American Chinese Pharmaceutical Association Newsletter

美洲華人藥學會通訊

Editor: James W. Shaw, Ph.D., Pharm.D., M.P.H. **July 2005 Vol. 20 No. 3**

Message from the President
Keith Chan, Ph.D.

It's all good news and no bad news.

As we step into summer, I have some good news to share with my friends and members of ACPA. Isn't it nice to have some good news during these tough pharmaceutical times?

First of all, ACPA will be receiving a US$6,250 donation from the GloboMax Foundation, a nonprofit organization co-founded by David Young and myself. As you all know, the parent company of the Foundation, GloboMax LLC, was acquired by ICON PLC. My partner and I decided to close the GloboMax Foundation, and I elected to donate my share of the residual funds to ACPA.

Second, we have planned a number of activities that will take place in the coming months as well as next year. These include the following:

- ACPA will co-sponsor a symposium with CACS on the topic of "Mass Spectrometry in Biomedical Research and Drug Discovery." The event will be held on September 30, 2005, at the Clarion Hotel and Towers in Edison, NJ.
- ACPA will host a Regional Conference on October 1, 2005 at the University of Maryland Shady Grove Center in Rockville, Maryland. The theme of the conference is "Biopharmaceutical Comparability." This is a very hot topic that is of particular importance in the development of therapeutic biotechnology products. The event will be co-sponsored by Centocor and GloboAsia LLC.
- We are in the early stages of planning an international conference with the National University of Singapore. This will likely be held in March or August/September, 2006. The theme of the conference will be "Health and Aesthetic Promoting Products to Improve Human Life—Challenges and Opportunities." I have received a tremendous response from some sponsors in Asia. For the ACPA members located in North America, please try to plan your vacation accordingly; there will be a very good vacation package for the conference participants. Our organization had the opportunity to work with the National University of Singapore in 2001 when Marina Chang was president. We had a grand time and were able to coordinate a very successful conference. We fully intend to repeat or even surpass the success of 2001.
- We have decided upon a location for the ACPA Annual Dinner Meeting. The meeting will be held in conjunction with the AAPS Annual Meeting, which is scheduled to take place November 6–10, 2005 in Nashville, Tennessee. We were unable to locate an authentic Chinese restaurant that had the capacity to hold all of the potential attendees. Therefore, we decided to hold the banquet at the conference site, i.e., the Gaylord Opryland Hotel. Please note that the dinner will be held on Wednesday, November 9, 2005, whereas in the past our annual banquet was held on a Tuesday evening. The change from Tuesday to Wednesday was made at the request of the UCSF group to avoid a scheduling conflict with their banquet. Please mark your calendar.
- As far as I know, the ACPA student chapter at the University of Houston (under the supervision of Professor Ming Hu) is planning to host some kind of activity, and we surely welcome that. I have also heard rumors that some NIH post-docs and graduate students at the University of Maryland and Johns Hopkins University will be organizing a career

conference later this year. I surely wish them the best of luck and hope to provide them with some measure of support.

As you can see, ACPA is currently very active in preparing for the future. This is the best news of all. I hope that you enjoy your involvement in ACPA as much as I do. Please do not hesitate to contact any of the Executive Committee members or myself with your thoughts or concerns. Our names and e-mail addresses are listed on the homepage of ACPA's website at www.acpa-rx.org. We will try to respond to your needs as quickly as possible.

Have a nice summer!

Donation Received from GloboMax Foundation

ACPA wishes to thank Dr. Keith Chan and the GloboMax Foundation for donating $6,250 to the organization. Dr. Chan's kindness and generosity are greatly appreciated.

Report from the Program Committee
Jinn Wu, Ph.D.

