



# Black Market, Counterfeit and Off-Label Drug Use

*Hot, Rot or Not*

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COLUMBIA UNIVERSITY  
MEDICAL CENTER

# Conflict of Interest

- No advisory or paid relationships with any pharmaceutical companies
- FDA – Scientific advisor to ophthalmic device panel

"Off-label" means the medication is being used in a manner not specified in the FDA's approved packaging label, or insert.

Every prescription drug marketed in the U.S. carries an individual, FDA-approved label.

# Off-Label Use

- Indications
- Dosage
- Age
- Route of Administration

# Off-Label Usage

- 2007 – 725 million FDA approved drugs prescribed by US office-based physicians
- 150 million (27%) were off-label
- 73% of off-label prescriptions lacked evidence of clinical efficacy

# Drugs Commonly Rx Off-Label

- Anti-seizure
- Antidepressants
- Antibiotics
- Anxiety Drugs
- Narcotic pain relievers
- Chemotherapy

# Off-Label Usage

- UK, Sweden, Germany, Netherlands
  - 624 children in pediatric units
  - 39% drugs prescribed for off-label usage
  - 67% of the children received off-label drugs

# Aspirin

- 1960s and 1970s evidence presented that Aspirin could lower the risk of a second heart attack
- 1998 FDA approved this labeling



# Pharmaceutical Advertising





# Money

SECTION B

Wednesday, August 30, 2006

## Schering-Plough to pay \$435M settlement

By Julie Schmit  
USA TODAY

Schering-Plough will pay \$435 million to settle federal civil and criminal charges that it illegally promoted several drugs, including one for brain tumors, and also defrauded Medicaid.

Its settlement with the Justice Department, announced Tuesday, is the third-largest since 2000 involving drug-makers, and the third for Schering in the past two years.

Schering Sales, part of Schering, agreed to plead guilty to one count of conspiracy for making false statements to the government and to pay a \$180 million criminal fine.

Justice alleges Schering illegally promoted the drug Temodar for types of brain cancer for which it was not then government-approved and did the same

by promoting hepatitis and cancer drug Intron A for superficial bladder cancer.

Such tactics are called "off-label" marketing. Drugmakers can promote drugs only to treat conditions for which the Food and Drug Administration approved them. Doctors can prescribe drugs for any conditions.

Serono settled similar charges last year involving its AIDS drug Serostim, as did Pfizer in 2004 in a case involving pain and anti-seizure drug Neurontin.

Schering told the FDA that the "off-label" promotions in 2001, 2002 and 2003 were isolated incidents. But the government alleges they were part of a national plan in which Schering salespeople were trained how to win off-label sales and were paid for doing so. Tactics included "illegal remuneration" to doctors for "sham advisory boards" and "lavish entertainment," government documents say.

### Case settlements

Biggest fraud cases settled by pharmaceutical makers:

Company	Year	Settlement/fine (in millions)
Tap Pharm.	2001	\$875
Serono	2005	\$704
<b>Schering-Plough</b>	<b>2006</b>	<b>\$435</b>
Pfizer	2004	\$430
AstraZeneca	2003	\$355
Schering-Plough	2004	\$345

Source: Taxpayers Against Fraud

Justice also alleges Schering defrauded Medicaid of \$4.3 million in 1998 and 1999 by failing to give the federal and state program for the poor the best price on antihistamine Claritin RediTabs.

Justice alleges Schering gave free drugs to a health maintenance organization in order to secure future purchases.

By law, it should then have given Medicaid bigger rebates to ensure that it got the best price for the drug. Schering also underpaid rebates for stomach ailment drug K-Dur, Justice says.

Schering in 2004 settled similar charges for Claritin. Six other drugmakers have done the same since 2000, says Taxpayers Against Fraud.

"We take full responsibility for the actions of the past and want to make sure they don't repeat," says Brent Saunders, Schering senior vice president.

He says the settlement ends major litigation against Schering specifically and marks its commitment to "lead the way" on proper marketing and sales tactics in the industry.

