FDA News & Information

A Comprehensive Weekly Guide to the Agency and Related Activities, Policies and Releases

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Documentation for Manufacturing and Control Records

By: Charles Celeste, RAC, Director, Regulatory Operations

As we all know, documentation is of the utmost importance to FDA. The agency expresses its requirements very explicitly in the current Good Manufacturing Practice (cGMPs) regulations in 21 CFR 211. The cGMPs, however, do not have a regulation *per se* that stresses actual ways to document activities.

Documentation is implicitly indicated by the words "record" and "written procedures". The latter words expressly indicate that standard procedures are needed to conduct the various operations in the manufacturing, packaging, labeling, distribution and control areas of a pharmaceutical operation. The word "record" throughout the regulations connotes a type of document that is needed to incorporate information from any of the mentioned operations. But yet the actual way of documenting is not defined.

Since, operations at all facilities are of different natures the mechanism of performing the documentation of information and recording data is left to the manufacturer. There have been many articles written in journals that provide general guides to help meet the GMPs. As part of their responsibility during an inspection, FDA investigators review pertinent documents and make determinations as to the adequacy of the documentation.

It should be kept in mind that all the operations in a manufacturing facility must be recorded, either from the point of an instructional aspect or the information/data obtained.

This advisory will present those areas of documentation that are commonly taken for granted in today's manufacturing and laboratory environment. The information presented is also applicable to clinical and full-scale production activities. This same information can also be used during the conduct of research and development operations of a company. The documentation practices as presented are also applicable to activities conducted under

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GLPs, whether testing specimens or conducting bioanalytical testing of urine or plasma. In these latter areas, proper documentation is necessary to determine the integrity and credibility of the information.

FDA looks for and expects data integrity to be foremost with any operation. Therefore, in order to accomplish this, proper documentation is necessary. Proper documentation also will provide some assurance of the credibility of the activities performed.

RESPONSIBILITY

Where does the responsibility lie? First of all, management has the overall responsibility to designate how documentation is to be accomplished during an operation. Corporate or plant site management must advise their employees how certain things are to be accomplished. Site management should have the final say as to how documentation is to be conducted since the activity can be site-specific. Quality Control or Quality Assurance managers, since they have the ultimate responsibility in the final sign-off of documents, need to establish the critical parameters. The ultimate responsibility for proper documentation is that of all personnel performing the operations as defined. All personnel must make a conscious effort to record their observations in the correct manner.

DOCUMENTATION PROCEDURES

What are some documentation practices that FDA investigators object to during their review of documents and operations? The following provides a list of those items that are consistently overlooked by employees or should be performed to avoid any citation by auditors or FDA investigators.

Responsibilities of all personnel

The following practices are those which need to be constantly emphasized by supervisors and performed by all personnel in the manufacturing, packaging, labeling and control areas. Note that all practices listed in this advisory should be followed in completing the pages of the representative documents.

1. Record all information and data only in the prescribed documents.

Listed below are the common types of documents designated by management to record information from prescribed operations. These documents detail the process and results of all activities that are pertinent to the manufacture and release of a product or conduct of an experiment.

Laboratory notebooks
Laboratory worksheets
Batch Records and all accompanying worksheets, orders or request forms
Company forms

a. Laboratory Notebooks

These should be issued as controlled documents to those individuals for recording information. Notebooks usually are provided with blank pages, thus providing the holder of the book with the latitude of incorporating multiple notes.

b. Laboratory Worksheets

Worksheets should be controlled documents with pre-assigned numbers. The

worksheets usually will contain pre-designated information with blanks to fill-in.

c. Batch Records (and accompanying orders or request forms)

These records should be controlled documents with pre-assigned numbers. The Batch Record will usually provide spaces in which the operator or analyst will fill in the appropriate information. Often full blank sheets are provided to provide space for listing deviations or any changes or making appropriate comments.

d. Company forms

These forms (other than those listed above) usually are records that the company (Corporate or Local site facility) requires for gathering information. These may be used for distribution of the product and thus become a part of the batch record. They may be forms for recording consumer complaints or other activities.

2. Perform all hand entries in a legible manner.

Where hand entries are required, the entries should be legible. It is the responsibility of the author of the entry to write the word, number, phrase or sentence so that it can be read. It is the responsibility of the peer reviewer and supervisor to bring any 'illegible' item to the attention of the author.

As an example: Depending on how it is written and the flourish of the writer's style, a "1" can be read as a "7" or a "9".

3. Fill in all blank spaces where provided on any record, form or worksheet.

It is FDA's contention that all spaces on a record, form or worksheet are placed there for a reason. Therefore they must be filled in. In those situations where the space is not applicable to the operation, the "N/A" (Not Applicable) should appear in the blank area.

4. Do not use scrap paper or "Post-it" sheets for recording <u>any</u> raw data or information.

Records, notebook pages and worksheets usually provide ample space for making any entry. Scrap papers and the "Post-it" sheets can easily become lost or misplaced.

Never use these sheets for recording weights. Always enter any weight information, if handwritten, on the respective document. "Post-it" sheets should not be permitted in a working area.

5. Do not use pencils or flair pens at any time.

Pencils are not to be used. Any information transcribed by pencil can easily be erased and smudged. Pencils recoding do not always copy completely.

Flair pens usually provide a wide spread when transcribing information. Flair pens are mainly used for graphic presentations. Because of the wide writing point and method of handwriting by the author, legibility of words, numbers, phrases or sentences can easily become last or illegible.

6. Use only pens with black ink to record any data or information.

It is a known fact that black ink photocopies and photographs well. Other colors tend to fade and can be obliterated easily.