Many exciting activities have been planned in the next few months for ACPA members and friends. The first program is a joint symposium with the Chinese American Chemical Association (CACS) on Friday, September 30. The symposium, which is titled "Mass Spectrometry in Biomedical Research and Drug Discovery," will be held at the Clarion Hotel and Towers in Edison, New Jersey. This is a one-day program sponsored by XenoBiotic Laboratories, Merck, Schering-Plough, Finnigan Instruments, Waters, and Applied Biosystems. The program will have many outstanding speakers, including Bogdan Matuszewski, Senior Director, Bioanalytical and Drug Metabolism, Merck; Walter Korfmacher, Director of Exploratory DMPK, Schering-Plough; Kate Yu, Waters; Y.X. Li, XenoBiotic Laboratories; Julie Wingate, Applied Biosystems; and others from Quest Pharmaceutical Services, SFBC, and Finnigan Instruments. This is an excellent opportunity to learn and exchange cutting-edge techniques in LC/MS/MS and its application. Coffee, snacks, and lunch will be provided. There will be no charge to attend the symposium; however, registration is required. If you are interested in attending, please contact me at wujinn@xbl.com or Yunsheng Hsieh at Yunsheng.hsieh@spcorp.com. Alternatively, you may visit ACPA's website at www.ACPA-Rx.org or CACS' website at www.cacshq.org for more information. A draft program announcement has been distributed with this issue of the newsletter.

The second program is a regional conference that will be held on October 1, 2005 at the University of Maryland Shady Grove Center in Rockville, Maryland. The theme of the conference is "Biopharmaceutical Comparability." This is a very hot topic that will have a significant impact on the field of therapeutic biotechnology products. The event is currently co-sponsored by Centocor and GloboAsia LLC. For detailed program information, please contact Jennifer Han at jhan1278@yahoo.com or Keith Chan at kchan@globoasia.com, or visit ACPA's website. A draft press release has been distributed with this issue of the newsletter.

The 2005 ACPA Annual Dinner Meeting will be held from 6–10:30 PM on Wednesday, November 9, 2005 at the Gaylord Opryland Resort & Convention Center in Nashville, Tennessee. As usual, the meeting will be held in conjunction with the AAPS annual conference. Please mark your calendar and join us for this exciting event. We are finalizing invitations for the keynote speaker. If you have any suggestions regarding speakers or topics of interest, please contact me at wujinn@xbl.com.

The 2nd AASP Symposium/2nd APEM Conference will be held from November 14–17, 2005 at the Monthien Riverside Hotel in Bangkok, Thailand. The event will be hosted by the Asian Association of Schools of Pharmacy (AASP) and the Pharmacy Education Consortium of Thailand (PECT) in collaboration with and the Pharmaceutical Association of Thailand under royal patronage, the Pharmacy Council of Thailand, and other professional pharmacy organizations and special interest groups. The theme for the event will be "Regional Cooperation in Pharmacy Education, Research and Services" with an emphasis on strategic collaboration to integrate pharmacy practice and pharmaceutical sciences for better outcomes. Specific information regarding the conference program and registration is provided in an attached document.

Report from the Communications Committee

James W. Shaw, Ph.D., Pharm.D., M.P.H.

The Communications Committee received affirmative responses from three members regarding the draft ACPA bylaws, which were distributed by e-mail to the membership on April 21, 2005. However, one ACPA member did provide substantive recommendations for revising the draft. Accordingly, this individual's comments will be incorporated into the document. The revised draft will be distributed to the members of the Executive Committee in July for their review. The final draft will be formally approved and put into effect at ACPA's 2005 Annual Dinner Meeting in November.

ACPA Promotes the Formation of Student Chapters

Ming Hu, Ph.D.

ACPA is promoting the formation of student chapters among universities in United States of America and Asian countries, where many members of the organization live and work.

Here I will briefly share with you how we formed the first ACPA student chapter at the University of Houston. All students who were eligible to be involved in the student chapter were invited to attend an organizational meeting. At the meeting, the students elected officers for the organization, including a President, Vice-President, and Treasurer. A memorandum was drafted to outline the objectives of the chapter.

Since the initial meeting, the members of the student chapter have registered the organization with the University of Houston and established a bank account. The ACPA leadership has approved funding of $500 to support activities of the student chapter that benefit its membership. These activities are to be decided upon at a future date.

Student chapter members must apply for membership in ACPA. The current annual membership fee for professional and graduate students is $10.00. The membership application can be downloaded from the ACPA website at http://www.acpa-rx.org/member.htm.

Venture Capitalism

Jonas Wang, Ph.D.
Sycamore Ventures

During an ACPA Executive Committee conference call held on July 9, 2005, Dr. Keith Chan asked me to write an article discussing venture capital (VC). As many of you know, after working in the pharmaceutical industry for 30 years, I joined Sycamore Ventures in mid-2002 as a venture capitalist. Most of my friends are interested in learning how I made the transition in the last three years from a dedicated pharmaceutical scientist to a financial manager. I have overheard questions such as, "Is Jonas happy or unhappy with the transition to a totally different field?", "Can Jonas manage financial matters as he did his research?", and "Is Jonas making any money yet?" To be honest, I do not have clear answers to these questions since I am relatively new to the VC world.