Schering's penalties include a \$255 million civil fine. The agreement is subject to court approval.

Schering-Plough shares closed at \$20.94, up 2.6% Tuesday.

Pfizer fined \$2.3 billion for illegal  
marketing in off-label case

*Sept 2, 2009*

2012 - GlaxoSmithKline paid \$3 billion for illegal off-label marketing:

- paroxetine in children (approved only for use in adults)
- antidepressant bupropion as a weight loss aid

# Genentech Suit

- McDermott worked as a “professional educator liaison” for Genentech
- Rituxan approved for non-Hodgkins Lymphoma
- Job involved recruiting doctors to promote Rituxan as a treatment for rheumatoid arthritis
- Alleges “sham” consulting agreements given to rheumatologists whom the company identified as “key opinion leaders” who were expected to influence other doctors to prescribe for arthritis

# Serona S.A. - 2005

- \$704 million – criminal and civil charges relating to deceptive marketing of Serostim
- Conspiracy to distribute an unapproved device and conspiracy to pay illegal remuneration to health-care providers to induce referrals to Medicaid pharmacies

2012 - Abbott paid \$1.6 billion for off-label marketing of anticonvulsant valproic acid. Paid Docs to Rx in older aggressive patients with schizophrenia and dementia

2009 - Eli Lilly paid \$1.4 billion in a settlement for off-label marketing of antipsychotic olanzapine for dementia

# Pfizer Suit

- 2004 - Warner Lambert pleaded guilty to federal charges that it promoted Neurontin for off-label uses beginning in 1990
- Pfizer acquired Warner Lambert in 2000
- Pfizer agreed to pay \$430 million to resolve the criminal charges and civil liabilities
- British public rebuke for promoting drugs before government approval given - Breached code of conduct and “discredited the industry”



# Indictment of Doctor Tests Drug Marketing Rules

By ALEX BERENSON

At first, Dr. Peter Gleason thought his arrest was a joke.

In the early afternoon of Monday, March 6, half a dozen men in suits surrounded Dr. Gleason, a Maryland psychiatrist, at a train station on Long Island and handcuffed him.

"I said, 'Well, this is a gag,'" Dr. Gleason recalled in a recent inter-

## SIDE EFFECTS

*The Spokesman*

view. "They said, 'No, this isn't.'"

Dr. Gleason, 53, was taken aback because he was arrested, and later charged, for doing something that has become common among doctors: promoting a drug for purposes other than those approved by the federal government.

But prosecutors say that Dr. Gleason went too far. At hundreds of speeches and seminars where he was rewarded with generous fees, Dr. Gleason advised other physicians that a powerful drug for narcolepsy could be prescribed for depression and pain relief. In doing so, he conspired with the drug's manufacturer to recommend it for potentially dangerous uses, the prosecutors claim.

The case has put the spotlight on the murky financial relationships between drug companies and the physicians they use to promote their medicines. Companies cannot directly ad-

vertise drugs for purposes not approved by the Food and Drug Administration. But getting drugs prescribed for unapproved uses can increase a drug's sales, so companies often skirt the rules by sponsoring seminars where doctors are paid to make presentations promoting their drugs, including the "off label" uses.

For doctors, these and other payments they receive for discussing drugs can be very lucrative. Dr. Gleason acknowledges that he received more than \$100,000 last year alone from Jazz Pharmaceuticals, which makes Xyrem, the narcolepsy drug he has promoted.

His case could establish limits on what doctors can do to help companies sell their drugs. But any precedent could be complicated by the history of Xyrem, which differs in one important way from other drugs. Because the active ingredient in Xyrem is gamma hydroxybutyrate, or GHB, an illegal street drug with a history

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Updated news: [nytimes.com](http://nytimes.com)

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# FDA Dealt Setback On Off-Label Use

8/8/15

BY THOMAS M. BURTON

A federal court in New York ruled the Food and Drug Administration can't bar a drug company from marketing a pill for off-label use as long as the claims are truthful, delivering a setback to the regulator.