7. Do not use "white-out" on any numerical or word mistake.

FDA frowns upon the use of any kind of "white-out' material. When using these materials, FDA investigators become very suspicious of information obtained and recorded in this manner. "White-out" liquids or pens should not be permitted in a working area.

8. Do not "Overwrite" letters or numbers.

"Overwrites" tend to obliterate the information recorded and becomes very difficult to read. FDA expects to see mistakes but with proper corrections. The correct way to handle a overwrite, is to strike out the written information and insert the correct information above or near the strikeout in a legible manner. In addition to the strikeout and the new information, the initials (or signature) and date the correction was made should be entered.

9. Initial (or sign) and date any printout material attached to any record.

Since a great majority of the information today comes from some sort of instrument, the printed material should be initialed or hand signed and dated. If the facility or company has instituted electronic signature procedure, then a handwritten signature may not necessary.

When attaching a printed record to a Batch Record page, on a worksheet or in a notebook, a signature should be appended to the edge of the taped material so that the signature covers both the taped sheet and the record page. This is to provide or indicate authenticity of the printed material and the operator.

10. Initial (or sign) and date any photocopied information to assure authenticity. Stamp any photocopied material with the required stamp (as designated by company policy, if required).

When photocopying or photographing any original information for attachment to multiple records, the copied material should be initialed (or signed) and dated. A stamp, such as, "Copy of an Original" or simply "COPY", should be placed on the copied material. A "CONFIDENTIAL" stamp should also be used for further assurance. The type of stamp used is dependent on company policy.

11. <u>Any</u> calculation must be reviewed, initialed and dated by a second qualified person.

When "any" calculation is made, even if it is a simple addition or subtraction, a second person must check the math. This person should then initial (or sign) and date when the checking operation was conducted.

12. Record any deviation - according to SOP requirements immediately.

When any deviation occurs in a manufacturing or laboratory process, it should be recorded immediately. All circumstances regarding the deviation should be listed on the batch record or in the notebook or on the worksheet with full explanation. If special forms are to be used per site SOPs, those should be completed. All deviations should be signed and dated. In addition to the documentation process, all deviations should be brought to the attention of the immediate supervisor as soon as possible.

13. Highlighting of Information

When information of any kind is highlighted by a yellow (or other color) highlighter pen, there usually is a reason. A note should be appended as to why it was done. This not should be placed near the highlighted information or asterisked with a note at the bottom of the page or on a comment page. There should be an initial (or signature) and date.

Quality Control or Laboratory Personnel

Because of the many and varied laboratory and analytical activities, the following procedures, in addition to those listed above, should be followed by QC and laboratory personnel:

1. Always record the associated method and any revision number when performing a test.

Any test conducted to release a raw material, during a critical batch step or as a final product for release, must be recorded with a specific method reference. The method reference (which should include any revision, as applicable) must be recorded on the work order request, the worksheet, batch record or in the notebook. This is for continuity purposes and as a point of reference when the document is reviewed in the future.

2. Always list the source of the methods when using a monograph from a reference source.

When making a reference to the source of a method, e.g., the USP, complete information using edition and page (and with section, if necessary) must be listed. When using a journal or other reference, such as, a notebook, the complete volume, number and page must be listed. Again, this is to insure complete information regarding a method is available and can be understood by review personnel, management, and future reviewers or auditors.

3. Circle all "Out-of-Specification" (OOS) results in red.

This is a good practice to highlight the result and insure that action is taken. This is the only time a red

pencil should be used. Initial (or sign) and date the circle.

4. Always have entries made in a notebook, on a worksheet, or QC form, et. al., reviewed by another qualified analyst or scientist to assure accuracy and correctness.

In order to maintain data integrity, all data and associated information must be reviewed by a second person. The person can be a peer level analyst, supervisor or QC section employee. This will depend on how the SOP is written and the availability of personnel. All second person reviews should be timely conducted. . The period of review should be as soon as possible following the completed activity and not be greater than 48 hours following the activity. The period must be spelled out in the respective SOP.

The need for a timely review is to assure the accuracy and correctness of the results. A timely review should be able to detectany mistakes that may have been made. In this manner corrective action can be instituted at once and avoid costly and embarrassing delays.

5. After completion of a test or a page, sign and date the page.

Any page of a worksheet, record or notebook must be signed and dated upon completion of an activity. Note that notebook pages may require more than one signature and date since an activity can end at any point on the page and a new activity begun immediately. It may be wise when an activity is finished and does not fill the page that a line be drawn to the bottom of the page and an initial and date be inserted on the line to indicate page completion. The respective SOP should provide instructions.

6. Notebook or worksheet continuation or completion.

When using a notebook or worksheet for ending or continuing an activity, "Continued on (next) page ___." should be completed or entry of "End" should be made. All pages should be properly addressed for a particular activity, e.g., "Page 5 of 6 pages".

Regulatory Documents

A compilation of regulatory significance from government authorities and industry experts, offered by Kendle Regulatory Affairs on a subscription basis. The list is sorted numerically, and contains the Document ID number, title, an executive summary, author, issue date, and document length.

Doc.# 001-2032

Electronic FOI LOG

This diskette contains a listing of the requests filed with the Food and Drug Administration under the Freedom of Information Act. The diskette covers the time period of February 26, 2007 through March 2, 2007. The following fields are included: agency file number, date requested, date agency is required to respond, responding office, name of requestor, firm name, and information requested.

Author: FOI, FDA
Date: 3/2/2007

Doc.# 009-3976

Petition: Zinc Gluconate

This petition submitted by David Richardson requests FDA to sanction third party independent scientific analysis of zinc gluconate and establish additional safety standards for the homeopathic industry.

