It assists them in navigating successfully through government regulatory requirements to approval. **The Bulletin will alert and analyze evolving FDA, Canadian, and European regulatory issues impacting on product development, the value of intellectual property, and regulatory strategy approvals options.**

Members of the TVM Regulatory Resource Team assist TVM in their due diligences before investments and prepare the Bulletin. These senior regulatory advisors have extensive working knowledge of US, and European, as well as Canadian, Japanese and Australian regulatory process:

Bruce F. Mackler, Ph.D., J.D., Editor
Gertrud Thorman-Huber, Ph.D.
Colin Bier, Ph.D.
Budd Colby, Ph.D.

The Bulletin will also feature occasional articles on individual TVM portfolio companies, contributions from biopharmaceutical industry leaders and announcements of TVM sponsored regulatory training workshops. Also, the Bulletin intends to provide access to regulatory resources, documents, reports and information that may be useful in making regulatory strategy decisions.

US Patent Term Extension Eligibility Requires an IND to Start The Clock

The **extension of the life of a US patent beyond 20 years** under Waxman-Hatch allows the recapture of the patent time lost during part of the clinical development process (half of the 3-8 years) plus all of the FDA review time. Obtaining patent term extension is now an important reason for both US and non-US pharmaceutical companies to interact early with FDA, and to file an Investigational New Drug (IND) application, irrespective of where they perform their clinical trials. Under Waxman-Hatch, **the time period for calculating the patent term extension begins when an IND is filed.**

US companies performing early clinical trials overseas without an IND can lose one or more years on their patent term extension time period. Even non-US companies, who perform early clinical studies outside of FDA's jurisdiction, can lose similar patent term extension benefits, when they eventually gain FDA approval.

As the European Good Manufacturing Practice (GMP) type requirements during the IND phase, approach if not in some cases exceed those of FDA, it becomes reasonable for European pharma/biotech companies to file FDA INDs for their non-US based clinical studies. This is especially true as ICH harmonization becomes a reality minimizing regulatory differences between FDA and EMEA.

Increasingly, non-US pharma/biotech companies are seeking early pre-IND meetings with FDA to validate their regulatory and clinical strategies and to facilitate the filing of an IND. Such FDA validation, as evidenced in formal FDA meeting minutes, is valuable in assuaging investor/partner concerns and minimizing the risk of drug/biologic development. The filing of an IND is merely an extension of this regulatory strategy and better assures FDA acceptance of the European clinical data as supporting the pivotal Phase III studies to be done in the US. Additionally, having an IND adds value in the eyes of investors and of potential partners.

Directors and Officers may be Personally Liable for Failing to Address FDA Non-compliance with cGMPs, GLPs, and GCPs Regulations

Officers and Directors of FDA regulated companies could be personally liable to shareholders for corporate losses for failing to "adequately" respond to FDA warnings regarding non-compliance with FDA regulations, advertising, promotion, GMPs, GLPs, GCPs, and quality systems. A U.S. Court of Appeals (7th Circuit) held that directors of Abbott Laboratories could be personally liable for their failure to take any corrective action in response to FDA's four warning letters issued from 1993 through 1999. Abbott Laboratories is currently under a Consent Decree and unable to sell many of its medical diagnostic kits until it takes appropriate, as judged by FDA, corrective changes to its quality control, quality assurance, and manufacturing procedures.

The Court appeared to find personal liability because of the repeated failure of Abott to take adequate corrective actions after receiving four FDA warning letters over a six year period. The failure of Abbott to act was imputed (ascribed) to the members of the Abbott Board of Directors, who either by omission or co-mission failed to direct the Company to comply. Obviously, the Board of Directors will argue a lack of knowledge or they assumed that the management was acting appropriately. However, under FDA statutes there is strict liability and the lack of knowledge is no excuse. FDA has in a prior C.R. Bard case held members of the Board personally liable for non-compliance under its criminal penalties statutes.