One thing I do know is that I have not made a lot of money yet. If you had asked me how I was doing in 2003 during my first year as a venture capitalist, I would have told you that it was a painful and difficult transition. In late 2003, there were several occasions where, if not for the help of my friends at Sycamore Ventures, I would have decided to quit my job as a venture capitalist. I found it terribly difficult dealing with portfolio companies since there were many unresolved problems in management, marketing, sales, and personnel issues. Such companies are always short of funds, and I constantly needed to help raise money from other VC firms. As many of you know, it is really tough to beg for funds for portfolio companies. After three years of torture, I am now pretty good at fundraising. If you were to ask me how I am doing now, I would have to say "a little bit better." Though I have become accustomed to the nature of the VC business, I would never tell you that it has been an easy transition.

When Keith asked me to write an article on VC, I was not sure if I understood correctly what he wanted me to do. I assumed that he wanted me to share with you my experience as a venture capitalist and to provide you with some advice for dealing with those who work in my field. I would like to provide you with some basic facts and fundamentals on VC. I believe that this information will help many of you to understand better the nature of the business.

VC is a term used to describe the financing of start-up and early stage businesses as well as businesses in "turn-

around" situations. *VC investments* are generally higher risk investments but offer the potential for above-average returns. A *venture capitalist* is a person who makes such investments. A *venture capital fund* is a pooled investment vehicle that invests the financial capital of third-party investors in enterprises that are too risky for the standard capital markets or bank loans. A *general partner* is a venture capitalist who manages the fund and makes investments. I am now a general partner at Sycamore Ventures. Investments by a venture capital fund can take the form of either equity participation or a combination of equity participation and debt obligation—often with convertible debt instruments that become equity if a certain level of risk is exceeded. In most cases, the venture capitalist becomes part owner or a member of the board of directors of the new venture. Most investments are structured as preferred shares—the common stock often reserved by covenant for a future buyout, as VC investment criteria usually include a planned exit event (an IPO or acquisition), normally within three to seven years. For IT deals, the exit time is normally much shorter than that of biotechnology or pharmaceutical deals (~2–3 years compared with ~5–7 years). If a venture fails, then the entire funding by the venture capitalist has to be written off.

A new venture may need several infusions of cash from venture capitalists as the business progresses.

1. *1st or "A" round*. Referred to as seed capital, this is obtained prior to company launch. It is for marketing research, concept testing, and alpha and beta testing.
2. *2nd or "B" round*. Referred to as start-up capital, this is for hiring staff, renting office space, completing product development, purchasing servers and other IT infrastructure, purchasing inventories, equipping the production system, and other activities involved in starting the business.
3. *3rd or "C" or additional rounds*. As sales (and production) levels increase, additional rounds could be needed to modify the site, re-equip the production system, expand plant capacity, or purchase new facilities. These additional rounds are sometimes called second- or late-stage financing or development capital.
4. *Mezzanine financing*. This is the final round of financing before going public. Once a company's stock is publicly traded on a stock exchange, capital is raised by issuing and selling shares.

During the 1990s and the dotcom boom, securing investment in the 1st or 2nd round (the so called "early stages") was somewhat easy. However, it is now quite difficult to get seed or start-up capital from VC firms anywhere other than on the US West Coast. It is well known that those early stage deals are high risk but yield a high return if successful, while investments in the later stages, i.e., "C", "D", "E" rounds, are low risk and safer deals but offer lower returns. The success rate (~50–70%) for the late-stage deals is normally much higher than the early stage deals (~20–30%). Due to the high-risk nature of the early stage deals, most of the institutional VCs now only invest in late-stage deals. Sycamore Ventures, like most other institutional VC firms, has adjusted its investment criteria in the 3rd round and later-stage deals to minimize risk. In pharmaceuticals, the late-stage deals are those in the Phase II or Phase III clinical trial stage. Most of the preclinical or Phase I deals are considered to be early stage deals. Angle investors, friends, or relatives invest in most of the early stage deals. Most entrepreneurs do not know this; thus, in the last three years I have spent a lot of time explaining to young businesspeople where and when they should focus on getting funds for their ventures.