Author: Richardson, David
Date: 3/6/2007 Page(s): 65

Doc.# 009-3977

Withdrawal: Labeling of Serono's REBIF Neither False nor Misleading

This letter to FDA states that the company in withdrawing their petition requesting that FDA assure that labeling of Serono, Inc.'s interferon beta-1a product, REBIF®, and any promotional or advertising materials for such product are neither false nor misleading by requiring that Serono supplement existing information in the label about the relative efficacy of REBIF and Biogen's Avonex® product from the first 24 weeks of Serono's 48-week evidence trial with data on the relative efficacy of the two products gathered during the second 24-week period of the trial.

Author: Biogen Idec, Inc.
Date: 3/2/2007 **Page(s):** 1

Doc.# 009-3978

Letter: Engineered Nanoparticles

This letter to The International Center for Technology Assessment is in response to their petition requesting that FDA amend its regulations for drug products composed of engineered nanoparticles, generally, and specifically sunscreen drug products. FDA has not yet reached a decision on this petition.

Author: FDA
Date: 11/9/2006 **Page(s):** 3

Doc.# 009-3979

Letter: Carbocaine Injection, 3%

This letter to Hospira, Inc. is in response to their petition requesting that FDA determine whether the discontinued formulation of Carbocaine Injection, 3% supplied in 1.8 mL cartridge was discontinued for safety or efficacy reasons.

Author: CDER, FDA
Date: 2/22/2007 **Page(s):** 1

Doc.# 009-3980

Letter: Reformulation of Central Nervous System Stimulant Drugs

This letter to John Kulli, MD is in response to this petition requesting that FDA require drug manufacturers to reformulate central nervous system stimulant drugs, such as Ritalin, Adderall, Dexedrine, Focalin, Concerta and others, as well as any generic versions, to inhibit illicit use of these drugs. FDA has not yet reached a decision on this petition.

Author: CDER, FDA
Date: 2/25/2007 **Page(s):** 1

Doc.# 009-3981

Petition Denial: Nail Polish Marketed to Children

This letter to US Public Interest Research Group is in response to their petition requesting that FDA require manufacturers to stop using xylene, toluene, and dibutyl phthalate in nail polish marketed for children under the age of 14. FDA is denying the petition because they do not have the statutory authority to require pre-market approval of cosmetic products or ingredient, except for most color additives, and because FDA does not feel that the organization presented data or evidence showing that the chemicals are deleterious substances that may cause adverse events in children under 14.

Author: FDA
Date: 3/6/2007 **Page(s):** 3

Doc.# 009-3982

Petition Response: Assessing the Performance of Medical Devices

This letter to the Clinical and Laboratory Standards Institute is in response to their petition requesting that FDA amend the recent practice of assessing the performance of medical devices for determining the in vitro susceptibility of bacteria or fungi to various antimicrobial agents using only the criteria included in the approved drug label rather than new or revised criteria published by CLSI and that CDRH "positively review" fluconazole disks for disk diffusion susceptibility testing of Candida spp. patient isolates for use in clinical laboratories. FDA is approving the first part of the petition, but denying the second.

Author: FDA
Date: 3/5/2007 **Page(s):** 3

Doc.# 009-3983

Supplement: Withhold Approval of an ANDAs for a Generic Version of Lovenox®

This document, submitted on behalf of Sanofi-Aventis US, contains additional information in support of their petition requesting that FDA withhold approval of any ANDAs for a generic version of Lovenox® (enoxaparin sodium injection). Specifically, the firm provides information regarding how the European Union is handling low molecular weight heparin products, of which Lovenox® is one.

Author: Covington & Burling LLP
Date: 3/2/2007 **Page(s):** 7

Doc.# 009-3984

Letter: Withdrawal Angiotensin Converting Enzyme Inhibitor and Angiotensin Receptor Blocker

This letter to Anil Mandal MD is in response to his petition requesting that FDA restrict or withdraw the use of angiotensin converting enzyme inhibitor and angiotensin receptor blocker therapy for a number of conditions. FDA has not yet reached a decision on this petition.

Author: CDER, FDA
Date: 3/1/2007 **Page(s):** 1

Doc.# 009-3985

Letter: Health Claim for Isomaltulose and Dental Caries

This letter to FDA was submitted on behalf of Cargill, Inc. and agrees to FDA's proposed 180-day extension deadline for a decision on Cargill's isomaltulose

noncariogenicity health claim petition. The deadline is now September 5, 2007.
Author: **Hyman, Phelps, & McNamara PC**
Date: **3/5/2007** **Page(s): 1**

Doc.# **009-3986**
Letter: Mepron Tablets, 250 mg
This letter to Lachman Consultant Services, Inc is in response to their petition requesting that FDA determine whether Mepron Tablets, 250 mg, has been voluntarily withdrawn from sale for safety or efficacy reasons. FDA has not yet reached a decision on this petition.
Author: **CDER, FDA**
Date: **3/6/2007** **Page(s): 1**

Doc.# **009-3987**
Petition: Refuse Approval of CIP-TRAMADOL ER
This petition, submitted on behalf of Perdue Pharma, requests that FDA take the following actions regarding a NDA submitted by Cipher Pharmaceuticals seeking approval for CIP-TRAMADOL ER, a 24 hour extended release oral formulation of tramadol: 1) if the Cipher NDA was submitted under Section 505(b)(2) of the FD&C Act, FDA should refuse to approve it until the company includes an appropriate certification with respect to U.S. Patent No. 6,254,887 listed in the Orange Book for the listed drug Ultram® ER; or 2) if the NDA was submitted under Section 505(b)(1), FDA should refuse to approve the NDA until Cipher complies with the requirement that the NDA include full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use.
Author: **Kleinfeld, Kaplan and Becker LLP**
Date: **3/13/2007** **Page(s): 12**

