appropriate for one or the other purpose.

• *Knowledge of Intended Drug Target and Pathway Pharmacology, Secondary and Off-Target Pharmacology, and Drug Target Distribution in Rats and Humans*

Target and pathway related mechanistic/pharmacologic and understood secondary pharmacologic characteristics can contribute to the prediction of outcomes of carcinogenicity studies and can improve prediction of potential human carcinogens. The CAD is expected to convey a thorough and critical assessment of the sponsor's knowledge of all such characteristics, including a comprehensive literature review specifically addressing carcinogenicity risk. Examples of such data sources include the following:

○ Prior experience with other molecules in the drug class

○ Experience with human genetic polymorphisms in the target or pathway

○ Clinical trial data

○ Genetically engineered rodent models

○ Unintended pharmacology

○ Hormonal perturbation

○ Targeted tissue genomic biomarker measurements

• *Genetic Toxicology Study Results*

The criteria in ICH S2(R1) [3] will be used to evaluate genetic toxicology data using a weight-of-evidence approach.

• *Histopathologic Evaluation of Repeated-Dose Rat Toxicology Studies*

Histopathologic risk factors of neoplasia should be evaluated in the 6-month chronic rat study. Findings seen only in shorter-term repeated dose rat toxicity studies are generally considered of less value for 2-year rat study outcome prediction, but should be addressed. Histopathologic findings of particular interest include cellular hypertrophy, diffuse and/or focal cellular hyperplasia, persistent tissue injury and/or chronic inflammation, preneoplastic changes, and tumors. It is important to note that liver tumors are observed at relatively high frequency in the rat, sometimes with Leydig cell and thyroid follicular cell tumors. Hepatocellular hypertrophy associated with increased liver weight often results from hepatic enzyme induction, the latter being a well-understood mechanism of rodent specific tumorigenesis at these sites with little relevance to humans (Refs. 1 and 2).

• *Exposure Margins in Chronic Rat Toxicology Studies*

A high exposure margin in a chronic rat toxicology study absent of any carcinogenic risk factors can provide additional support for a carcinogenicity study waiver. The inability to achieve high exposure margins in a chronic rat toxicology study because of limitations of tolerability, pharmacology, or absorption would not preclude a carcinogenicity study waiver.

• *Evidence of Hormonal Perturbation*

Evidence of hormonal perturbation should be considered from both repeated-dose and reproductive toxicology studies. Such evidence can come from weight, gross and/or microscopic changes in endocrine organs, or parameters from reproductive toxicology studies. Serum hormone levels can be useful to address findings but are not always essential.

• *Immune Suppression*

Immunosuppression can be a causative factor for tumorigenesis in humans. As such, immunotoxicological parameters should be examined according to the ICH S8 guidance.[4]

• *Special Studies and Endpoints*

Data from special stains, new biomarkers, emerging technologies, and alternative test systems can be submitted with scientific rationale to help explain or predict animal and/or human carcinogenic pathways and mechanisms when they would contribute meaningfully.

• *Results of Non-Rodent Chronic Study*

Assessment of carcinogenic risk factors in the non-rodent toxicology studies should be considered for human risk assessment regardless of results in the chronic rat study.

• *Transgenic Mouse Study*

A transgenic mouse carcinogenicity study (usually rasH2 or p53+/− mouse) is not required for the WOE argument. However, if conducted on a case-by-case basis, a transgenic mouse carcinogenicity study can contribute to the WOE.

References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov.*

1. Cook, J.C., G.R. Klinefelter, J.F. Hardisty, et al., ''Rodent Leydig Cell Tumorigenesis: A Review of the Physiology, Pathology, Mechanisms and Relevance to Humans'', *Critical Reviews in Toxicology,* vol. 29, pp. 169–261, 1999.

2. McClain, R.M., ''The Significance of Hepatic Microsomal Enzyme Induction and Altered Thyroid Function in Rats: Implications for Thyroid Gland Neoplasia'', *Toxicologic Pathology,* vol. 17, pp. 294–306, 1989.

Dated: March 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–06145 Filed 3–15–13; 8:45 am]

BILLING CODE 4160–01–P

[3] See the ICH guidance ''S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use,'' available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

[4] See the ICH guidance ''S8 Immunotoxicity Studies for Human Pharmaceuticals,'' available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0001]

General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on FDA's regulatory issues.

