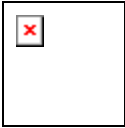


# A March 15<sup>th</sup> 2002 thru April 15<sup>th</sup> 2002 Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights

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## **1. On March 18<sup>th</sup>, 2002 the press released an article titled "Supplement Linked to Seven Cases of Liver Damage"**

A supplement touted for weight loss appears to have caused severe liver toxicity in seven healthy people who developed symptoms within 3 months of starting the product, US researchers reported Monday.

Last November, the US Food and Drug Administration (FDA) warned consumers to stop using the supplement, called LipoKinetix, after receiving reports of liver injury and liver failure among people using the product. The agency also told the supplement's manufacturer, Syntrax, of Cape Girardeau, Missouri to take it off the market.

In the new report, researchers from the FDA and Cedars-Sinai Medical Center in Los Angeles, California, describe seven patients who developed liver inflammation between July and December 2000--including one

who developed liver failure.

All of the patients recovered spontaneously after stopping LipoKinetix, and none was taking prescription or over-the-counter drugs, according to Dr. Joya T. Favreau and colleagues.

Their report was released Monday on the Web site of the *Annals of Internal Medicine* ([www.annals.org](http://www.annals.org)), ahead of its April 16 publication in the journal's print edition.

Five of the patients came to Cedars-Sinai with symptoms of acute hepatitis, such as abdominal pain and fatigue. The researchers describe one case in detail, a 20-year-old woman who developed symptoms such as fever, abdominal pain and jaundice (a yellowing of the skin). Tests revealed breakdown in the liver tissue. The patient had been taking LipoKinetix for 2 weeks when she sought medical care.

The two other cases had been reported to the FDA's MedWatch program. These two patients were bodybuilders who sought medical attention 9 to 12 weeks after starting LipoKinetix.

According to the researchers, it is unclear how the supplement could be toxic to the liver, as none of the individual substances in the product are known to have such effects. They speculate that an interaction between the various ingredients could be to blame.

LipoKinetix contains norephedrine, a stimulant found in some diet aids that have been linked to such serious effects as heart attack and stroke. Other ingredients include caffeine and yohimbine, a product derived from tree bark that has been linked to nausea, vomiting, abdominal pain and other symptoms, Favreau's team reports.

These seven cases highlight the larger issue of whether it is time to put tighter regulations on the dietary supplement industry, according to an editorial accompanying the report.

Unlike the prescription drug industry, supplement manufacturers do not have to show the FDA their products are safe and effective before putting them on the market, nor are they required to report adverse events to the agency, point out Drs. James D. Lewis and Brian L. Strom of the University of Pennsylvania in Philadelphia.

"Perhaps the time has come to hold the manufacturers of any product with a health claim to the same standards as the pharmaceutical industry," the editorialists write.

For now, however, consumers should discuss their supplement use with their doctors, and doctors should remember that patients might not mention such products when they are asked about medication use, Lewis told Reuters Health.

"This is particularly important as we become aware of how supplements can interact with prescription medications," he said, citing as example St. John's wort, which can dull the effectiveness of certain prescription drugs.

"One other important thing for people to remember," Lewis added, "is that 'all natural' does not necessarily mean something is safe. There are many poisons that exist naturally.... The consumer should maintain a cautious level of skepticism."

This data will be published in the April 16<sup>th</sup>, 2002 issue of the *Annals of Internal Medicine* publication; 136:590-595, 616-618.

## **2. On March 18<sup>th</sup>, 2002 the press also released another article related to drug-induced liver damage titled "Liver Damage Reported in Man Taking Diabetes Drug"**

A man with diabetes developed liver damage after taking the diabetes drug Pioglitazone for 6 months, according to a new report.

This case does not prove that the drug was to blame, the report's authors say, but the man's liver returned to normal after he stopped taking the drug. A similar diabetes medication was pulled from the market after it was linked to potentially fatal cases of liver failure.

Based on the case, Dr. Louis D. May of Gastrointestinal Associates of Rockland in New City, New York, and colleagues recommend that people taking pioglitazone be monitored for signs of liver damage.

Pioglitazone belongs to a class of drugs called thiazolidinediones, which help lower blood sugar, or glucose, in people with type 2 diabetes. These drugs work by helping the body to use its own stores of the glucose-regulating hormone.

Pioglitazone, which is made by Takeda Pharmaceuticals North America in Lincolnshire, Illinois, is the newest type of thiazolidinedione approved for use in the US. The drug company Lilly co-markets the drug with Takeda. In 2000, the thiazolidinedione drug troglitazone (Rezulin) was taken off the market in the US and Europe after it was linked to dozens of deaths and cases of severe liver damage.

Another drug from this class, rosiglitazone (Avandia), has been linked to a handful of cases of liver damage, although the drug is still on the market. Before the current report, only one instance of liver injury had been reported among users of pioglitazone.

In an article in the March 19th issue of the journal *Annals of Internal Medicine*, May's team describes the case of a 49 year old man who was taking pioglitazone to treat type 2 diabetes. After taking the drug for 6 months, 15 milligrams (mg) per day for 4 months and 30 mg for 2 months, the man began to experience abdominal pain, nausea, loss of appetite and weight loss. Despite these symptoms, the patient had normal results on blood tests, including ones that measure liver function.

After the man's blood sugar levels rose, the physician increased the daily dose of pioglitazone to 45 mg. A few days later, the whites of the man's eyes began to turn yellow and his bowel movements were lighter than usual. Another round of tests showed signs of liver damage.

The man did not have any other risk factors for liver damage, such as alcohol or recreational drug use. And the results of a liver biopsy suggested that the damage was caused by medication.

Suspecting that pioglitazone was responsible, doctors took the patient off the drug, but he continued to take his other medications. His symptoms gradually improved and his liver tests returned to normal within 6 weeks.

Physicians should be aware of the possibility that pioglitazone may cause liver damage, May and his colleagues conclude. "Patients receiving this drug should be monitored for evidence of liver dysfunction, particularly during the first year of therapy," the authors write.

"Takeda and Lilly are absolutely committed to patient safety and have in place a multi-layered system of adverse event surveillance," the companies said in a written response to the report. "As with all medications, there have been adverse event reports involving patients taking Actos."

The companies note that the drug's labeling recommends that patients' liver enzymes be monitored when they begin taking the drug and every two months during the first year that they are on the drug, and that the drug should not be given to patients with active liver disease.

According to Dr. David W. Nierenberg of Dartmouth Medical School in Hanover, New Hampshire, it is "highly probable" but not certain that pioglitazone can cause mild to moderate liver damage. How often such side effects occur is uncertain, however, he notes in a related editorial.

Liver damage “almost certainly” occurs less frequently among people taking pioglitazone than among those who took troglitazone, the similar drug that was taken off the market, Nierenberg points out.

He notes that rosiglitazone, which is still on the market, “has been shown to cause serious liver damage or liver failure, but such severe acute drug reactions appear to be rare.” Whether pioglitazone has the same side effect and how often it occurs will not be known until many more people have taken the drug, Nierenberg states.

This data was published in the March 19<sup>th</sup>, 2002 issue of the Annals of Internal Medicine publication; 136:449-452, 480-483.

### **3. On March 20<sup>th</sup>, 2002 the press released the following article as a result of a living donor transplant complication. “Vital Signs: Liver Donors Face Perils Known and Unknown”**

When Laurie Post's family took her to an emergency room in Somerset, N.J., in September 2000, her temperature was 104.7. She was weak, anemic, vomiting and short of breath. Her abdomen was swollen and painful. Trim to begin with, she had lost 15 pounds. Her kidney function was poor.