Doc.# **119-0041**
Comments: Use of Carbon Monoxide in Case-Ready Fresh Meat Packaging
These comments are in response to comments and the petition submitted by Kalsec regarding a ban on carbon monoxide gas in fresh meat packaging. Hogan & Hartson refutes what Kalsec claims in their comments and states again that the petition should be denied.
Author: **Hogan & Hartson LLP**
Date: **2/28/2007** **Page(s): 6**

Doc.# **300-1407**
Comments: Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants
These comments, submitted by GlaxoSmithKline, Sanofi Aventis, and AdvaMed, are in response to the proposed rule regarding the use of materials derived from cattle in medical products. The companies offer their suggestions on how to improve and clarify the rule.
Author: **Various**
Date: **2/12/2007** **Page(s): 8**

Doc.# **300-1408**
Comments: Prescription Drug User Fee Act
These comments are in response to the Federal Register from January 16, 2007, regarding new initiatives for the Prescription Drug User Fee Act IV, specifically the issuance of a new guidance on End-of-Phase II meetings. The company offers their opinions on how to improve this initiative.
Author: **Sepracor**
Date: **2/23/2007** **Page(s): 2**

Doc.# **301-0270**
Guidance on Drug Safety Information--Food and Drug Administration's Communication to the Public; Availability
FDA is announcing the availability of a guidance titled "Drug Safety Information--FDA's Communication to the Public." This guidance describes FDA's current approach to communicating important drug safety information, including emerging drug safety information, to the public and the factors that influence when such information is communicated. This guidance was developed in connection with FDA's Drug Safety Initiative. This guidance is the final version and supersedes the previously issued draft guidance titled "FDA's Drug Watch for Emerging Drug Safety Information" (70 FR 24606, May 10, 2005).
Author: **FDA, HHS**
Date: **3/7/2007** **Page(s): 19**

Doc.# **332-0672**
Statistical Report - February 2007
This document contains OGD's statistical report for February 2007. It specifically contains quantitative information about OGD's receipts, actions, and pending review status for both original and supplemental applications for the past month and for the 11 preceding months.
Author: **Office of Generic Drugs**
Date: **3/6/2007** **Page(s): 24**

Doc.# **532-0677**
USDA/FSIS Weekly Update: March 12-16, 2007
Topics include: What They're Saying About the Administration's Farm Bill Proposals; Johanns Names Members to the U.S. Highbush Blueberry Council; Johanns Announces Urban and Community Forestry Grants; USDA Awards More Than $415,000 in Weather Radio Transmitter Grants to Bring Early Warning Broadcasts to Rural America; Johanns Signs Framework Agreement with United Nations' Food and Agriculture Organization Director General Diouf Johanns' One Year Report on Avian Influenza Actions; What They're Saying About Risk-Based

Inspection in Processing Plants; and Washington Firm Recalls Summer Sausage Due To Undeclared Allergen.
Author: **USDA, FSIS**
Date: **3/16/2007** **Page(s): 17**

Doc.# **650-1152**
Morbidity and Mortality Weekly Report: Vol. 56, No. 10
Topics include: National Nutrition Month --- March 2007; Fruit and Vegetable Consumption Among Adults --- United States, 2005; Postmarketing Monitoring of Intussusception After RotaTeq™ Vaccination --- United States, February 1, 2006--February 15, 2007; Increases in Gonorrhea --- Eight Western States, 2000--2005; Kidney Disease Mortality --- Michigan, 1989--2005; Notice to Readers: National Colorectal Cancer Awareness Month --- March 2007; Notice to Readers: World Water Day --- March 22, 2007; QuickStats: Percentage of Office-Based Primary-Care Physicians Who Did Not Accept New Patients, by Expected Payment Source --- National Ambulatory Medical Care Survey, United States, 2003--2004; and Notifiable Diseases/Deaths in Selected Cities Weekly Information.
Author: **CDC**
Date: **3/16/2007** **Page(s): 32**

Doc.# **660-0879**
CPSC Public Calendar
This is the schedule of meetings between Commission staff members and outside parties for the week of March 19 through March 25, 2007.

Doc.# **800-1079**
Temperature-Indicating Devices; Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers
FDA is proposing to amend its regulations for thermally processed low-acid foods packaged in hermetically sealed containers to allow for use of other temperature-indicating devices, in addition to mercury-in-glass thermometers, during processing. FDA also is proposing to establish recordkeeping requirements relating to temperature-indicating devices and to clarify other aspects of low-acid canned food processing such as FDA's interpretation of some requirements of the current regulations that will, in part, allow the use of advanced technology for measuring and recording temperatures during processing. Finally, FDA is proposing to include metric equivalents of avoirdupois (U.S.) measurements where appropriate.
Author: **FDA, HHS**
Date: **3/14/2007** **Page(s): 35**

PUBLISHED FDA IMPORT DOCUMENTS
All current published import alerts, import bulletins, and import guidance documents are available through FOI. These cover all new alerts and bulletins and updates to these issued by the Division of Import Operations and Policy, Office of Regulatory Affairs. These alerts and bulletins include identification of responsible foreign companies and their products that may be subject to Detention without Physical Examination (DWPE) or exempt there from. If you wish Kendle Regulatory Affairs to perform a search, or request copies of any specific document, please contact us.