The court held that a six year pattern of not addressing the FDA non-compliance constituted gross negligence in that they were "omissions not in good faith" and "intentional misconduct [concerning] violations of the law." The message here is that companies, whose management fails to "adequately" respond to repeated FDA warnings about ongoing regulatory non-compliance, may find themselves individually liable as a member of the Board of Directors for corporate losses, FDA fines paid and possibly to loss equity value (economic losses) to shareholders.

Board of Directors, of public and private companies, presumably have similar liability exposures under this Abbott case. Arguably this liability exposure may also extend beyond the Directors, but also to the venture capitalist investors, corporate partners, or any institutions that the Directors are agents for or represent on the Board. Thus, Directors must become more aware of and take responsibility for oversight of their company's level of FDA regulatory compliance status; ignorance of this status is no defense against liability. One approach several companies have taken is to have annual comprehensive regulatory audits performed by internal or external experts.

For copies of In Re: Abbott Laboratories Derivative Shareholder Litigation or talk about the issues the case raised contact Bruce F. Mackler.

CBER's Office of Therapeutics (Protein Biologics) is Transferred to CDER (Drugs)

FDA announced it is planning to transfer oversight and review of the approvals (licenses) for therapeutic biologics **(biotech derived biologic drugs)** from CBER

to CDER. This change dramatically affects the regulatory environment and raises the possibility of regulatory confusion until clear CDER administrative processes for protein therapeutics are established. However, it should be remembered that Dr. Janet Woodcock, now Director of CDER, previously was the Director of the Office of Therapeutics (Biologics) in CBER. Also, the people in the Office of Therapeutics and its various review Divisions have been told its business as usual. Dr. Murray Lumpkin, CDER, is now developing an integration plan to be finalized by January, 2003.

One would anticipate that Dr. Woodcock, given her prior CBER experience, will both maintain existing regulatory understandings between FDA and biotech companies developing therapeutic biologics, as well as be cognizant of the congressional mandate to speed up approvals. **No disruption is contemplated,** since the reviewers themselves would only be administratively switching from CBER to CDER. As a result, therapeutic **biologic reviews may now employ many of the same review standards as applied to drugs,** which has been the tendency for several years with Oncological and Neuropharmalogical biologics. This change may also facilitate CDER use of the new quality systems inspection approaches that were announced as being applied to biologic and drug cGMPs.

Immunogenicity Priority Increased in CBER/CDER

CBER/CDER has required **post licensure (approval) assessments of human anti-biologic antibody responses** for all 5 licensed therapeutic biologics in 2002. FDA is also stressing in pre-IND meetings and critiques of Phase I clinical study protocols questions about a company's immunogenicity study plans at all stages of clinical development. Failure to have appropriate assays to assess these immunogenicity issues are resulting in clinical holds on INDs.

The CBER concerns about **anti-biologic antibody responses** have arisen from emerging data that chimeric and humanized antibody products are inducing antibody responses, when a biologic is used for **chronic dosing** regimens. There is much less concern about immunogenicity of biologics used for **acute (single use) dosing.**

It is recommended that companies in early development of biologic increase their focus on assay development to detect immunogenicity responses. The questions CBER will be asking are:

- **the sensitivity and specificity of the immunogenicity assay(s)?**
- **can the assays detect all isotypes?**
- **characterize the nature and biologic functionality (neutralizing, precipitating, fixing,...) of any anti-biologic antibodies found?**
- **plans to "improve" and "validate" immunogenicity assays?**

TVM portfolio companies interested in access to and receiving FDA/CBER documents on this new immunogenicity concern are welcome to contact Bruce F. Mackler for copies.

Disclosure of Financial Association of Authors Publishing Sponsor Funded Clinical Study/Research Articles

The editors of the *New England Journal of Medicine* and other journals (*Nature, Lancet, JAMA, Science, Brit. Med. J*) have set new policies to ensure **disclosure of the financial association of authors** with their commercial sponsors. Disclosures should raise the reader's awareness of possible **inherent conflicts-of-interest** in medical research. Disclosure is required by all authors of a paper, when at least $10,000 is annually received from either **public or private companies** (cash, honorarium, stock, options, patent royalties, equipment, etc.).