The decision, by the federal district court in the Southern District of New York, is the latest of a line of such cases. It concerns the Irish company **Amarin Pharma Inc.** and its fish-oil-derived drug Vascepa, and it has been closely watched by the pharmaceutical industry. The company asked the court to stop the FDA from enforcing its off-label marketing ban, and the court agreed.

The ruling means Amarin can give doctors and others truthful accounts of medical studies of the drug for reducing moderately high blood fats, even when the FDA hasn't approved it for

tended that such off-label marketing isn't lawful, but recent court decisions have held that the First Amendment restricts the FDA's power to limit truthful speech.

U.S. District Judge Paul A. Engelmayer ruled that Amarin "may engage in truthful and non-misleading speech promoting the off-label use of Vascepa." More specifically, he

**A court ruled an Irish drug company can tout other uses as long as the claims are truthful.**

ruled, disseminating such information cannot serve as the basis for the FDA or the government to charge the company and its sales personnel. He said the First Amendment allows the company to make such state-

Please see *AMARIN* page B4

# Fed Court FDA Ruling 2015

- FDA has long insisted that companies break the law if they market a drug for a purpose not approved
- Amarin asked the court to stop the FDA from enforcing its off-label marketing ban
- “FDA can’t bar marketing as long as claims are truthful and not misleading”

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"We decided to recall our new drug because  
a common side-effect is lawsuits."

# Why Drugs Remain Off-Label

- Responsibility of pharmaceutical company to seek supplemental marketing approval for new uses
- FDA approval slow
- Limited patent time is financial disincentive to fund studies for new indications

# Age Related Macular Degeneration

- Lucentis - \$1887/dose      FDA approved
- Eylea      - \$1850/dose      FDA approved
- Avastin      - \$25/dose      Off-label

# Physician Risk



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**67**  
EDITION  
2013

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DESK  
REFERENCE<sup>®</sup>

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[PDR.net](http://PDR.net)

FDA-approved Drug Alerts  
Label Updates and CME

Adverse Drug Event Reporting  
Provider and Patient Resources



FDA regulates drug approval, not drug prescribing

Doctors are free to prescribe a drug for any reason they think is medically appropriate

“Off-label use is a key component of mainstream medical practice”

“Because the pace of medical discovery runs ahead of the FDA’s regulatory machinery, the off-label use of a particular drug or device may even define the standard of care”

Richardson v Miller Tenn Ct. Apr 2000

“while attempts have been made to use the term “off-label” to imply recklessness in the malpractice arena  
....failure to use off-label medicine when appropriate under the standard of care may also constitute malpractice”

*American Academy of Pediatrics*



## Off-Label Drug Use

by: Michael Ball, DVM

April 2000 Article # 215



“Off-label drug use, which technically was illegal until recently, might be one of the most beneficial things we as veterinarians do in the treatment of disease in animals. The technically illegal part was a result of the way a drug was licensed by the ...”

# What should I ask the Doctor?

- Is it FDA approved or “off-label”
- If “off-label”
  - What is it approved for?
  - What scientific evidence supports its use
  - Check on-line
- Don't accept “everyone uses it, don't worry”



# Counterfeit Drugs

- \$75 billion per year industry
- Low Risk – High Reward
- Sold through rogue internet sites





# Counterfeit Drugs

- China and India major producers
- Eastern Europe: up to 20%
- Middle East
- Estimated 700,000 death from malaria and TB

- **New Zealand** Citizen Pleads Guilty in US Counterfeit Drug Case: July 19, 2012
- **Canadian** Citizen & Online Pharmacy Entrepreneur Arrested in Florida: June 15, 2012
- MHRA Seizes £14 Million in Assets from Convicted **UK** Drug Counterfeiter: April 27, 2012
- Two **Israeli** Citizens Plead Guilty to Importing Counterfeit Drugs to US: April 24, 2012
- **Chinese** National Flees Justice After Counterfeit Drug Importation Conviction: April 4, 2012
- **New York** Pharmacists Indicted for Purchasing Black Market HIV Drugs for Resale: April 4, 2012