In general, venture capitalists are very selective in deciding what to invest in. A common figure is that they invest in approximately one in four hundred ventures. They are only interested in ventures with high growth potential. Venture capitalists usually expect to be able to assign personnel to key management positions and to obtain one or more seats on the company's board of directors. This is to promote corporate governance and avoid accounting scandals and incompetent management. Managerial authority is even more critical for biotechnology and pharmaceutical investments and is often the biggest challenge to young and inexperienced venture capitalists. This turns out to be one of my key strengths. With 30 years as a pharmaceutical executive, I have sufficient knowledge of the technology, its potential, the market size, IP strength, and regulatory restrictions. I also know a lot of people in academia and the pharmaceutical industry, which helps me to recruit and put in place capable managers to build company business. Only ventures with high growth potential are capable of providing the return that venture capitalists expect and structure their businesses to expect.

After investment, venture capitalists will normally participate in the operation, support business development, and create liquidity opportunities, i.e., IPO or acquisition, for the company. After the liquidity

event, venture capitalists expect to be able to sell their stock, warrants, options, convertibles, or other forms of equity in three to ten years or sooner. This is referred to as *harvesting*. Venture capitalists know that not all of their investments will pay off. The failure rate for investments can be high; anywhere from 20–90% of funded enterprises fail to return the invested capital. Because many businesses cannot create the growth required to have an exit event within the desired time frame, VC is not suitable for everyone. The venture capitalist must be a high-risk professional.

Many venture capitalists try to mitigate risk through diversification. They invest in companies in different industries and different countries so that the systematic risk of their total portfolio is reduced. Others concentrate their investments in the industry they are most familiar with, such as biotechnology or IT. VC partners may be former chief executives at firms similar to those that the venture capitalists funds. In any case, they work on the 2:6:2 assumption, which states that for every ten investments made, two will be failures, two will be successful, and six will be marginally successful. Venture capitalists expect that the two successes will pay for their time and risk the exposure of the other eight. In good times, the funds that do succeed may offer returns of 300–1000%. However, current returns are much lower. In most cases, the two successes will not be able to pay for the other eight; thus, more successes are needed. This makes the venture capitalist's job even tougher.

Due almost entirely to the dotcom boom, the late 1990s were very profitable for the globally renowned VC firms on San Hill Road in the San Francisco area. IPOs took truly irrational leaps, and access to "friends and family" shares became a major determinant of who benefited from any IPO. The ordinary investor rarely got a chance to invest at the strike price during this period. However, the NASDAQ crash and technology slump that started in March 2000—and the resulting catastrophic losses on overvalued, non-performing start-ups—has shaken VC funds. Even in 2003, many venture capitalists were focused on writing off companies that they had funded only a few years ago. At the same time, VC investors were seeking to reduce the large commitments they had made to VC funds. As of mid-2003, the conventional wisdom was that the VC industry would shrink to about half its capacity. Being a VC professional is tougher than ever before, and this is especially true for biotechnology and pharmaceutical venture capitalists.

In the past, US firms have traditionally been the biggest participants in venture deals, but non-US venture investment is growing. In China, venture funding more than doubled from $420 million in 2002 to almost $1 billion in 2003. During the first half of 2004, VC investment rose 32% from the level in 2003. The Indian Venture Capital Association estimates that the funding of Indian companies will reach $1 billion in 2004.

This article just a scratches the surface. I hope that I have been able to provide you with some of the fundamentals of the VC world. I do not want to encourage or discourage anyone from becoming a VC professional. Due to space limitations, I was unable to go into detail on how VC operates, investment criteria are established, due diligence is performed, or one determines the likely financial return of an investment. However, if you are interested in knowing more about the VC world, then I will be happy to write more on this topic in the future.

Special Topic—Safety Testing of Drug Metabolites

Jinn Wu, Ph.D.
XenoBiotic Laboratories, Inc.