Seven weeks earlier, at the New York University Medical Center, Ms. Post had been a living organ donor, allowing 60 percent of her liver to be removed to provide a transplant for her cousin. The cousin had recovered. But Ms. Post, then 34, had been in and out of the hospital several times and was still suffering an infection, a blood clot and a bile leakage in her abdomen.

Ms. Post's complications were precisely the ones that surgeons warn people about when they agree to become liver donors. The complication rate is estimated at 10 percent and the risk of death from 0.5 to 1 percent.

But those figures really are estimates. No one knows for sure how many donors have experiences like Ms. Post's. There is no formal reporting system or tracking of what happens to people who are living donors in liver transplants.

### **4. On March 21<sup>st</sup>, 2002 Roche informed the press that Pegasys is cleared for take-off in Europe**

Roche Holding AG, the embattled Swiss drug maker, was given a shot in the arm on Thursday after a European Union advisory panel recommended approval for its hepatitis C drug Pegasys.

Roche is relying on the interferon medicine to revive its fortunes after a dismal year of product setbacks and weak sales. Analysts at UBS Warburg believe that Pegasys could achieve sales of \$1 billion by 2006.

The panel's recommendation of Pegasys covers use of the drug alone or in combination with ribavirin for adults with hepatitis C, a viral infection that attacks the liver. More than 170 million people have contracted the disease.

“It's a relief that Pegasys is now on track in Europe, given its history of delays, and that they have got combination- and mono-therapy approval,” said Paul Diggle, industry analyst at WestLB Panmure in London.

“But the key development that the market is awaiting is its approval in the U.S.”

Pegasys's approval by the U.S. Food and Drug Administration has been delayed because Roche has had to provide “bioequivalence” data to prove that material from new production capacity is identical to earlier batches.

Roche reiterated it expected Pegasys to go on sale in the United States in the fourth quarter of 2002 putting it around a year behind Schering-Plough Corp's rival PEG-Intron product, which has already been launched.

## **5. On March 21<sup>st</sup>, 2002 it was announced that HepaSense has Initiated a Phase II Clinical Trial of ISIS 14803 for Hepatitis C**

HepaSense(TM), Ltd., a joint venture of Isis Pharmaceuticals, Inc. and Elan Corporation, plc ("Elan"), of Dublin, Ireland, announced today that it has initiated a Phase II clinical trial of ISIS 14803 in patients with chronic Hepatitis C Virus infections (HCV). The Phase II clinical trial will evaluate the safety and tolerability of ISIS 14803, an antisense drug that inhibits HCV replication, when administered by intravenous infusion (IV).

The open-label, dose escalation Phase II study is planned to enroll 40 patients at six sites across the U.S. Two dosing regimens of ISIS 14803 administered IV over 12 weeks will be studied. The primary endpoint in the clinical trial is reduction in viral titer, or level of virus in blood.

"We are pleased to continue the development of ISIS 14803 in HCV, a disease where improved therapies are much needed. We observed encouraging results in the initial Phase I/II trial that provided us with a foundation for further study of this drug," said F. Andrew Dorr, M.D., Isis' Vice President and Chief Medical Officer. "Results from this study, in which patients will receive doses of ISIS 14803 for three months, will help us determine the next steps in developing this drug."

Ivan Liebenberg, Élan's Chief Scientific and Medical Officer stated, "Isis' approach to HCV therapy is unique in the field and we look forward to the results of this study."

In June, 2001, HepaSense reported preliminary data from a small group of patients in a Phase I/II clinical trial in which ISIS 14803 demonstrated antiviral activity by reducing viral titers in patients with drug-resistant chronic HCV. Patients in the study received escalating doses of ISIS 14803 by IV for one month. All patients in the report had the most common and drug resistant form of HCV, genotype 1, and all but one patient had failed previous interferon-based therapy. Clinical trials of ISIS 14803 using Elan's MEDIPAD(TM) Drug Delivery System, a minimally invasive microinfusion pump, are planned for the future.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene(R) (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 12 products in its development pipeline, with two in late-stage development and six in Phase II human clinical trials. LY900003 (ISIS 3521), an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III human clinical trials for Crohn's disease. Isis has a broad patent estate, as the owner or exclusive licensee of nearly 900 issued patents worldwide. Isis' GeneTrove(TM) division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics(TM) is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at <http://www.isispharm.com/>

## **6. On March 22<sup>nd</sup>, 2002 it was announced that "J&J Buys Belgian Biotech Company"**

Johnson & Johnson said on Friday it agreed to acquire private Belgian biotechnology company Tibotec-Virco NV for \$320 million in cash and debt to expand its ability to offer treatments for such viruses as HIV and hepatitis C.

Industry analysts said similar deals could be in store for J&J, as the U.S. health care giant's leading position in the lucrative race to get a revolutionary heart device to market is expected to provide a hefty boost to sales and earnings over the next 12 to 24 months.

"The Tibotec deal is an incremental acquisition that strengthens an area where Johnson & Johnson is not as strong as its other therapeutic divisions," said analyst Stephen O'Neil of J.J.B. Hilliard, W.L. Lyons.

Tibotec-Virco focuses on developing antiviral treatments, including those for HIV and hepatitis C. It also develops HIV/AIDS compounds that are active against both wild-type HIV and strains of HIV that have developed drug resistance.

Company spokeswoman Karen Manson said Tibotec-Virco is still years away from making a profit. "(The acquisition) affords us financial stability," she said. "Johnson & Johnson has huge resources that we can tap into in terms of drug discovery and we bring in a drug-discovery operation that is fully operational and functioning. "The company recently marketed two HIV resistance-testing products and has two anti-retroviral compounds in Phase II clinical trials". Putting the two drugs through development could cost up to \$100 million a year, Manson said. "It's a very cash-intensive business at this stage," she added.

Tibotec-Virco employs about 235 people worldwide and operates subsidiaries in Ireland and North Carolina.

The biotechnology sector has seen a spate of mergers since the end of last year as companies seek to gain critical mass by accessing each other's products, cash and markets.

Amgen Inc. in December launched a record \$16 billion bid for Immunex Corp., and a number of major pharmaceutical companies have been active in acquiring biotech businesses. Earlier this week, Germany's Schering AG announced a \$140 million deal to buy Collateral Therapeutics Inc.

### **7. Also on March 22<sup>nd</sup>, 2002 the press released an article titled "Bush Acts to Drop Core Privacy Rule on Medical Data"**

The Bush administration today proposed dropping a requirement at the heart of federal rules that protect the privacy of medical records. It said doctors and hospitals should not have to obtain consent from patients before using or disclosing medical information for the purpose of treatment or reimbursement.

The proposal, favored by the health care industry, was announced by Tommy G. Thompson, the secretary of health and human services, who said the process of obtaining consent could have "serious unintended consequences" and could impair access to quality health care.

The sweeping privacy rules were issued by President Bill Clinton in December 2000. When Mr. Bush allowed them to take effect last April, consumer advocates cheered, while much of the health care industry expressed dismay.

Today's proposal would repeal a provision widely viewed as the core of the Clinton rules: a requirement that doctors, hospitals and other health care providers obtain written consent from patients before using or disclosing medical information for treatment, the payment of claims or any of a long list of "health care operations," like setting insurance premiums and measuring the competence of doctors.