International Update

Compiled by Stephen Simpson, RAC, CCRP

Australia

- On March 7, 2007 the Australia New Zealand Therapeutic Products Authority (ANZTPA) released a ***Guidance Tool for Assessing the Appropriate Regulatory Coverage for Products at the Food-Medicine Interface***. The tool is intended to be used to determine whether a product that falls within the "grey area" at the food-medicine interface would be regulated as a food or as a therapeutic product. The objective in applying the tool is to determine whether a "reasonable person," when faced with the product in its final presentation, would consider that the product was intended for therapeutic use. The guidance is intended only for determining the appropriate regulatory coverage for the product and does not enable a determination to be made about whether the product would meet all the requirements of relevant legislation.

- A ***Guidance Document on the Regulation of Nutrigenetic Tests in Australia*** was released by the Australian Therapeutic Goods Administration (TGA) on March 7, 2007. Nutritional genomics is a science studying the relationship between the human genome, nutrition and health. Dependent upon the claims made by the manufacturer of each test, nutrigenetic tests are considered to be therapeutic goods and therefore must comply with the requirements of the *Therapeutic Goods Act 1989*. Any tests that are intended to be used, or that are marketed for their potential to influence a physiological process will be required to fulfill both current and future regulatory requirements.

Ireland

The Irish Medicines Board (IMB) announced the launch of RIO (Regulatory Information Online), its online submission system for medicinal products on March 15, 2007. The system will commence operation on March 30, 2007 and registered users of the system will be able to complete and submit online applications for Type 1A, 1B, and Type 2 variations for human medicines. The system provides online forms, documentation upload facilities, and online tracking services for all applications submitted. The system will be expanded to include other submission types over the coming months.

United Kingdom

On March 15, 2007 the Medicines and Healthcare products Regulatory Agency (MHRA) released ***Further Guidance on Designing Patient Information Leaflets and How to Achieve Success in User Testing***. The document was written as a result of a recent survey of those companies who undertake user testing of patient information leaflets on behalf of marketing authorization holders. The guidance document discusses the importance of the design and layout of Patient Information Leaflets and the use of templates.

European Union

- On February 22, 2007 the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) issued a ***Recommendation on the Need for Revision of the CHMP Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP)***. This document outlines the issues to be considered when updating the existing Points to Consider document on OIPs, particularly with regard to demonstration of therapeutic equivalence (TE). The EMEA is accepting comments on the document through May 31, 2007.

- A draft ***Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease*** was issued by the CHMP on February 22, 2007. This draft guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with Crohn's disease. It will replace the "Points to Consider on Clinical Investigation of Medicinal Products for Management of Crohn's Disease."

- The CHMP issued a ***Recommendation for Revision of the Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection*** on February 22, 2007. This document outlines the issues to be

considered when updating the existing HIV Notes for Guidance document in order to update sections related to confirmatory studies in heavily pre-treated patients, studies in children, PK interactions, conditional approval and information in the Summary of Product Characteristics (SPC).

EIR/483s

A compilation of the establishment inspection reports, Form FDA 483s and firm's responses obtained by Kendle Regulatory Affairs through Freedom of Information requests submitted to the FDA. The list is sorted numerically, and contains the Document ID number, company name and location, an executive summary, the starting date of the inspection, the FDA investigator(s) and the document length.

Each of these documents contains one or more of the following: EIR and/or 483 and Firm's Response.

Doc. # 083-8216
Bayer Corporation, Elkhart, IN
This inspection of an OTC pharmaceutical and vitamin products manufacturer was conducted in accordance with CP 7356.002 and CP 7303.803. No significant deviations were noted, and no FDA 483 was issued.
Investigator(s): George Calafactor
Date: 1/8/2001 Page(s): 14

Doc. # 083-8217
Bayer Corporation, Elkhart, IN
This inspection of a class I/II medical device manufacturer was conducted in accordance with CP 7383.001 and CP 7382.830. The inspection focused on PMA P990055, Complexed Prostate Specific Antigen Assay. While no FDA 483 was issued during this inspection, the following observations were verbally noted: the number of significant digits for pH differs between the device master record specifications, the recorded data, and the pH papers; there is no approved calibration schedule for test equipment utilized at the Elkhart, In location; and minor changes to instructions in 3 device history records were made, without changing the appropriate device master records.
Investigator(s): George Calafactor
Date: 5/24/2000 Page(s): 12

Doc. # 083-8218
Bayer Corporation, Elkhart, IN
This inspection of a children's chewable vitamins manufacturer resulted in the issuance of an FDA 483. The following observation was noted: manufacturing presses and air handling systems used to manufacture chewable vitamin tablets are not being maintained in acceptable cleaned and sanitized fashions.
Investigator(s): William Nelson, George Calafactor
Date: 3/29/2000 Page(s): 13

FDA Federal Register Notices

A compilation of regulatory significance from government authorities and industry experts, offered by Kendle Regulatory Affairs on a subscription basis. The list is sorted numerically, and contains the Document ID number, title, an executive summary, author, issue date, and document length.

Date	Document Description	Docket No.
3/13/07	♦ Draft Final Guidance for Industry: Guide to Minimize Food Safety Hazards for Fresh-Cut Fruits and Vegetables; Availability; Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request.	2006D-0079
	♦ Guidance for Industry and Food and Drug Administration Staff; Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Availability.	2003D-0044