# Counterfeit Drugs - Poisons

- Heavy Metals – carcinogenic or toxic to CNS, kidneys, liver, skin and bones
- Common Household Supplies – floor wax, sheet rock, cement powder, paint thinner
- No medications at all



West Africa: 40% of drug supply



# CHRISTIE'S



Estimate (Set Currency)

HK\$24,000 - HK\$40,000

(\$3,111 - \$5,186)

This lot is offered without reserve

TRACK LOT

PLACE BID

Sale Information

Sale 2969

Important Watches

28 November 2012

Hong Kong

## Lot Description

FRANCK MULLER. AN 18K WHITE GOLD TONNEAU-SHAPED WRISTWATCH WITH SWEEP CENTRE SECONDS SIGNED FRANCK MULLER, GENEVE, COLOUR DREAMS MODEL, NO. 18, REF. 5850, CIRCA 2000







政府註冊 正版正貨

MEDICINE NO FAKES





## China takes it to the counterfeiters

October 10, 2012 | By Eric Palmer

When a serious discussion of counterfeit drugs is held, China and India invariably come up in the conversation. That is not a surprise. The FDA says those two countries now account for 80% of the drugs and ingredients now sold in the U.S. And both are known to have lax regulatory systems.

China, egged on by local media, has been making some high-profile efforts. Earlier this year it announced that it had sent out 18,000 Chinese police officers to round up nearly 2,000 drug counterfeiting suspects. They were said to have destroyed 1,100 production plants. The fake drugs they confiscated were valued at \$182 million. The Ministry of Public Safety said the counterfeits had been advertised to treat everything from hypertension to cancer and rabies.







A steamroller destroys fake medicine  
Suqian, Jiangsu province.

# Counterfeit Cancer Drug Ring Exposed in Chinese Trial

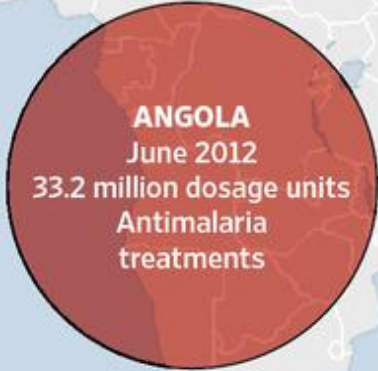
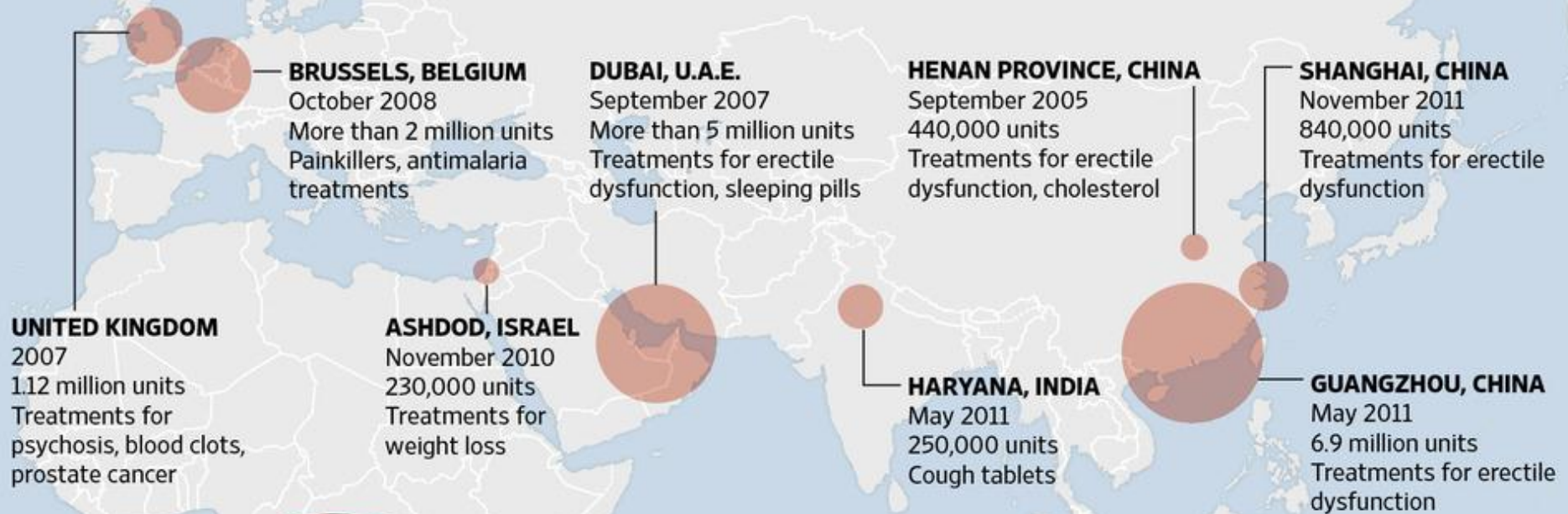
Updated Feb 16