The proposal is to be published in the Federal Register next week, with 30 days for public comment. The government will consider the comments and then issue a final rule, with the force of law.

Secretary Thompson said he wanted to remove the consent requirements because he believed they could delay care.

Pharmacists and hospitals had expressed the same concern. Drugstores said they could not fill prescriptions phoned in by a doctor for pick-up by a patient's relative or neighbor. Hospitals said they could not schedule medical procedures until the patient had read a privacy notice and signed a consent form.

Hospitals and insurance companies praised today's proposal as a victory for common sense, but consumer advocates and Democratic members of Congress denounced it as a threat to privacy.

"In general, this is great for the health care industry," said Elisabeth Belmont, corporate counsel for Maine Health, which operates seven hospitals, a nursing home and a home health agency in Maine. Mary R. Grealy, president of the Health Care Leadership Council, which represents drug makers, drugstores, insurers and hospitals, said: "The new proposal strikes an appropriate balance. It's a workable compromise."

But Janlori Goldman, coordinator of the Consumer Coalition for Health Privacy, an alliance of more than 100 groups favoring patients' rights, said the administration was proposing "a destructive change."

Representative Edward J. Markey, Democrat of Massachusetts, said: "By stripping the consent requirement from the health privacy rule, the Bush administration strips patients of the fundamental right to give their consent before their health information is used or disclosed. The administration's proposal throws the baby away with the bath water."

Senator Edward M. Kennedy, Democrat of Massachusetts, said he was "very concerned" because he believed that "an individual should have to give permission before medical information is disclosed."

The Bush administration denied that it was eviscerating privacy protections. "The president believes strongly in the need for federal protections to ensure patient privacy, and the changes we are proposing today will allow us to deliver strong protections for personal medical information while improving access to care," Mr. Thompson said.

Under the rules, doctors and other health care providers would still have to notify patients of their rights and the providers' disclosure policies. Patients would be asked to acknowledge in writing that they had received such notice, but could receive care without the acknowledgment.

Ms. Goldman, director of the Health Privacy Project at Georgetown University, said: "It's absurd to suggest that a notice serves the same purpose as consent. Signing the consent makes it more likely that people will understand their rights."

Some parts of the Clinton rules would survive the changes proposed by the Bush administration. Patients would, for example, have a federal right to inspect and copy their records and could propose corrections.

Congress could try to set privacy standards by law, overriding decisions by the Bush administration. But that appears unlikely. Under a 1996 law, Congress instructed the secretary of health and human services to issue rules on medical privacy in the absence of action by Congress, and lawmakers have never been able to agree on standards.

In its proposal today, the Bush administration tries to ensure that parents have "appropriate access" to medical records of their children, including information about mental health, abortion and treatment for drug and alcohol abuse. The Clinton rules "may have unintentionally limited parents' access to their child's medical records," the Bush administration said. The proposal makes clear that state law governs disclosures to parents.

The Bush proposal would also relax some consent requirements that medical researchers saw as particularly onerous.

The rules, the first comprehensive federal standards for medical privacy, affect virtually every doctor, patient, hospital, pharmacy and health plan in the United States.

Health care providers and insurers must comply by April 14, 2003. Anyone who violates the rules after that date will be subject to civil and criminal penalties, including a \$250,000 fine and 10 years in prison for the most serious violations.

When Mr. Clinton issued the rules in December 2000, he described them as "the most sweeping privacy protections ever written." Mr. Bush took political credit for accepting those rules last April. White House officials said Mr. Bush would back a wide range of privacy protections for consumers, even if he had to defy his usual business allies.

The White House wanted to avoid the political embarrassment Mr. Bush suffered when he altered Clinton policies on arsenic levels in drinking water, global warming, ergonomic rules and the contamination of school lunch meat with salmonella. But after studying the medical privacy rules and listening to the concerns of

companies in the health care industry, the administration concluded that major provisions of the Clinton rules were unworkable.

## **8. On March 27<sup>th</sup>, 2002 the FDA Warns that Kava Supplements May Harm the Liver**

Kava, an herb used in dietary supplements and said to promote relaxation, may be linked to rare cases of severe liver injury, U.S. regulators warned consumers Monday.

The Food and Drug Administration said it had not yet determined whether kava was responsible for liver damage but felt consumers should be aware of the potential risk.

The FDA said it had received a report of a previously healthy young woman who required liver transplantation as well as several reports of liver-related injuries in people taking kava products.

Outside the United States, kava has been associated with 25 reports of liver-related injury, including hepatitis, cirrhosis and liver failure, the FDA said in its advisory to consumers.

“FDA will continue to investigate the relationship, if any, between the use of dietary supplements containing kava and liver injury,” the FDA said, adding it would alert consumers if necessary as more information becomes available.

Patients who have liver problems or who are taking drugs that can affect their livers, should consult a physician before taking kava-containing supplements, the FDA said.

Also, anyone taking kava should contact a doctor if they experience possible signs of liver problems, such as yellowing of the skin or whites of the eyes or brown urine.

Other symptoms of liver disease can include nausea, vomiting, light-colored stools, tiredness, weakness, stomach or abdominal pain and loss of appetite.

Countries including Germany, Switzerland, France, Canada and Britain have taken action on kava ranging from warnings to removing kava products from the market.

Industry groups representing dietary supplement makers did not quarrel with the FDA's advice, noting that several companies have included cautions about kava use on their product packaging. The groups stressed, however, that the FDA had not ruled that kava caused liver damage.

“The jury is still definitely out,” said Robin Gellman, a spokeswoman for the American Herbal Products Association, adding that “consumers need to read the FDA advisory. That's important information.”

The Center for Science in the Public Interest, a consumer group, said it was pleased with the FDA's action, adding “we urge consumers to steer clear of kava altogether unless directed otherwise by a physician.”

Kava, a plant found in South Pacific islands, is an ingredient in dietary supplements promoted for a variety of uses, including relaxation and treatment of sleeplessness and symptoms of menopause. Kava commonly is served in a traditional drink in the South Pacific.

The FDA urged consumers and physicians to report any cases of liver or other injuries that may be related to kava use.

## **9. Also on March 27<sup>th</sup>, 2002 the press released an article titled “Italy to Allow Liver Transplants in HIV Patients”**

Italians with HIV can now receive liver transplants from deceased donors after the country's AIDS Commission and National Transplant Centre overturned a ban on the procedure. The ban had stirred

accusations of discrimination from HIV patients. In a statement released Tuesday, the Health Ministry said some details remain to be established, such as criteria according to which HIV-infected patients will be included in the transplant lists.

Working out the fine print will not take too long, the statement said: "The parameters for evaluating the admissibility of HIV patients in the lists are at an advanced stage of preparation."

"Finally, the anachronistic barriers that prevented HIV patients to access liver transplants have fallen," said Angelo Magrini, president of the Associazione Politrasfusi Italiana, a group representing multiple transfusion recipients. "Until now, these patients have been discriminated against, as they were barred from transplants in favor of 'common patients' who would have a longer life expectancy, theoretically." According to Magrini, only Modena and Palermo's transplant centers have offered to carry out the transplants so far. "Such transplants have given positive results in the US in these years. Now we hope that the ministry will also authorize kidney transplantations in HIV patients," said Dr. Ignazio Marino, director of Palermo's Mediterranean Transplants Institute. Last year, Marino carried out a kidney transplant from a living donor to an HIV-infected patient. The intervention raised controversy, as the ministry did not authorize it. The ministry asked Palermo's Council of Doctors to investigate the possibility of sanctions against Marino, but found the council's president agreed with the intervention.