	♦ Agency Information Collection Activities; Proposed Collection; Comment Request; Control of Communicable Diseases; Restrictions on African Rodents, Prarie Dogs, and Certain Other Animals. ♦ Agency Information Collection Activities; Announcement of Office of Management and Budget Approval; Food Labeling; Trans Fatty Acids in Nutrition Labeling. ♦ Agency Information Collection Activities; Announcement of Office of Management and Budget Approval; Recordkeeping Requirements for Human Food and Cosmetics Manufactured From, Processed With, or Otherwise Containing, Material from Cattle. ♦ Electronic Case Report Form Submission; Notice of Pilot Project.	2007N-0073 2006N-0130 2004N-0257 2007N-0064
3/14/07	♦ Temperature-Indicating Devices; Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers. ♦ Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Experimental Evaluation of Variations in Content and Format of the Brief Summary in Direct-to-Consumer Print Advertisements for Prescription Drugs.	2007N-0026 2006N-0133
3/15/07	♦ Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Substances Prohibited From Use in Animal Food or Feed; Animal Proteins Prohibited in Ruminant Feed. ♦ Medical Devices Regulated by the Center for Biologics Evaluation and Research; Availability of Summaries of Safety and Effectiveness Data for Premarket Approval Applications.	2006N-0472 2006M-0384, 2006M-0385, etc.
3/16/07	♦ Food Substances Affirmed as Generally Recognized as Safe in Feed and Drinking Water of Animals: 25-Hydroxyvitamin D-3.	1995G-0321
3/19/07	♦ Draft Guidance for Industry on Indexing Structured Product Labeling; Availability. ♦ Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Technical Amendment.	2007D-0080 1976N-0052G

RECALLS

The recalls appearing below have been abstracted from the FDA's Enforcement Report

DRUGS

- **Novopharm Ltd, Scarborough, Ontario Canada**
  Product: Care340B Glyburide Tablets, 5 mg, 30 tablet bottles, Rx only, Product # CC528, NDC 66336-938
  Recall #: D-467-2007
  Date: 12/22/06
  Recall Class: III
  Reason: Ingredient statement incorrectly reports that each tablet contains 5 mg Glipizide instead of 5 mg Glyburide.

DEVICES

- **Siemens Medical Solutions Diagnostics, Flanders, NJ**
  Product: Sample Management System software for in vitro diagnostic testing Product # 030102-03
  Recall #: Z-0545-2007
  Date: 1/15/07
  Recall Class: II
  Reason: Under limited circumstances, an incorrect patient result could be printed on the optional chartable patient report.

FDA Advisory Committee Meetings

March 29, 2007
Anesthetic and Life Support Drugs Advisory Committee
The committee will do the following: (1) Receive presentations regarding neurodegenerative findings in juvenile animals exposed to anesthetic drugs (e.g., ketamine); and (2) discuss the relevance of these findings to pediatric patients and provide guidance for future preclinical and clinical studies. FDA intends to make background material available to the public no later than 1 business day before the meeting. If FDA is unable to post background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting.

March 29, 2007
Food Defense Workshop; Public Workshop
The Food and Drug Administration (FDA), Office of Regulatory Affairs (ORA), Southwest Regional Office (SWRO), in co-sponsorship with the Risk Management Small Business Development Center (RMSBDC), is announcing a public workshop entitled "Food Defense Workshop." This public workshop is intended to provide information about food defense, the regulations authorized by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act), and other related subjects to FDA-regulated food facilities (farms, manufacturers, processors, distributors, retailers, and restaurants).

March 29 & 30, 2007
Cellular, Tissue, and Gene Therapies Advisory Committee
On March 29, 2007, in open session, the committee will discuss Sipuleucel-T, Dendreon (BLA-STN 125197) indicated for the treatment of men with asymptomatic metastatic hormone refractory prostate cancer. The committee will also hear overviews of research programs in the Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research. On March 30, 2007, in open session, the committee will discuss the draft document entitled "Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies." For a copy of the draft guidance visit http://www.fda.gov/cber/gdlns/cordbld.pdf. The committee will also discuss scientific issues regarding minimally manipulated, unrelated allogeneic peripheral blood stem cells.

April 10 & 11, 2007
University of Arkansas/Food and Drug Administration Food Labeling Workshop; Public Workshop
FDA, Office of Regulatory Affairs, Southwest Regional Small Business Representative Program, in collaboration with The University of Arkansas, is announcing a public workshop entitled ``UA/FDA Food Labeling Workshop." This public workshop is intended to provide information about FDA food labeling regulations and other related subjects to the regulated industry, particularly small businesses and startups.

April 11, 2007
Anti-Infective Drugs Advisory Committee
The meeting will be open to the public from 8:30 a.m. to 9:30 a.m., unless public participation does not last that long, from 9:30 a.m. to 4 p.m., the meeting will be closed to permit discussion and review of trade secret and/or confidential commercial information.

April 11, 2007
Pediatric Advisory Committee
The Pediatric Advisory Committee will hear and discuss reports by the agency, as mandated in section 17 of the Best Pharmaceuticals for Children Act, on adverse event reports for fluvastatin (Lescol) and octreotide (Sandostatin). The committee will also receive updates to adverse event reports for orlistat (Xenical) and oxybutynin (Ditropan) which were requested by the Pediatric Advisory Committee when the reports were first presented.

April 12, 2007
Joint Meeting of the Anti-infective Drugs Advisory Committee and the Pediatric Advisory Committee
The committee will discuss clinical trial designs for products that seek indications for the prevention and/or treatment of disease caused by Shiga toxin-producing bacteria.

April 12, 2007
Arthritis Advisory Committee
The committee will discuss new drug application (NDA) 21-389121-772, ARCOXIA (etoricoxib), Merck & Co., Inc., proposed treatment for the relief of signs and symptoms of osteoarthritis.

April 18, 2007
Cardiovascular and Renal Drugs Advisory Committee
The committee will discuss supplemental new drug application (sNDA) 20-7581s-037, AVALTDE (irbesartan plus hydrochlorothiazide), Bristol-Myers Squibb Co. The sponsor is seeking approval for first-line use in hypertensive patients unlikely to achieve blood pressure goals on one drug. The committee will be asked to consider what constitutes adequate data to support such a claim and how the information can be most usefully displayed in labeling.