Biopharmaceutical companies selecting principal investigators initiating Phase III pivotal studies, who will be responsible for publishing and presenting the data in scientific journals and at scientific conferences, now need to be aware of this new disclosure policy. Disclosures of significant economic positions by the authors may diminish the potential acceptance and creditability of the scientific article, abstract or their presentations, as a potential marketing tool. It is likely that this **policy will be adopted** by all scientific medical journals, as well as by societies with major conferences where abstracts and presentations are published.

During the planning for Phase III pivotal studies that will be published, companies need to identify the potential authors and discuss the implications of disclosure of financial associations of the authors with

the company. This also has implications for authors in their employment situations with medical institutions, where the institution (a.k.a., the Dean) may not be aware of the level of economic value is being received by the author. The Companies need to also anticipate the financial disclosure requirements of FDA which these publication policies now parallel.

Evolving EU & FDA IND Issues: GMPs, Screening INDs,

Evolving GMPS for INDS:
Companies contemplating submitting investigational new drug (IND) applications in Europe may, in the near future, have to **increase their level of compliance with EU good manufacturing practice (GMP) requirements.** For example, the investigation drug (biologic) manufacturing process, as well as any changes in the production and quality control specifications, must be **validated before being made.** EU and US companies contemplating early INDs in Europe will now need to increase their investment and commitment in GMP compliance. EU inspectors have also been complaining about the low level of GMP compliance, particularly the lack of validation compliance.

FDA Screening INDs:
FDA has also indicated some policy flexibility in that a single IND may cover closely structurally related compounds, i.e., **a screening IND.** The MAPP 6030.4, Manual of Policies and Procedures, CDER, allows for the review of multiple active moieties or formulations under a single IND. Screening INDs are related active moieties, multiple salts, esters, or physichemically related but slightly different molecules. Screening INDs are appropriate for single-dose protocols, – pharmacokinetic, pharmacodynamic, and early pilot efficacy studies.

Concerns About GMP Compliance Increasing in EU and US

European GMP inspectors have been outspoken about the poor regulatory compliance to GMPs. The **worst level of regulatory compliance** has been observed in many global operating multi-national companies. One of the major areas of cGMP concerns have been the failure of compliance:

- To establish scientifically sound product and lot release specifications, but merely provide EU authorities with specifications they believe the authorities would like in order not to cause any delays in obtaining approval.
- To perform adequate validation of a process change before implementing the change and releasing product.
- To submit amendments to marketing licenses for process and specification changes.

European companies should establish strong GMP compliance during the IND stage. The above failures identified by European inspectors also suggest the need for stronger scientific efforts during the IND stage to **provide a scientific basis for the choice of specifications** and to confirm the **robustness of processes.** In the US, FDA would consider the above failures to have compromised the integrity of the products and render them adulterated.

GMP inspections will change because FDA believes that some companies are not making the necessary investments to assure GMP compliance. The Center for Biologics/Drugs Evaluation & Research (CBER/CDER) believes that Prior "Team Biologics" inspections, which are frequently characterized as SWAT-team approach, have shown that biologic manufacturers have not upgraded their facilities to better comply with current GMP. CBER/CDER Team Biologics inspections in the future will be similar in nature to **inspections of CBER/CDER regulated products, which are becoming systems-based inspections.**

Nasdaq Proposes Changes to Corporate Governance Standards

In response to SEC Chairman Harvey Pitt's February 12, 2002 letter to the Chairmen of the New York Stock Exchange and the Nasdaq Stock Market, Nasdaq has recently proposed a number of changes to its corporate governance standards including:

- **narrowing the definition of "independent director"**
- **audit committee approval of related-party transactions**
- **stockholders approval of stock options plans in which directors and officers may participate**
- **public notice regarding disclosure practices**
- **disclosure of going concern qualifications by auditors**

A courtesy copy of the Heller Ehrman memorandum on the **"Nasdaq Corporate Governance Proposals":** can be obtained on request.