Still cautious, the health ministry remarked that liver transplantation in HIV-infected patients is not a well-established procedure and is subject to strict control

### **10. On March 28<sup>th</sup>, 2002 an article titled "Group Urges Ban of Rheumatoid Arthritis Drug, Citing Liver Failure Link" was published by the press**

A prescription drug for rheumatoid arthritis has been linked to dozens of serious liver injuries and 12 deaths and should be banned, a consumer advocacy group told the government Thursday. Arava began selling in 1998 as a competitor to the gold-standard treatment for rheumatoid arthritis, called methotrexate. When the Food and Drug Administration approved Arava, the agency noted Arava worked no better than the older drug, but said patients needed some different options. Since then, the FDA has received at least 130 reports of severe liver toxicity linked to Arava use, including 56 hospitalizations and 12 deaths, said Dr. Sidney Wolfe of the consumer advocacy group Public Citizen. Two of the deaths were people in their 20s.

Since Arava and methotrexate work equally well, and methotrexate also bears a warning about possible liver damage, Wolfe compared the two. The FDA has six times more reports of liver damage among Arava users than methotrexate users - even though thousands more people use methotrexate, he said. Citing similar reactions abroad, the European Union last year warned patients and doctors about Arava's toxicity, Wolfe said. He wants the FDA to go further and ban Arava's sales. The FDA said it would carefully consider Wolfe's petition.

A spokeswoman for Arava manufacturer Aventis Pharma said she had not seen the petition and declined comment about liver damage. Lise Geduldig said Arava was "an important therapeutic option" taken by 200,000 people. The American College of Rheumatology last summer warned doctors to take special care in prescribing Arava, by repeatedly testing patients' livers for signs of harm. Unlike other drugs that can clear the body shortly after patients swallow a dose, Arava can take months to dissipate. Yocum said that means there is not much doctors can do if a patient shows signs of trouble. Yet some insurance companies pay only for Arava, not more expensive newer therapies that do not come with the same risks, Yocum complained. "I do not believe that the general rheumatologist understands or has any knowledge about these serious and potentially life-threatening complications," he said. Rheumatoid arthritis affects about 2 million Americans, the vast majority of them women. It is not the kind of arthritis that plagues the elderly as their joints essentially wear out. Instead, the immune system goes awry and attacks patients' own cartilage. It typically strikes between ages 25 and 50. Liver damage is not the only Arava concern, Wolfe said. FDA records show more reports of lymphoma, high blood pressure and a life-threatening autoimmune disorder called Stevens-Johnson syndrome among Arava users compared with methotrexate, he said.

## **11. On April 2<sup>nd</sup>, 2002 an article was written titled “Sharing Injection Equipment Spreads Hepatitis C”**

A new report underscores the risks injection drug users face for infection with the hepatitis C virus (HCV) from sharing commonly used drug paraphernalia other than syringes, such as drug "cookers" and cotton filters.

While many anti-drug campaigns have warned of the hazards of sharing hypodermic needles, the new study found that injection drug users who shared cookers, containers used to dissolve and heat illicit drugs including heroin and cocaine, were four times more likely to contract HCV. Those who shared cotton filters more than doubled their risk of contracting the virus. Sharing syringes and rinse water also boosted risk, but not significantly.

“In most injection sessions, drugs are placed in a cooker and dissolved in water. The solution is then drawn into a syringe through a cotton filter to strain out ‘impurities’,” Dr. Lorna E. Thorpe of the University of Illinois at Chicago and colleagues explain in the April issue of the *American Journal of Epidemiology*.

Thorpe's team followed 702 injection drug users from 1997 to 1999. All of the young adults in the study provided blood samples and those who did not already have HCV were retested 6 months and 1 year later.

About one quarter of the drug users were already infected with HCV at the beginning of the study, the authors report.

During the study period, 29 more became infected with the virus. After adjusting for the sharing of syringes, the researchers calculated that injection drug users who shared cookers were more than three times more likely to contract HCV. Sharing cotton filters more than doubled a person's risk of contracting HCV, the report indicates.

“This study provides...evidence that sharing of drug injection paraphernalia other than syringes may cause transmission of HCV among injection drug users,” Thorpe and colleagues write.

“Prevention messages and campaigns should be revised to alert active injection drug users to the importance of reducing or eliminating all equipment-sharing practices,” they conclude.

Currently in the US, injection drug users are the group at highest risk for infection with HCV, with experts attributing more than 60% of new HCV cases to people who inject illicit drugs.

This data will be published in the April 2002 issue of the *American Journal of Epidemiology*; 155:645-653.

## **12. On April 2<sup>nd</sup>, 2002 the San Francisco Chronicle released information related to “High hepatitis C rates in SF Bay Area - UCSF Study Finds Possible Links to Herpes, Cocaine use”**

Young low-income women in San Francisco and Alameda County are infected with potentially deadly hepatitis C at more than double the national average, according to a study by the University of California at San Francisco.

Beside the shocking infection rates on both sides of the bay among poor women ages 18 to 29, the research found a possible connection to herpes and non-injection drug use, namely cocaine snorting.

Herpes produces a sore that may be a “portal of entry” for hepatitis C, said lead author Dr. Kimberly Page-Shafer, assistant professor of medicine at UCSF's Center for AIDS Prevention Studies.

She and her researchers found that 34.2 percent of the women in the study had genital herpes and that 17.5 percent reported having snorted powder cocaine. They concluded that those numbers are too large to ignore

when looking at the spread of hepatitis C.

The research, published in the April issue of the *American Journal of Public Health*, covered 1,707 women in four counties -- San Francisco, Alameda, San Joaquin and San Mateo.

The study showed 4.3 percent of the women studied in San Francisco and 3.8 percent of those in Alameda County were infected with hepatitis C, well above the national average of 1.8 percent.

Young poor women in two other counties, San Joaquin and San Mateo, had infection rates below the national average at 1.4 percent and zero, respectively.

The overall findings supported the researchers' theory that the more urban a community is, the more likely it is to have higher hepatitis C infections among young low-income populations.

Hepatitis C usually strikes drug users who share needles.

Experts underscored the need to combat HCV by including interventions to reduce sexually transmitted diseases and non needle drug use.

"I think the study shows that hepatitis C prevention needs to extend beyond just blood-to-blood transmission," Page-Shafer said. "The population at risk for hepatitis C requires a more complex risk-reduction strategy that addresses both STD (sexually transmitted disease) prevention and reduction of intravenous drug use. It shows these risk factors go hand in hand. And this is a significant population to target services for."

The door-to-door study, conducted between April 1996 and January 1998, looked at the women's socioeconomic status, sexual behavior, substance abuse and medical history. African American women represented 39.2 percent of the study participants, followed by Latinas at 31.9 percent, Caucasian women at 15.4 percent, and Asian women with 6.7 percent. Women identified as "other" or mixed race were 6.7 percent of the participants.

"The presumption is people contract this from needles" said Joey Tranchina, CEO of the HCV Global Foundation in Redwood City. But, he noted, blood has also been found on straws used to snort cocaine. "We need to be looking for other sources, including home remedies involving use of needles in immigrant communities, tattoos and piercings and sex involving a lot of blood. If you don't know your partner's status in all areas, practice safe sex, use a condom."

Dr. Jeffrey Klausner, director of STD prevention for the San Francisco Department of Public Health and a co-author of the UCSF study, said the research underscores the need for people with HCV to know their status and be screened for other STDs.