On May 20, 2011 eleven defendants pleaded guilty to producing and selling fake cancer drug medication that caused eye infections in 61 people in Shanghai, China.

**FAKE  
FAKE  
DRUGS**



# Some of the Largest Seizures of Counterfeit Drugs



Sources: Pharmaceutical Security Institute; U.K.'s Medicines and Healthcare Products Regulatory Agency; U.S. Food and Drug Administration; The United States Pharmacopeial Convention Inc.; Chinese state media

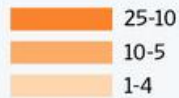
# Avastin Trail

Fake Avastin, a cancer drug, passed through middlemen in Turkey and Europe before reaching Canada Drugs' Nottingham, U.K., wholesale arm, River East. From there, the counterfeits were channeled through Canada Drugs' distribution network to physician offices throughout the U.S.

- 1 The original source of the Avastin remains unknown.
- 2 Kirbac Medikal, a firm not registered with Turkish authorities, is the first known entity to handle the fakes.
- 3 Hadicon AG obtained the fake Avastin from the Turkish distributor. It said it didn't know the drugs were fake.
- 4 CareMed ApS bought the fake Avastin, not knowing it was counterfeit, before selling it to a U.K.-based wholesaler.
- 5 River East Supplies Ltd., which supplies discount medicines for Canada Drugs' American customers, obtained the fakes.
- 6 Canada Drugs hired a Tennessee distributor to receive packages from the U.K. and reship them to U.S. doctors.



Number of doctors warned by the FDA about fake Avastin



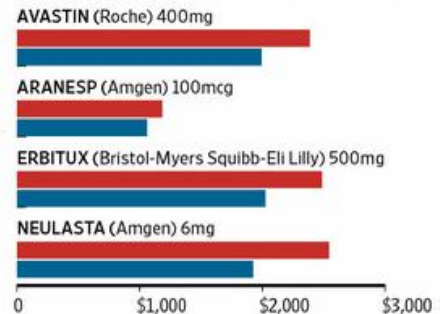
TOTAL  
**76**

Sources: WSJ reporting; FDA; the Centers for Medicare & Medicaid Services; Montana Healthcare Solutions invoices

One of Canada Drugs' companies, Montana Healthcare Solutions, offered oncologists discounts on these physician-administered medicines, compared with the U.S. average sale price.

## 1Q 2011 UNIT PRICES

■ U.S. AVERAGE SALE PRICE  
■ MONTANA HEALTHCARE/CANADA DRUGS





WSJ  
8/19/15

# Arraignment Set In Fake-Drug Case

BY JEANNE WHALEN

The first defendant will be arraigned in U.S. federal court next week in connection with an indictment involving **Canada Drugs**, the Winnipeg-based company accused of selling counterfeit drugs in the U.S.

The indictment against the company and several of its executives and associates, including founder Kris Thorkelson, a Canadian citizen, was unsealed in federal court in Montana last week. It charges the defendants with nine counts of money laundering and conspiring to smuggle illegal goods to the U.S. between 2009 and 2012.