Areas of Continuing FDA cGMP Concerns

Computer Systems: FDA inspectors will focus on change controls during a plant inspection to see: (1) where and how computers are used in the processes; (2) what is the change control process for computers and can the changes be tracked; (3) what the validation plans and implementation reports are; and (4) what the specifications are and their robustness.

Flexible Standard Operating Procedures (SOP): Companies frequently want to keep their procedures **"flexible"** to avoid having deviations in their manufacturing operations which is a red flag to FDA inspectors. However, in the eyes of FDA inspectors "flexible SOP" is a **contradiction of concepts.** FDA believes employees should be able to follow an SOP and know what needs to be done.

FDA Drugs & Biologics Adopt Quality Systems Inspection Techniques

The FDA Centers for Drug and Biologics Evaluation & Research (CDER & CBER) announced that they are adopting the use of a quality system inspection technique ("QSIT"), which begins to mirror the quality system theories inherent in ISO 9000. The immediate implications of this announcement will be:

- Rule 11 (Electronic Signatures/Records) oversight will be done by CDER;
- Operations of Team Biologics will be improved to focus on systems-based quality inspections;
- A technical dispute resolution process will be established using experts from CDER & CBER to get technical consistency between these three FDA operating groups;
- The power of the local district offices will be eroded by having the Centers (CDER & CBER) review all proposed warning letters citing scientific and technical issues generated by local district offices.

TVM portfolio companies can get an appreciation of these new quality system inspection techniques by reviewing the existing **Quality System Regulations ("QSR")** in the medical and diagnostic Good Manufacturing Practice (GMP) regulations. Copies of these materials can be obtained by contacting.

Abbreviations in this Bulletin

CBER = Center for Biologics Evaluation & Research
CDER = Center for Drug Evaluation & Research
cGMP = Current GMP = current Good Manufacturing Practice Regulations
CMO = Chief Medical Officer
CRO = Contract Research Organization
FDA = Food & Drug Administration
GCP = Good Clinical Practice Regulations
GLP = Good Laboratory Practices Regulations
IND = Investigational New Drug
MAPP= Manual of Policies and Procedures
QSR = Quality System Regulations
SOP = Standard Operating Procedures

Invitation to TVM Portfolio Companies

TVM portfolio companies are invited to submit one page cameo description for publication in future issues of the TVM Regulatory Resource Bulletin. These cameos can describe their corporate strategies, technologies, product development activities, and even interest in partnering out-licencing with other TVM companies who receive courtesy copies of this Bulletin.
Interested TVM companies should contact Bruce F. Mackler, Ph.D., J.D. to discuss the content of their contribution and scheduling for publication.

TVM FDA Workshop Announcement:

Holding Effective Meetings & Teleconferences with FDA in Today's Regulatory Environment

February 18, 2003 (10:00AM - 5:00PM)
Munich, Germany

Interactions with FDA have significant value in **reducing development risks** to the company and investors, increasing a company's attractiveness for partnering and securing financing. As FDA evolves policies and regulatory requirements, it is critical that interactions with FDA be sensitive to such changes:

- Office of Therapeutic Proteins Moving Over To CDER;
- Quality System Emphasis in Biologic & Drug GMP Inspections;
- IND issues - Immunogenicity; Level of GMP compliance in clinical studies; screening INDs;

Companies must factor such changes into their strategies for interactions with FDA to achieve the success. This workshop is intended to discuss the practical and subtle issues in deciding to have a meeting or discussion with FDA, organizing, conducting and memorializing all types of interactions with FDA, and other governmental regulatory agencies. Model documents and case study materials on how to facilitate and organize FDA interactions will be available.