As a scientist who has worked in the drug metabolism and pharmacokinetics area for a long time and provided professional services and consulting in this area, I am very pleased to see the first Draft Guidance for Industry—Safety Testing of Drug Metabolites, which was released by the FDA in June 2005. I would like to provide a summary for all ACPA members to have some general idea and understanding in this specific Guidance. Drugs entering the body undergo biotransformation via Phase I and Phase II metabolic pathways. Based on the nature of the chemical reactions involved, metabolites formed from Phase I reactions (e.g., oxidation, reduction) are more likely to be pharmacologically active, and require safety evaluation, than Phase II products (e.g., glucuronidation, sulfation). Although conjugated metabolites from Phase II reactions are generally pharmacologically inactive, more water soluble, and readily eliminated from the body, some are toxic. Sulfate and some glucuronide metabolites (e.g., acyl glucuronides of carboxylic acids) may retain pharmacological activity as well as toxicity of the parent drug and may require toxicological evaluation. Demonstration that a metabolite is pharmacologically

inactive at the target receptor does not guarantee that it is not toxic, however. If the unique or major metabolites are suspected to contain a reactive functional group, it is important to assess the toxicity potential of these reactive metabolites. Chemically reactive intermediates are rarely detectable due to their short half-life, although stable products (i.e., glutathione conjugates) resulting from such intermediates can provide some indication of exposure to these potentially toxic species.

Generally, compounds with the following characteristics are of particular concern and may warrant additional investigation:

- Narrow therapeutic indices
- Significant toxicity
- Significantly diverse metabolic profiles between human and nonclinical species

- Irreversible toxicity, or adverse effects not readily monitored in the clinic

Traditionally, drug metabolites in general have not been routinely evaluated in cross-species safety assessments because their specific contribution to the overall toxicological potential of the parent drug has been unknown. With the availability during the past decade of technologies that can identify, measure, and characterize metabolites, we have gained a better understanding of the role metabolites play in drug safety assessment.

Generally, we have used measurements of circulating concentrations of a parent drug in animals as an index of systemic exposure in humans. Quantitative and qualitative differences in metabolite profiles are important when comparing exposure and safety of a drug in a nonclinical species relative to humans during risk assessment. Based on data obtained from in vitro and in vivo metabolism studies, when the metabolic profile of a parent drug is similar qualitatively and quantitatively across species, we can generally assume that potential clinical risks of the parent drug and its metabolites have been adequately characterized during standard nonclinical safety evaluations. However, metabolic profiles and metabolite concentrations can vary across species, and there are cases when clinically relevant metabolites have not been identified or adequately evaluated during nonclinical safety studies. This may be because the metabolite being formed in humans was absent in the animal test species (unique human metabolite) or because the metabolite was present at much higher levels in humans (major metabolite) than in the species used during standard toxicity testing. The Agency recommends that—and this Guidance encourages—attempts be made to identify as early as possible during the drug development process differences in drug metabolism in animals used in nonclinical safety assessments compared to humans (Baillie and Cayen et al. 2002; Hastings et al. 2003). It is especially important to identify metabolites that may be unique to humans. The discovery of unique or major human metabolites late in drug development can cause development delays and could have possible implications for marketing approval. Early identification of unique or major metabolites will allow for timely assessment of potential safety issues.

FDA recommends that metabolites identified in human plasma that account for greater than 10% of drug-related material (administered dose or systemic exposure whichever is less) be considered for safety assessment. The rationale for setting the level at greater than 10% for characterization of metabolites reflects consistency with other FDA and EPA regulatory Guidances (US Food and Drug Administration 2002; US Environmental Protection Agency 1998) and is supported by actual cases, described below, in which it has been determined that the toxicity of a drug could be attributed to one or more metabolites present at greater than 10% of the administered dose. Of the cases that follow, the last two are examples of a situation when a metabolite present at less than 10% caused toxicity. As a result, depending on the situation, some metabolites present at less than 10% should also be tested.

- Halothane, an inhalation anesthetic, has a metabolite, trifluoroacetylchloride, which represents less than 20% of the administered dose. Yet this metabolite is responsible for halothane-induced liver toxicity, a major safety concern that has led to limited use of the drug (Pohl et al. 1989).
- Use of felbamate for the treatment of several forms of epilepsy has been associated with adverse events of aplastic anemia and hepatotoxicity that are attributed to a reactive metabolite, atropaldehyde, which was detected indirectly as the urinary metabolites mercapturic acid (2.3% of felbamate concentration in urine) and mercapturic alcohol (13.4% of felbamate concentration in urine) (Thompson et al. 1999).
- The anticancer drug, cyclophosphamide, has no direct cytotoxic action. However, its toxicity is attributed to a number of metabolites. One of these metabolites, 4-hydroxycyclophosphamide,