Mr. Thorkelson and the other defendants didn't respond to phone calls or emails seeking comment on Tuesday. A lawyer

## Canada Drugs of Winnipeg is accused of selling counterfeit drugs in the U.S.

for Canada Drugs, Curtis Unfried, said the company was aware of the indictment and declined to comment further.

A spokeswoman for the U.S. attorney's office in Montana said defendant Ram Kamath will be arraigned in federal court in Missoula, Mont., on Aug. 25. Ac-

were first reported by The Wall Street Journal in July 2012.

"Canada Drugs was in fact purchasing [its] drugs from questionable sources that ultimately supplied Canada Drugs with counterfeits," the indictment says. It also accuses the company of falsifying customs documents to conceal cargo and failing to keep drugs at the cold temperatures needed to maintain quality.

The discovery of the counterfeit cancer drugs caused alarm among patients and doctors when the FDA first issued warnings about them in 2012, and led to a crackdown on the trade that resulted in the imprisonment of several doctors who bought foreign-made drugs. The drugs—typically infusions or injections administered at a doctor's office—were attractive to doctors because they were often cheaper than the equivalent U.S. brands.

The other defendants include Thomas Houghton, a Canadian citizen who was president of two Canada Drugs subsidiaries involved in the sales, according to the indictment. In an interview with the Journal in 2012, Mr. Houghton said that he was "horrified" to learn the drugs were fake. He said his businesses were "separate and distinct" from Canada Drugs, adding that he considered his business "safe" and "legal."

Also charged in the indictment are Ronald Sigurdson, Troy



## Canadian pharmacy sold unapproved and counterfeit drugs online, US alleges

US government prosecutors say the online store sold US\$78m worth of fake, unapproved or mislabelled drugs to doctors, including some to treat cancer

An online Canadian pharmacy sold US\$78m worth of unapproved, mislabelled and, in two cases counterfeit cancer drugs to doctors across the United States over three years, US government prosecutors have said

# Counterfeit Drugs

- US Customs and Border Patrol made 1239 seizures worth \$16.9 million in counterfeit drugs bound for the US market
- 2010 -2012: 227 rogue internet pharmacy investigations initiated resulting in conviction of 560 individuals



- Burglary, robbery , embezzlement
- Illegal diversion in the distribution chain
  - Approved for sale in one country yet illegally intercepted and sold in a second country

# Black Market Drugs

- Medications bought from hijackers, black market dealers and directly from patients to resell back into the supply chain with forged papers
- Find way to legitimate drug distributors to retail pharmacies to unsuspecting patients

08.06.12

# How did \$14 million in drugs vanish from a UM pharmacy?

Technician is charged with stealing \$14 million in expensive cancer drugs over three years before he was discovered.



- **New York** Pharmacists Indicted for Purchasing Black Market HIV Drugs for Resale: April 4, 2012



# U.S. busts \$108 million black market in Medicaid drugs



(Reuters) - Operators of a nationwide black market have illegally sold more than \$100 million of expensive HIV medications and other drugs obtained from patients on the government-run Medicaid U.S. authorities said on Tuesday.

# The Wall Street Journal

March 22, 2012

## Drug Re-sales Get Scrutiny

Some drug distributors are setting up fake pharmacies that allow them to obtain and then artificially raise the prices for cancer drugs and other medicines that are in short supply, according to letters written by lawmakers Wednesday.

WSJ's Jennifer Corbett-Dooren reports on scrutiny by lawmakers of efforts by drug distributors to artificially raise the cost of cancer drugs and other medications in short supply. Photo: Joe Raedle/Getty Images

Lawmakers are looking into what they claim is a "gray market" for scarce prescription drugs that has emerged in recent months. The U.S. is grappling with a shortage of some cancer and other critical-care drugs used in hospital emergency rooms and intensive-care units, the result of manufacturing glitches and shifts in supply.



# Should I purchase the drug?



- Determine country of origin
- Inspect packaging
- Check expiration date
- If price too low , stay away

# Buyer Beware