The workshop topics and discussions will cover the following areas critical to assuring success:

- **Developing strategies for when to interact with FDA during the early and late stages of product development;**
- **The choice of what technical vs. regulatory questions that need to be resolved;**
- **How and when to organize interactions - telephone, written correspondence versus face-to-face meetings;**
- **FDA Guidance on requesting and conducting meetings: Type A, B & C;**
- **The formal request letter for scheduling an interaction:**
  content, amount of information needed, structuring the letter to achieve what is requested;
- **Preparing the questions and Technical Dossier packages - how big, how much detail, addressing FDA's sensitivities;**
- **Conducting the interaction whether by telephone or face-to-face;**
- **Memorializing the meeting discussion in minutes - official versus sponsor's minutes and getting FDA to make changes in their Official Minutes;**
- **Follow-up to FDA interactions to set & maintain a regulatory record.**

Who Should Attend:
This workshop is intended for biopharm (drugs, biologics, medical device) companies management and regulatory personnel who need to understand, plan for or organize interactions with FDA. Space is limited to TVM portfolio company, management and employees.

Cost:
The low workshop fee is subsidized by TVM to support its portfolio companies with only a nominal fee of Euro/$ 200 charged to attend for the reimbursement of the cost of food, meeting room and handout materials.

Registration:
Please use the attached Fax Reply Form to indicate your interest in attending this and future workshops. For specific questions on the workshop program and how it may benefit your company, you are welcome to call or contact the Workshop Director, Bruce F. Mackler at T: 1-202-912-2626 or e-mail mackler@tvmvc.com

TVM Regulatory Support For Portfolio Companies

If TVM companies need an unbiased, fresh perspective on a regulatory issue, they can call „without charge" for a telephone consultation with the TVM Regulatory Resource Group for input, answers, referrals, etc.:
All initial inquiries should be sent to:
Bruce F. Mackler, Ph.D., J.D. by either -
E: mackler@tvmvc.com
T: 1-202-912-2626
F: 1-301-762-2957
Who will either respond directly or have another group member respond.

TVM Regulatory Resource Bulletin Fax Reply Form

To
Bruce F. Mackler, Ph.D.
Venture Partner,
Techno Venture Management
F: 1-301-762-2957
E: mackler@tvmvc.com

From
Name _____
Title _____
Company _____
Address _____
_____
T: _____ **F:** _____
E: _____

Please use this fax (or e-mail) reply form to register for TVM Regulatory Resource Workshop or to receive courtesy copies of FDA information future Bulletins by sending to Bruce F. Mackler.

☐ Please register me for the February 18, one-day workshop in Munich
List all Names, Titles and E-mails

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☐ Please send me a copy of the „Nasdaq Corporate Governance Proposal" memorandum by Heller Ehrman
List all Names, Titles and E-mails

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☐ Please send me a copy of the „General Principles of Software Validation Final Guidance for Industry & FDA Staff"
List all Names, Titles and E-mails

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☐ Please add a colleague's name below to receive an electronic copy of the TVM Regulatory Resource Bulletin
List all Names, Titles and E-mails

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Survey on Future Workshop on FDA Issues:

High Interest Low (☐ Location preference)

1 3 5 ☐US ☐EU	Developing A Toxicology (pre-clinical) Program to Support Phase I, II and III Drug or Biologic Development through Registration.
1 3 5 ☐US ☐EU	Lauching Analytical Assey Development. What Needs to be Done for Phase I and II and When?
1 3 5 ☐US ☐EU	Negotiating Service Agreements With CROs, CMOs, Contract Testing Laboratories, Contract Manufacturers, Clinical Sites & Investigators.
1 3 5 ☐US ☐EU	Manufacturing Strategies for the Pre-Clinical and Phase I; In-house Versus Outsourcing (lab → pilot → early scale-up).
1 3 5 ☐US ☐EU	Overview of the FDA and EU Regulatory Processes for Drugs and Biologics: The Processes, Orphan Status, Fast Track, Surrogate Markers.
1 3 5 ☐US ☐EU	Planning For & Implementing the IND Process from the Pre-IND Meeting through Phase I, II, III and to Licensure /Approval for Biologics and Drugs.