"It's been known the association of hepatitis C and drug use, but the association with STDs is new and parallels what we're finding in HIV. It's not the only STD you're going to get. We can now use hepatitis C as a marker for potential risk for other STDs and improve screening."

The federal Centers for Disease Control and Prevention recommends people get tested if they've ever injected illegal drugs, received a blood transfusion or organ transplant before July 1992, received a blood product for clotting problems before 1987 or been on long-term kidney dialysis.

*Background on the different hepatitis viruses and symptoms:*

- *Hepatitis A -- A readily transmissible less dangerous form of the virus that is transmitted through fecal contaminated food or water. Vaccination available.*
- *Hepatitis B -- Contracted through contact with blood or body fluids of someone who has the virus, including intercourse without a condom, infected mother to newborn and sharing of needles. Vaccination available.*

- *Hepatitis C -- The most common chronic blood borne infection in the United States, affecting an estimated 4 million people. It is most commonly associated with injecting drug use. No vaccine is available.*
- *Hepatitis D -- A defective virus that needs the hepatitis B virus to exist. Most common methods of transmission -- contact with blood or body fluids of someone who has the virus. Prevalent in Mediterranean regions and intravenous drug users. Prevented through hepatitis B vaccine.*
- *Hepatitis E -- Transmitted through sewage contamination of food or water. Widespread in developing countries. No treatment available.*
- *Symptoms of viral hepatitis include jaundice (yellowing of the skin and eyes), fatigue, abdominal pain, loss of appetite, nausea, diarrhea and vomiting. However some people do not have symptoms until the disease is advanced.*

### **13. On April 1<sup>st</sup>, 2002 GenPhar Announces Novel Vaccines for HIV, Hepatitis B, Hepatitis C, And Marburg Viruses; GenPhar Partners with NIH and U.S. Army to Pursue Animal Trials of Vaccines**

GenPhar today announced it has developed a promising genetic vaccine platform that it has adapted to create vaccines for HIV, hepatitis B, hepatitis C, Marburg virus and other agents causing infectious diseases of public health and biodefense importance.

This versatile platform has been demonstrated to induce potent and long-lasting humoral and cellular immune responses in mice and monkeys with a single vaccination. GenPhar has developed partnerships with the National Institutes of Health (NIH) and with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) for further testing including additional preclinical trials of new genetic vaccines developed with this groundbreaking universal vaccine platform in guinea pigs and monkeys.

Unlike other HIV vaccines currently in testing phases, GenPhar's multivalent vaccines have demonstrated immunogenicity for different subtypes and mutations of HIV and hepatitis B. The vaccine for hepatitis C is currently being tested by GenPhar internally. The NIH has agreed to fund and perform its own trials for GenPhar's multivalent HIV-1 vaccine in rhesus monkeys. USAMRIID signed a formal collaborative research and development agreement (CRADA) with GenPhar to procure and test a multivalent vaccine for Marburg virus in animals. Prior to securing these partnerships, GenPhar induced a full range of immune responses in mice and monkeys against viruses that cause immunosuppressive diseases.

“The prototype products which are being developed based on this platform are unprecedented,” said Dr. John Dong, chief scientific officer of GenPhar. “GenPhar's vaccine platform is efficient and versatile. It constitutes a significant enhancement over existing vaccine technologies. The science underlying the vaccines makes it highly likely that results in mice and rhesus monkeys will be replicated in humans. We also believe that these vaccines will prove to have important therapeutic properties.”

The vaccine platform was developed upon novel scientific concepts that resulted from years of innovative laboratory research by members of the GenPhar scientific team. The scientific approach differs substantially from those that provide the basis for existing vaccines.

GenPhar's vaccines consist of a complex vector system as a “transport vehicle” that carries genetic fragments of an infectious disease agent inserted in such a way that allows the vaccine virus to effectively mimic the disease, which in turn, triggers the body's natural immune response, but without actually causing the disease. This method allows vaccines to be created that cause the immune system to generate a strong, fully natural immune reaction to an infectious disease agent, and thereby provides natural, lifetime immunity against the targeted infectious disease agent. Virtually no immune response is generated against the “transporter” adenovirus, allowing it to be used as the basis for many different vaccines. No other vaccine technology demonstrated to date has shown itself capable of inducing strong natural production of both highly specific neutralizing antibodies and a potent cytotoxic T -lymphocyte (CTL) or cellular immune responses.

*About GenPhar, Inc.*

*GenPhar, Inc. is a biopharmaceutical company that aims to become the leader in the development of molecular diagnostics, vaccines, and therapeutics for infectious diseases and cancers. GenPhar will develop, manufacture, and market biopharmaceutical products. Its products are divided into three main areas: a vaccine platform applicable to HIV, hepatitis B, hepatitis C, and other infectious diseases; an HIV drug resistance test; and a molecular therapy for solid tumors. These products will have a large-scale impact and transformative effect on current research and treatments. GenPhar was co-founded in 1999 by scientists Dr. John Dong and Dr. Danher Wang and others. Headquartered in the Charleston area of South Carolina, GenPhar can be found online at [www.genphar.com](http://www.genphar.com).*

#### **14. On April 3<sup>rd</sup>, 2002 the press released an article titled “Iron Depletion in Carbohydrate-intolerant Patients with Nonalcoholic Fatty Liver Disease”**

Iron and hyperinsulinemia both play a key role in the pathogenesis of nonalcoholic fatty liver disease, claim researchers from Germany and the USA.

The team studied the effect of iron depletion in carbohydrate-intolerant patients with clinical evidence of nonalcoholic fatty liver disease.

Increased body iron, genetic hemochromatosis (GH) mutations, and nonalcoholic fatty liver disease (NAFLD) tend to cluster in carbohydrate-intolerant patients.

In an attempt to further clarify the interrelationships among these conditions, the authors studied 42 carbohydrate-intolerant patients.

All were free of the common GH mutations, C282Y and H63D, and had a serum iron saturation lower than 50%.

Iron depletion improved plasma insulin concentrations.

The researchers measured body iron stores, and induced iron depletion to a level of near-iron deficiency (NID) by quantitative phlebotomy.

In the 17 patients with clinical evidence of NAFLD, they could not demonstrate supranormal levels of body iron (1.6 vs. 1.4 g).

However, at NID, there was a 40%-55% improvement of both fasting and glucose-stimulated plasma insulin concentrations. There was also a near-normalization of serum alanine aminotransferase activity (from 61 to 32 IU/L).

Francesco S. Facchini, of the University of California San Francisco and San Francisco General Hospital, concluded on behalf of fellow authors, "These results reflect the insulin-sparing effect of iron depletion, and indicate a key role of iron and hyperinsulinemia in the pathogenesis of NAFLD."

This data is being published in the April, 2002 issue of *Gastroenterology*; 122(4):931-9

#### **15. On April 5<sup>th</sup>, 2002 the press issued an article titled “State Checks 41 liver Surgery Cases at Hospital Where Donor Died”**

State health officials are now responding to requests to investigate 41 liver surgery cases at Mount Sinai Hospital, where a patient died in January after donating part of his liver.

Robert Kenny, a spokesman for the State Department of Health, said 32 cases involved deaths. In the nine

remaining cases, survivors requested inquiries based on claims of inadequate care, and two of those cases concerned liver donors.

The state began receiving calls for investigations after the death of Michael Hurewitz, a healthy man who had donated part of his liver to his brother in January. Although the operation was completed without complications, Mr. Hurewitz died three days later, and a state investigation held the hospital accountable and cited poor post-surgical care.