Date and Time: The meeting will be held on May 2, 2013, from 8 a.m. to 6 p.m.

Location: Hilton Washington DC North/Gaithersburg, Salons A, B, C and D, 620 Perry Pkwy., Gaithersburg, MD 20877. The hotel's telephone number is 301–977–8900.

Contact Person: Jamie Waterhouse, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area). A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly

enough to provide timely notice. Therefore, you should always check the Agency's Web site at *http://www.fda.gov/AdvisoryCommittees/default.htm* and scroll down to the appropriate advisory committee meeting link, or call the advisory committee information line to learn about possible modifications before coming to the meeting.

Agenda: On May 2, 2013, the committee will discuss, make recommendations and vote on information related to the premarket approval application for the Juvéderm Voluma XC sponsored by Allergan, Inc. Juvéderm Voluma XC is a dermal filler comprised of hyaluronic acid with lidocaine. Juvéderm Voluma XC is indicated for deep (dermal/subcutaneous and/or submuscular/supraperiosteal) implantation to restore lost volume in the mid-face for aesthetic improvement.

FDA intends to make background material available to the public no later than 2 business days 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. Background material is available at *http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm.* Scroll down to the appropriate advisory committee meeting link.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before April 25, 2013. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. on May 2, 2013. Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before April 12, 2013. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by April 16, 2013.

Persons attending FDA's advisory committee meetings are advised that the Agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact AnnMarie Williams, Conference Management Staff, at *AnnMarie.Williams@fda.hhs.gov,* 301–796–5966, at least 7 days in advance of the meeting.

FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at *http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm111462.htm* for procedures on public conduct during advisory committee meetings.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: March 12, 2013.

Jill Hartzler Warner,

Acting Associate Commissioner for Special Medical Programs.

[FR Doc. 2013–06167 Filed 3–15–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0233]

Impax Laboratories, Inc.; Withdrawal of Approval of Bupropion Hydrochloride Extended-Release Tablets, 300 Milligrams

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of Bupropion Hydrochloride (HCl) Extended-Release Tablets, 300 Milligrams (mg) (Bupropion HCl Extended-Release Tablets 300 mg), under Abbreviated New Drug Application (ANDA) 77–415, held by Impax Laboratories, Inc. (Impax), 30831 Huntwood Ave., Hayward, CA 94544, and marketed under the name BUDEPRION XL. Impax has voluntarily requested that approval for this product be withdrawn and waived its opportunity for a hearing.

DATES: Effective March 18, 2013.

FOR FURTHER INFORMATION CONTACT: Carolina M. Wirth, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6282, Silver Spring, MD 20993–0002, 301–796–3602.

SUPPLEMENTARY INFORMATION: FDA approved ANDA 77–415 for Bupropion HCl Extended-Release Tablets 300 mg (marketed under the name BUDEPRION XL) on December 15, 2006 pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). Bupropion HCl Extended-Release Tablets 300 mg was indicated for the treatment of major depressive disorder. On September 27, 2012, FDA requested that Impax voluntarily withdraw its Bupropion HCl Extended-Release Tablets 300 mg from the market after results of an FDA-sponsored bioequivalence study showed that Impax's Bupropion HCl Extended-Release Tablets 300 mg are not therapeutically equivalent to the 300-mg strength of the reference listed drug. In a letter dated September 30, 2012, Impax requested that FDA withdraw approval of the 300-mg strength of Bupropion HCl Extended Release Tablets, approved under ANDA 77–415, pursuant to § 314.150(d) (21 CFR 314.150(d)). In that letter, Impax also waived its opportunity for a hearing. The Agency acknowledged Impax's requests in a letter dated November 2, 2012.

Therefore, under section 505(e) of the FD&C Act (21 U.S.C. 355(e)) and § 314.150(d), and under authority delegated by the Commissioner to the Director, Center for Drug Evaluation and Research, approval of the 300-mg strength of Bupropion HCl Extended-Release Tablets under ANDA 77–415 is withdrawn (see **DATES**). Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d)).

Dated: March 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–06144 Filed 3–15–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Indian Health Service

Indian Health Professions Preparatory, Indian Health Professions Pre-graduate, and Indian Health Professions Scholarship Programs

Announcement Type: Initial.