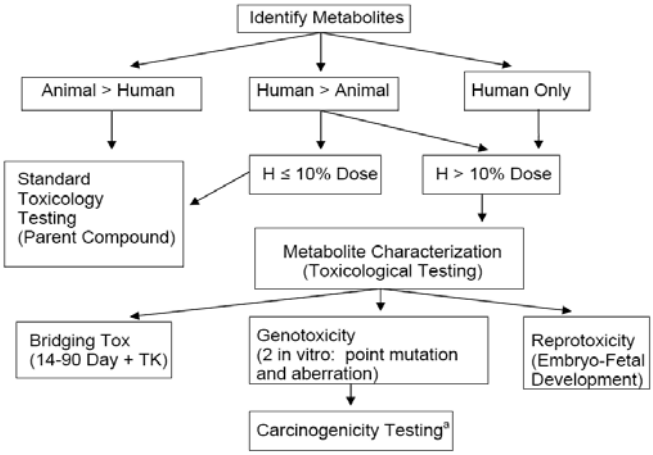
represented approximately 8.3% of the total plasma exposure (Sladek et al. 1984).

- Acetaminophen liver toxicity is attributed to N-acetyl-p-benzoquinone imine (NAPQI), a toxic reactive intermediate of acetaminophen, detected in urine as thioether metabolites. The latter were found to constitute approximately 9% of a therapeutic dose of acetaminophen (Manyike et al. 2000).

From the summaries on the safety issue of drug metabolites as described above, four key words/phrases should be remembered:

1. Major metabolite—A metabolite in humans that accounts for plasma levels greater than 10% of the administered dose or systemic exposure, whichever is less.
2. Metabolite—A compound derived from the parent compound through Phase I and/or Phase II metabolic pathways.
3. Pharmacologically active metabolite—A metabolite that has pharmacological activity at the target receptor that is greater than, equal to, or less than the parent compound.
4. Unique human metabolite—A metabolite produced only in humans.

A decision tree flow diagram also has been proposed by the Agency:



[a] Carcinogenicity testing may be needed on a case-by-case basis, independent of the results of genotoxicity testing (see Section IV.D).

For more information, please see the Draft Guidance at http://www.fda.gov/cder/guidance/6366dft.htm (6/3/05) or send suggestions to the FDA Division of Dockets Management (HFA-305), 5630 Fishers Lane, RM 1061, Rockville, MD 20852.

References

Baillie, TA, MN Cayen, H Fouda, RJ Gerson, JD Green et al., 2002, Drug Metabolites in Safety Testing, Toxicol Appl Pharmacol, 182, 188-196.

Hastings, KL, J El-Hage, A Jacobs, J Leighton, D Morse, R Osterberg, 2003, Drug Metabolites in Safety Testing, Toxicol Appl Pharmacol, 190(1), 91-92.

Manyike, PT, ED Kharasch, TF Kalhorn, JT Slattery, 2000, Contribution of CYP2E1 and CYP3A to Acetaminophen Reactive Metabolite Formation, Clin Pharmacol Ther, 67, 275-282.

Pohl, LR, JG Kenna, H Satoh, D Christ, JL Martin, 1989, Neoantigens Associated with Halothane Hepatitis, Drug Metab Rev, 20(2-4), 203-217.

Sladek, NE, D Doeden, JF Powers, W Krivit, 1984, Plasma Concentrations of 4-Hydroxycyclophosphamide and Phosphoramide Mustard in Patients Repeatedly Given High Doses of Cyclophosphamide in Preparation for Bone Marrow Transplantation, Cancer Treat Rep, 68(10), 1247-1254.

Thompson, CD, MT Barthen, DW Hopper, TA Miller, M Quigg et al., 1999, Quantification in Patient Urine Samples of Felbamate and Three Metabolites: Acid Carbamate and Two Mercapturic Acids, Epilepsia, 40(6), 769-776.

U.S. Environmental Protection Agency, 1998, Health Effects Test Guidelines, OPPTS 870.7485, Metabolism and Pharmacokinetics. (www.epa.gov/epahome/research.htm)

U.S. Food and Drug Administration, 2002, Guideline for Metabolism Studies and for Selection of Residues for Toxicological Testing, U.S. Food and Drug Administration, Center for Veterinary Medicine. (www.fda.gov/cvm/guidance/guideline3pt1.html)

Published quarterly by ACPA as part of the annual membership

P.O. Box 2623, Cherry Hill, NJ 08034, U.S.A.

Visit us at http://www.acpa-rx.org