Mount Sinai is considered a leader in the field of adult living-donor transplants, and the January death was the first in the program. Mr. Hurewitz was one of 34 patients in the transplant ward being cared for by one first-year resident, the state inquiry found. The hospital was fined \$48,000 and banned from performing living-donor surgery for six months.

The hospital submitted a report to the state last month saying it was making changes to improve the care in the transplant ward. The changes included increasing medical staff levels and barring first-year residents from treating patients in the ward.

The hospital report, called a "plan of correction," will be made public after the state completes its investigation, Mr. Kenny said.

Joan Lebow, a spokeswoman for Mount Sinai, said the hospital would cooperate with the state but added that she could not discuss details of any of the cases being investigated.

## **16. On April 8<sup>th</sup>, 2002 the press announced that “InterMune Licenses Promising Oral Drug to Expand Anti-Fibrotic Franchise”**

InterMune, Inc. announced today that it has licensed worldwide rights, excluding Japan, Korea and Taiwan, to develop and commercialize pirfenidone for all fibrotic diseases, including renal, liver and pulmonary fibrosis. Pirfenidone is an orally active small molecule drug that appears to inhibit collagen synthesis, down regulate production of multiple cytokines and block fibroblast proliferation and stimulation in response to cytokines. Pirfenidone, which has demonstrated activity in multiple fibrotic indications, is currently in Phase II clinical development for fibrotic diseases of the lung, kidney and liver.

InterMune signed an exclusive license agreement with Marnac, Inc., a privately held biopharmaceutical company in Dallas, Texas, and with their co-licensor KDL GmbH in Basel, Switzerland, for the rights to pirfenidone in exchange for an up-front cash payment and future milestone and royalty payments.

“This license continues the expansion of InterMune's portfolio of promising anti-fibrotic agents so that we can become a leader in this therapeutic category,” said W. Scott Harkonen, M.D., President and CEO of InterMune. “We intend to develop pirfenidone for a broad range of potential indications, enhancing our efforts to deliver new treatment options for patients suffering from life-threatening fibrotic diseases.”

“We are extremely pleased to license pirfenidone to InterMune because it has the focus, resources and breadth of development capabilities necessary to maximize the potential of pirfenidone as a commercial, anti-fibrotic product,” said Solomon Margolin, M.S., Ph.D., President of Marnac.

### *Background on InterMune's Anti-fibrotic Programs*

*InterMune is developing Actimmune (Interferon gamma 1-b) as a treatment for fibrotic diseases. The company is currently conducting a Phase III clinical trial of Actimmune in IPF, a debilitating and usually fatal treatment for which there is no effective therapy. The company expects to report Phase III study results by the end of 2002.*

*InterMune is also conducting a Phase II study of Actimmune for the treatment of severe liver fibrosis, or cirrhosis, caused by hepatitis C virus (HCV). The objective of the study, called*

*AEGIS (Anti-fibrotic Efficacy Gamma Interferon Study), is to evaluate the safety and anti-fibrotic activity of Actimmune in HCV patients who have failed standard antiviral therapy.*

## **17. On April 8<sup>th</sup>, 2002 data was released that stated “Disease Progression in HCV-infected African Americans May be Slower”**

HCV infection may have less immune recognition in African Americans, which may result in a slower disease progression, according to a study reported in the March issue of the *American Journal of Gastroenterology*.

A team from Chicago, Illinois, USA, determined the natural history of hepatitis C virus (HCV) infection in African Americans.

The demographics, mode of infection, virological features, and histological progression of HCV infection in African Americans versus non-African Americans were retrospectively examined.

A total of 355 patients met criteria based on adequate liver biopsy specimens and exclusion of other hepatic diseases.

African Americans (n = 112) were found to be significantly more likely to be infected with genotype 1 virus (88%) than were non-African Americans (n = 243, 67%).

Baseline HCV RNA levels were similar, although baseline ALT values were significantly lower in African Americans (80 vs. 112).

African Americans were also significantly older at the time of presentation and were significantly more likely to be women.

Patients with cirrhosis:  
African Americans: 22%  
Non-African Americans: 30%

The researchers found that, in African Americans, there was a trend toward less cirrhosis (22% vs. 30%) and significantly less piecemeal necrosis on liver biopsy.

Non-African Americans had significantly higher fibrosis scores, ALT values, and piecemeal necrosis ratings, and tended to progress more rapidly to cirrhosis.

This difference in histological progression between the two groups was not explained by differences in alcohol consumption.

Dr T. E. Wiley, of the College of Pharmacy, at the University of Illinois at Chicago, concluded on behalf of fellow authors, “The lower ALT, piecemeal necrosis scores, and slower progression of fibrosis in African Americans may reflect less immunological recognition of HCV-infected liver cells.”

In an accompanying Editorial, Drs Damien B. Mallat and Lennox Jeffers point out that the study addresses a very important and lingering issue in the natural history of HCV.

“Even though HCV infection in African Americans might have less immune recognition, which results in a slower disease progression, this issue needs further exploration in a randomized, controlled trial,” they comment.

“Only a few studies have been done to evaluate the natural history of HCV in African Americans. This under representation has been detrimental to our understanding of the HCV epidemic in this group,” they concluded.

This data is published in the March 2002 issue of the *Am J Gastroenterol*; 97(3): 700-6

**18. On April 8<sup>th</sup>, 2002 an article was printed by the press titled “Chronic Alcohol Intake Enhances Acetaminophen Hepatotoxicity in Overdoses”**

Chronic alcohol intake enhances acetaminophen hepatotoxicity, whereas acute alcohol intake does not affect the clinical course of acetaminophen overdose, claim researchers from Denmark and the USA.

The team investigated the influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose.

The findings of the trial were reported in the April issue of *Alimentary Pharmacology & Therapeutics*.

Some 209 consecutive patients, with single-dose acetaminophen overdose, were studied. Of these, 27% of the patients had chronic alcohol intake and 22% had acute alcohol intake.

Relative risks for chronic drinkers:  
Hepatic coma: 5.3  
Death: 1.4

Some 21% of the patients developed hepatic coma, and 44% of these patients died.

Chronic alcohol intake was found to be significantly and independently associated with the development of hepatic coma, with a lower prothrombin index, lower platelet count, higher creatinine, and higher bilirubin.

The relative risks for hepatic coma and death were 5.3 and 1.4, respectively, in the chronic alcohol intake group compared with the non-chronic alcohol intake group.

Acute alcohol intake was not significantly associated with any of the dependent variables studied (death, development of hepatic encephalopathy, and biochemical liver markers).

Dr Frank V. Schiodt, of the University of Texas Southwestern Medical Center, Dallas, Texas, concluded on behalf of his group, “Chronic alcohol intake enhances acetaminophen hepatotoxicity, whereas acute alcohol intake does not affect the clinical course.”

This data is being published in the April 2002 issue of the *Aliment Pharmacol Ther*, 16(4): 707-15

**19. On April 10<sup>th</sup>, 2002 as a result of research that will be published in the April 8th issue of the *Archives of Internal Medicine* an article was released titled “Smoking Can Aggravate Hepatitis C Liver Damage”**

Patients infected with the hepatitis C virus (HCV) should avoid smoking cigarettes and drinking alcohol because both habits can further damage their livers, according to Taiwanese researchers.

About 4 million people in the United States and 150 million worldwide have HCV, an infection of the liver that is spread by contact with blood and other body fluids. About 20% of people infected with HCV will develop severe and potentially fatal liver damage, or cirrhosis, which in turn increases a person's risk of liver cancer.