April 24, 2007
Antiviral Drugs Advisory Committee
The committee will discuss new drug application (NDA) 022-128, maraviroc 300 milligram tablets, Pfizer, Inc., proposed for the treatment of antiretroviral-experienced patients with chemokine (c-c motif) receptor 5 (CCR5)--tropic human immunodeficiency virus (HIV). FDA intends to make background material available to the public no later than 1 business day before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting.

April 24, 2007
Animal Drug User Fee Act; Public Meeting
The Food and Drug Administration (FDA) is announcing a public meeting on the Animal Drug User Fee Act of 2003 (ADUFA) to seek public comments relative to the program's overall performance and reauthorization as directed by Congress.

April 25 & 26, 2007
Immune Globulins for Primary Immune Deficiency Diseases: Antibody Specificity, Potency and Testing: Public Workshop
FDA is announcing a public workshop entitled: Immune Globulins for Primary Immune Deficiency Diseases: Antibody Specificity, Potency and Testing. The purpose of the public workshop is to discuss approaches to identify the most relevant antibody specificities in Immune Globulins for the prevention of infections in patients with primary immune deficiency diseases (PIDD), and current and potential potency tests for Immune Globulins. The public workshop will also include a discussion about the declining measles antibody levels in U.S. licensed Immune Globulins and the potential clinical impact on patients with PIDD. The public workshop sponsors are FDA, the Immune Deficiency Foundation, and the Plasma Protein Therapeutics Association.

April 30, 2007
Manufacturing Subcommittee of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
The subcommittee will do the following: (1) As an awareness topic, discuss issues pertaining to the stability of tablets split for patient use; (2) receive a general update and discuss current strategies on quality by design and the Office of Generic Drugs' question-based review; and (3) receive an update on and discuss the status of the Office of New Drug Quality Assessment Chemistry, Manufacturing, and Controls Pilot Program.

May 1 & 2, 2007
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
On May 1, 2007, the committee will do the following: (1) Receive and discuss updates from the October 18 and 19, 2006, Clinical Pharmacology Subcommittee Meeting and the April 30, 2007, Manufacturing Subcommittee Meeting; (2) receive an update, discuss and make comments on current strategies and directions for the Critical Path Initiative; (3) receive an update and discuss revisions to the FDA draft guidance for industry entitled "Comparability Protocols --Chemistry, Manufacturing, and Controls Information;" (4) discuss current thinking on risk-based approaches to managing post-approval activity. On May 2, 2007, the committee will do the following: (1) Receive an update from the Office of Generic Drugs (OGD) on the bioequivalence of highly variable drugs, (2) receive an update on and discuss general strategies within the OGD pertaining to the bioequivalence of narrow therapeutic index drug products, and (3) discuss and provide comments on the topic of alcohol-induced dose dumping.

May 22 & 23, 2007, in Lakewood, CO
June 6 & 7, 2007, in Pittsburgh, PA
The Essentials of Food and Drug Administration Medical Device Regulations: A Primer for Manufacturers and Suppliers; Public Seminar

The Food and Drug Administration's Center for Devices and Radiological Health and Office of Regulatory Affairs, in cooperation with AdvaMed's Medical Technology Learning Institute, is announcing a series of three seminars on FDA medical device regulations. These 2-day seminars, which are designed to address the training needs of start up and small device manufacturers and their suppliers, will include both industry and FDA perspectives and a question and answer period. The seminars are planned for the dates listed above.

May 23 & 24, 2007
Food Defense Workshop; Public Workshop
The Food and Drug Administration (FDA), Office of Regulatory Affairs (ORA), Southwest Regional Office (SWRO), in co-sponsorship with the University of Arkansas (UA) Institute of Food Science and Engineering (IFSE), is announcing a public workshop entitled "Food Defense Workshop." This public workshop is intended to provide information about food defense, the regulations authorized by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act), and other related subjects to FDA-regulated food facilities (farms, manufacturers, processors, distributors, retailers, and restaurants).

Warning Letters *Compiled by: Research Associates*

A compilation of the Notices of Violation and Warning Letters placed on public display by FDA. The list is sorted numerically, and contains the Document ID number, company name and location, an executive summary, the issue date, and the document length.

FOODS

Doc.# 085-6317
Lanners, Roger and Julie, Royalton, MN
An investigation of this dairy operation conducted on October 26, 2006, confirmed that animals were offered for sale for slaughter as food were adulterated under sections 402(a)(2)(C)(ii) and 402(a)(4) of the FD&C Act. It was also revealed that the new animal drugs sulfadimethoxine, oxytetracycline hydrochloride, penicillin G procaine, amoxicillin, and isoflupredone acetate to be unsafe under section 512 of the Act and adulterated within the meaning of section 501(a)(5) of the Act. The following was noted: the presence of drugs in above –tolerated levels in tissues from the animal were found; failure to maintain in the treatment records a reliable system to ensure that treated cattle were not culled before labeled meat and milk withhold times were met; and extralabel use of certain drugs were not in compliance with 21 CFR Part 530.
Date: 2/28/2007 Page(s): 3

Doc.# 085-6318
Pacific International Seafood, LLC, Honolulu, HI
An inspection of this seafood processing and importer establishment, conducted November 21 and 29, 2007, revealed serious deviations from 21 CFR Parts 123 and 110, which caused the fish or fishery products to be adulterated within the meaning of Section 402(a)(4) of the FD&C Act. The following observations were noted: the firm does not have a HACCP plan for refrigerated yellowtail, to control the food safety hazard of histamine formation as a result of time/temperature abuse during the receipt, re-packing, and storage of the product at the facility; and the firm did not perform an affirmative step for the refrigerated yellowtail fish and the refrigerated vacuum packaged yellowtail that was processed.
Date: 3/1/2007 Page(s): 4