The new study, published in the April 8th issue of the *Archives of Internal Medicine*; 161:811-815 used levels of the enzyme ALT to gauge liver damage. The study's authors note that ALT is “the most suitable and useful protein enzyme” for evaluating damage to the organ.

While drinking alcohol is known to boost ALT levels, lead author Dr. Chong-Shan Wang of the A-Lein Community Health Center in Kaohsiung County and colleagues note, the effects of cigarette smoking on the liver are less clear. To investigate, they checked the ALT levels of 6,095 men and women living in an area

known to have high rates of HCV and hepatitis B virus (HBV), another type of liver infection.

All of the participants also answered detailed questionnaires that assessed their smoking habits and alcohol consumption.

While nearly 4% of people who were free of HCV and HBV infection had elevated ALT levels, 11% of people infected with HBV and 31% of people with HCV had high levels of the liver enzyme, the investigators report.

Drinking alcohol more than doubled the risk of having high ALT levels in people infected with HCV, while smoking almost doubled this risk. But for those with HBV, no such association was seen.

And for people with HCV who smoked a pack or more of cigarettes each day and frequently drank alcohol, the risk of elevated ALT levels was seven times higher than for those who did not drink or smoke.

Patients who are infected with HCV "are strongly advised not to smoke and drink alcohol to reduce the possible risk for aggravating (their) liver dysfunction," Wang and colleagues conclude.

## **20. On April 11<sup>th</sup>, 2002 the National Institutes of Health and ES Cell International PTE Ltd. Signed an International Stem Cell Research Agreement**

The National Institutes of Health and the ES Cell International Pte. Ltd. of Singapore and Melbourne, Australia, announced today the signing of a Memorandum of Understanding (MOU) for research use of ES Cell International's six existing stem cell lines that meet the criteria articulated by President Bush in his August 9, 2001 address. This is the federal government's first international agreement involving the distribution of human stem cell lines.

Scientists at the NIH and elsewhere will be able to access these cell lines to explore new areas of research in this emerging field of technology. In compliance with the NIH guidelines for the transfer of research materials, this agreement permits NIH scientists to freely publish the results of their research. The NIH will retain its ownership to any new intellectual property that might arise from the conduct of research in this area. In addition, the MOU governs the transfer of cell lines to individual laboratories with minimal administrative burden.

ES Cell International will retain commercial rights to its materials and will receive a fee to cover its handling and distribution expenses in supplying these cell lines. Furthermore, ES Cell International has agreed to make stem cell lines available for use by non-profit institutions that receive grants from the NIH under the same terms and conditions as those available to NIH scientists, provided these institutions enter into a separate written agreement with ES Cell International.

"We are very pleased with this agreement for our scientists who are interested in pursuing research on human embryonic stem cells. It will allow science to move forward freely in an important and promising field. The cell lines being offered are genetically diverse and as such will expand opportunities for researchers to explore important differences among cell lines," said Ruth Kirschstein, M.D., Acting NIH Director.

"This agreement is of major importance to ES Cell International. It will ensure that we are able to distribute our cell lines widely via the NIH's considerable network of stem cell researchers while maintaining our primary focus, which is on the development of therapeutic products," said Robert Klupacs, CEO of ES Cell International. "NIH researchers and those in their collaborative networks are among the best in the world and all of us in the field will benefit from their input. We look forward to distributing our cells and providing training to researchers where required."

ES Cell International is a regenerative medicine company focusing on developing therapeutic products from human embryonic stem (hES) cells. ES Cell International was incorporated in Singapore in July 2000. Its corporate headquarters, together with a dedicated research and production facility, are housed within a leading Australian Medical Research Precinct. ES Cell International funds research collaborations with the

Monash Institute of Reproduction and Development (Australia), the National University of Singapore (Singapore), Hadassah Medical Organisation (Israel), and the Hubrecht Laboratory (the Netherlands).

The National Institutes of Health (NIH) is a component of the U.S. Department of Health. Contact NIH Communications Office at (301)496-6641. <http://www.nih.gov/>

## **21. On April 11<sup>th</sup>, 2002 the press released the article titled “Outcome of fight with Giant Schering-Plough to Determine Tiny Cranberry Drug Maker's Fate”**

Schering-Plough's lawsuit against Three Rivers is a David vs. Goliath story with hundreds of millions of dollars in sales of ribavirin at stake.

Three Rivers Pharmaceuticals is a small, new pharmaceutical company, just trying to break into the business. At this point, it has no sales, not even a pill that it's permitted to sell.

All it really has is an application with the Food and Drug Administration to produce ribavirin, a generic form of Rebetol, which is used in combination with interferon to treat hepatitis C, a liver disease that could reach epidemic scale because it is transmitted most commonly by blood through intravenous drug use and other uses of unsterilized needles (such as tattooing).

Still, Three Rivers already is embroiled in the kind of lawsuit that has become almost a core business activity among generic drug makers.

The tiny Cranberry-based company filed for FDA approval in August. In October, drug giant Schering-Plough filed suit to block Three Rivers' application. Schering holds exclusive marketing rights for ribavirin from ICN Pharmaceuticals.

Like all such suits, those involving ribavirin (there are two others) are complex, involving not just the drug itself but also the manufacturing processes and potentially other issues including how the drug is used.

The stakes in the battle are high. For Schering, a third of whose revenue already is jeopardized as it faces patent expiration for its blockbuster allergy drug, Claritin, the possible loss of Rebetol sales could erode potentially vast opportunities in a fast-growing market.

For Three Rivers, the issue is survival. Whether or not it prevails, how the company got to this point is a tale in itself. Three Rivers roots are in a Pittsburgh North Side drugstore, Fisher's Pharmacy and a sister company; Fisher's SPS that the owners established to compound or hand make prescription drugs.

The pharmacy actually started making and selling ribavirin in 1999. According to Three Rivers, that was the year ICN's patent expired, but three years before any generic competition could begin because of the post-expiration exclusivity the FDA allows brand-name drug developers to retain to compensate them for the time it took to obtain their initial marketing approvals.

Fisher's, however, availed itself of an exception the FDA provides for pharmacies to "compound" drugs that are not commercially available.

Although Schering was selling its brand version for the treatment of hepatitis C at the time, it was marketing it in a package with a form of interferon on which it holds a patent.

The Rebetol pills were in a bottle, boxed along with a form of interferon that could be injected.

Because of the packaging, physicians sometimes couldn't prescribe doses they wanted to try on patients without causing them to waste portions of one of the drugs. Physicians who wanted to try their patients on the ribavirin but use another manufacturer's interferon also couldn't do so without waste.

The drug package, priced at about \$1,400 for a month's supply, was too precious to allow for the discarding of any part of it, said Donald Kerrish, a former Fisher's pharmacist and now chief executive officer of Three Rivers, which he founded with Fisher's owners. Of course, at that price, there also were patients who couldn't afford the therapy at all.

It was because the ribavirin wasn't available by itself that Fisher's was able to compound it, said Paul Fagan, Three Rivers' attorney and one of its investors.

Schering made no attempt to block the compounding, though a spokesman, Robert Consalvo, said Fisher's was stretching rules under which FDA usually finds there to be a lack of commercial availability. The exception, he said, is typically one permitted to help patients obtain medication in a form that doesn't exist such as a liquid formulation for someone who can't swallow a pill.