Doc.# 085-6319
Uwajimaya, inc., Seattle, WA
An inspection of this facility, conducted October 4-6, 2006, revealed serious deviations from 21 CFR Parts 123 and 110, which caused the fishery products to be adulterated within the meaning of Section 402(a)(4). The following observations were noted: the firm did not monitor the following five areas of sanitation with sufficient frequency to ensure compliance with the current good manufacturing practice requirements; the firm's HACCP plan for Uwajimaya and Cho Cho Brand Sushi does not list critical control points for finished product refrigerated storage for controlling the food safety hazards of pathogen growth and toxin production; and the firm's HACCP plan for Uwajimaya and Cho Cho Brand Sushi lists a critical limit of "Cooler/Freezer temperatures cannot exceed certain °F for certain hours" at the raw material "Storage of Filling Mixture" critical control point that is not adequate to control pathogen growth and toxin formation.
Date: 2/16/2007 Page(s): 5

Doc.# 085-6320
Mary Ellen Maryland Crab Meat Company, Inc., Egg Harbor City, NJ
An inspection of this seafood processing facility conducted on November 2, 3 & 14, 2006, revealed significant deviations from 21 CFR Parts 123 & 110 which caused the fishery products to be adulterated within the meaning of Section 402(a)(4) of the FD&C Act. The following was noted: the firm did not record

monitoring observations at the receiving critical control point to control histamine as listed in your HACCP plan for histamine producing fish; the firm did not follow, and was not able to implement, the monitoring procedures and frequency related to the electronic alarm system at the storage critical control point to control pathogen growth/temperature abuse as listed in the HACCP plan for vacuum-packaged smoked fish, canned pasteurized crab meat, fresh crab meat, seafood salads and seafood soups; and, the HACCP plan for vacuum-packaged smoked fish, canned pasteurized crab meat, fresh crab meat, seafood salads and seafood soups listed inadequate monitoring procedures at the receiving critical control point to control pathogen growth and toxin formation.
Date: 2/7/2007 Page(s): 3

DRUGS

Doc.# 087-4577
Beehive Botanicals, Inc., Hayward, WI
An inspection of this firm, conducted November 14 and 15, 2006, and a review of the website, www.beehivebotancials.com revealed that the labeling for several of the firm's products cause them to be drugs within the meaning of 201(g)(1)(B) of the FD&C Act. The following claims were noted: "It also destroys harmful bacteria in the intestines…," and "Propolis is proven to have distinct antibacterial, antiviral, and antifungal properties." Because these products are not generally recognized as safe and effective they are also new drugs within the meaning of Section 201(p) of the Act, and require an approved New Drug Application.
Date: 3/2/2007 Page(s): 5

MEDICAL DEVICES

Doc.# 089-5975
Newport Medical Instruments, Inc., Costa Mesa, CA
An inspection of this firm conducted on October 31 through November 7, 2006, revealed deviations from 21 CFR Part 820 which caused the devices manufactured to be adulterated within the meaning of section 501(h) of the FD&C Act. The following was noted: failure to establish and maintain plans that defined the responsibility for implementation of design and development activities and failure to review, update, and approve the plans as the design development evolved; failure to establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation; and failure to verify the device design to confirm that the design output met the design input requirements and a failure to document in the design history file the results of the design verification, including the identification of the design, method(s), the date, and the individual(s) performing the verification.
Date: 2/21/2007 Page(s): 6

Now Available From Kendle Regulatory Affairs
Newly Released New Drug Approval Packages

Doc.#	Trade	Generic	NDA #	Indication	Date	Pages	Manufacturer
091-4758	Urso Tablets	ursodiol	20675/ S-006	Provides for the addition of Schwarz Pharma Manufacturing Inc. as an additional site for tablet manufacture, with storage of bulk tablets up to three months; packaging as bottles of 100 tablets; release and stability testing; and revised packaging component suppliers for the 100 tablet package.	3/8/2001	46	Axcan Scandipharm, Inc.
091-4759	Urso Tablets	ursodiol	20675/ S-007	Provides for a new tradename, URSO® 250.	3/8/2001	46	Axcan Scandipharm, Inc.

091-4760	Celexa 10 mg, 20 mg, and 40 mg	citalopram	20822/ S-019	Provides for revisions to the Adverse Reactions-Other Events observed During the Postmarketing Evaluation of Celexa (citalopram HBr) section of prescriber labeling in order to make it more consistent with the Lexapro (escitalopram oxalate) labeling.	11/19/2002	16	Forest Laboratories, Inc.
091-4761	Celexa 10mg/5ml Oral Solution	citalopram hydrobromide	21046/ S-003	Provides for revisions to the Adverse Reactions-Other Events observed During the Postmarketing Evaluation of Celexa (citalopram HBr) section of prescriber labeling in order to make it more consistent with the Lexapro (escitalopram oxalate) labeling.	11/19/2002	16	Forest Laboratories, Inc.

Pocket Guides for 21 CFR

A Pocket Guide for 21 CFR
Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General
Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals
Part 11 – Electronic Records; Electronic Signatures

A Pocket Guide for 21 CFR
Part 820 - Quality System Regulation
Part 11 - Electronic Records; Electronic Signatures

These pocket guides were prepared by Kendle Regulatory Affairs to be used as a reference tool for the Regulatory Affairs Professional. One contains 21 CFR: Part 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General; Part 211- Current Good Manufacturing Practice for Finished Pharmaceuticals and as an extra Part 11 - Electronic Records; Electronic Signatures. And the other 21 CFR: Part 820 – Quality System Regulation; and as an extra Part 11 - Electronic Records; Electronic Signatures.

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