Schering, which declined to discuss its lawsuit against Three Rivers, said it packaged the two drugs in one box to protect patients against uses with other forms of interferon, which physicians are permitted to recommend but which might not have been subjected to enough study. It has since begun marketing the two separately because sufficient studies have since been done, Consalvo said.

Three Rivers' attorney, however, said he suspected the packaging was designed to give Schering a lock on treatment of hepatitis C, protecting its hold with a "bundled" product. Moreover, Fagan contended Schering didn't sue Fisher's because it didn't want to chance an earlier challenge to its patent.

Whichever is the case, Fisher's found plenty of takers for its compounded ribavirin. Kerrish wouldn't disclose actual sales but acknowledged there was enough demand -- considering Fisher's version cost \$1.25 per tablet vs. \$10 for Schering's to make it worth the pharmacy's while.

With no factories, Three Rivers expects to purchase its production from a large contract manufacturer, assuming it wins its legal battle and gets FDA approval. It also would attempt to develop additional generics, possibly investigating some of the compounds used in treating HIV infections, Kerrish said.

Kerrish also wouldn't say how much Three Rivers would charge for ribavirin if it gets approval. But he said he believed that the company's pricing would be such that it would significantly widen the market by making the drug affordable to more people.

The number of people in need of the drug is rising, particularly in prison populations where the incidence is deemed to be around 40 percent, said Fagan.

Fagan said he was optimistic about Three Rivers' chances because it's much like the companies that started the generic industry but have since become large pharmaceutical concerns themselves, sometimes making brand name products along with generics.

"There's no one like us. We're small and nimble," he said.

## **22. On April 12<sup>th</sup>, 2002 the press released an update on the status of Ribapharm, a biotech spin-off of ICN who makes the hepatitis C drug ribavirin**

Shares of Ribapharm Inc. rose 8 percent in their stock market debut on Friday after the initial public offering price for the biotechnology spin-off from ICN Pharmaceuticals Inc. was lowered due to a lack of demand.

Shares of Costa Mesa, California-based Ribapharm, which makes the hepatitis C drug ribavirin, rose 80 cents to close at \$10.80 on the New York Stock Exchange (news - web sites).

The shares were priced at \$10 in the IPO managed by investment bank UBS Warburg -- well below the expected range of \$13 to \$15 per share.

Under pressure from several large shareholders, ICN agreed nearly two years ago to divide into three separate publicly-traded companies. The \$260 million in proceeds from the Ribapharm offering will go to ICN, which will use them to fund its restructuring plans.

ICN has said plans to distribute the remaining 83 percent of Ribapharm to its stockholders in a tax-free spin-off within six months, but it is still waiting for Internal Revenue Service approval.

The company earlier this week dropped plans to give its management and director's stock options on Ribapharm, opting instead to pay them cash bonuses from a \$50 million pool.

Ribavirin, also known as Rebetol, is used as part of Schering-Plough Corp.'s combination treatment for hepatitis C. Last year, Schering paid drug royalties of \$137 million to ICN.

Meanwhile, shareholders continue to pressure ICN to restructure and are seeking control of the company's board.

Last June, three directors backed by dissident shareholders were elected to the company's 12-member board. Last month, institutional shareholders Iridian Asset Management and Franklin Mutual Advisors announced plans to again nominate three members for election to the board at ICN's annual meeting in May.

ICN's board has established an independent nominating committee.

The company, founded in 1960 by Milan Panic, who for a short time in the early 1990s was prime minister of Yugoslavia, is the subject of a U.S. Securities and Exchange civil suit related to statements in 1994 and 1995 about the regulatory status of ribavirin as a stand-alone treatment for hepatitis C.

Shares of ICN rose 12 cents to close at \$28.07 on the New York Stock Exchange.

The health care industry leads the IPO market with four sales this year, more than any other sector, as investors buy into companies that are less sensitive to economic downturns. In terms of stock performance, however, health care is the worst performing group with a post-IPO average return of 3.4 percent.

### **23. On April 12<sup>th</sup>, 2002 the press released an article titled “Risk of HCV Transmission from Infected Gynecologists to Patients is Rare”**

Transmission of hepatitis C virus from infected health care workers to their patients is relatively rare, claims a team from Germany.

The researchers determined the rate of hepatitis C virus (HCV) transmission from an infected gynecologist to his patients.

They reported their findings in the latest issue of the *Archives of Internal Medicine*.

The gynecologist was proven to have infected one of his patients with HCV during a cesarean section.

All 2907 women whom the HCV-positive gynecologist had operated on, between July 1993 and March 2000, were notified about potential exposure and were offered free counseling and testing.

Epidemiological investigations, nucleotide sequencing, and phylogenetic analysis were used to differentiate between HCV transmissions caused by the gynecologist and infections contracted from other sources.

Of the women affected, 79% were screened for markers of HCV infection.

Of these former patients, 7 were found to have HCV. HCV transmission rate was 0.04%.

Phylogenetic analysis of HCV sequences from the gynecologist and the women did not indicate that the virus strains were linked.

Therefore, no further iatrogenic HCV infections caused by the gynecologist could be detected.

The resulting overall HCV transmission rate was 0.04% (1 per 2286).

Dr R. Stefan Ross, of the National Reference Centre for Hepatitis C, University of Essen, said on behalf of his colleagues, "To our knowledge, this is the largest retrospective investigation of the risk of provider-to-patient transmission of HCV conducted so far."

"Our findings support the notion that such transmissions are relatively rare events and might provide a basis for future recommendations on the management of HCV-infected health care workers," he concluded.

This data will be published in the April issue of the *Arch Intern Med*; 162: 805-10

#### **24. On April 12<sup>th</sup>, 2002 there was an article released titled "Citalopram Safely Relieves Depression in Patients with Hepatitis C"**

Citalopram appears to be a safe, effective, and well-tolerated agent for the treatment of major depression in patients with hepatitis C, according to results of an open-label trial.

Dr. Ondria C. Gleason and colleagues, of the University of Oklahoma College of Medicine-Tulsa, chose to evaluate citalopram for this purpose because of "its favorable side effect profile and its limited interaction with cytochrome P450 enzymes," they note in *The Journal of Clinical Psychiatry*, for March.

The trial involved ten men and five women with hepatitis C but no evidence of cirrhosis or liver failure. Dosage was initiated at 20 mg/day then adjusted as necessary. At week 4, doses ranged from 10 to 40 mg/day.

Mean scores on the Hamilton Rating Scale for Depression (HAM-D) decreased significantly from 19.2 at baseline to 7.7 at the end of 8 weeks ( $p = 0.0001$ ). Thirteen subjects, including all four concurrently treated with interferon-alpha, exhibited at least a 50% reduction in HAM-D score.

Psychiatric symptoms, as measured by the Hopkins Symptom Checklist-90-Revised, and quality of life, assessed by the Medical Outcomes Study Short Form Health Survey, also improved significantly. Meanwhile, no significant changes in alanine aminotransferase, aspartate aminotransferase, or gamma-glutamyltransferase levels were observed during the course of the trial.

Previous studies of patients with chronic hepatitis C documented rates of depressive disorders ranging from 22.4% to 28%, about twice the lifetime prevalence reported in the general population. Interferon treatment itself is associated with increased depression. Thus, Dr. Gleason's group concludes, "management of depression in the setting of hepatitis C...may also improve the patient's candidacy for and possible successful completion of interferon therapy for hepatitis C, which otherwise may be contraindicated."

This data was published in the April 2002 issue of *J Clin Psychiatry*; 63:194-198.