BOXED WARNINGS

The following are relevant examples of Boxed Warnings for two classes of drugs—one conveying information on a potential adverse event if the drug is used in an inappropriate patient population, and the other conveying information on monitoring to avoid an adverse event. Although FDA can locate a Boxed Warnings anywhere in the labeling, they usually appear first in a package insert, right after the name of the drug (title).

BOXED WARNING

This example is included in the currently approved labeling for low molecular weight heparins and heparinoids.

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions).

BOXED WARNING

This boxed warning is included in labeling for acetanilid, non-steroidal antiandrogens such as flutamide.

WARNINGS

Hepatic Injury

There have been post-marketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy and death related to acute hepatic failure. The hepatic injury was reversible after discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, hyperbilirubinuria, jaundice or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

PATIENT PACKAGE INSERTS AND MEDICATION GUIDES

Since the final rule for medication guides was published December 1, 1998, no patient-directed labeling has yet been approved under this regulation. However, the following examples are patient package inserts formatted according to the requirements under the Medication Guide regulations. These examples are focused on conveying safety information to the patient.

Information for the Patient

EVISTA® raloxifene HCl

EVISTA® (e-VISS-tah) Tablets
Generic name: raloxifene hydrochloride

Important Information for Patients Using EVISTA for the Prevention of Osteoporosis after Menopause

Please read this information carefully before you begin taking EVISTA. It is important to read this information each time your prescription is refilled in case new information is available. This summary does not tell you everything about EVISTA. Your doctor is your best source of information about this medicine. You should talk with him or her before you begin taking EVISTA and at regular checkups.

What is the most important information I should know about EVISTA?

EVISTA is for use only by women after menopause to prevent osteoporosis.

If you are pregnant or can become pregnant you should not take EVISTA because it could harm your unborn child.

Do not take EVISTA if you have or have had blood clots, if you will be immobile for a long time or if you have liver disease.

What is EVISTA?

EVISTA is a medicine used by women after menopause to prevent osteoporosis (thin, weak bones).

How does EVISTA work?

In most women, EVISTA stops the loss of bone that often occurs after menopause. EVISTA acts like estrogen on the bones, although it builds bone to a lesser extent than estrogen. It is not known if EVISTA prevents fractures. EVISTA does not act like estrogen on the breast or uterus.

What does EVISTA not do?

EVISTA will not treat hot flashes (see **What are the possible side effects of EVISTA?**). EVISTA does not stimulate the breast or the uterus. This means that some of the common side effects of estrogen, such as spotting or menstrual-type bleeding and breast tenderness, may be avoided. EVISTA did not increase the risk for breast cancer or cancer of the lining of the uterus in clinical studies up through two and one-half years.

Who should not take EVISTA?

Do not take EVISTA:

- unless you have been told by your doctor that you have passed menopause. EVISTA is for use only by women after menopause.
- **IF YOU ARE OR CAN BECOME PREGNANT BECAUSE IT COULD HARM YOUR UNBORN CHILD.**
- if you have or have had blood clots that required a doctor's treatment. These may include clots in the legs, lungs or eyes (thrombosis or phlebitis). Taking EVISTA may increase the risk of these blood clots. These clots can cause serious medical problems, disability or death. If there is anyone in your family with a history of blood clots, or if you have congestive heart failure or active cancer, you should discuss this with your doctor.
- if you have liver disease, unless your doctor says it is all right to take EVISTA.
- if you are allergic to EVISTA or to any ingredients in it.

How should I take EVISTA?

- Take one EVISTA tablet once each day.
- EVISTA can be taken with or without food and at any time of the day.
- If you miss a dose, start taking the medicine again as soon as possible, on your normal schedule. You do not have to make up for the missed dose.

Patient Information

What You Should Know About

BETAPACE AF

sotalol HCl

(Bay' tah pace)

6071800

This summary contains important patient information that has been reviewed and approved by the U.S. Food and Drug Administration. This summary is not meant to take the place of your doctor's instructions. Read this patient information carefully before you start taking BETAPACE AF™. Each time you get a refill, you will receive patient information. Be sure to read it because it may contain new information that you need to know.

What is the most important information I should know about BETAPACE AF?

Because you have irregular heartbeats (atrial fibrillation) that are troublesome to you, BETAPACE AF has been prescribed to help your heart to beat in a more normal way. However, in some patients BETAPACE AF can cause a different type of abnormal heartbeat that can be dangerous, and in rare instances can even cause death. You may feel this different type of abnormal heartbeat as a fast beating of the heart with lightheadedness and fainting. The possibility of this different type of abnormal heartbeat is the reason you and your doctor have discussed whether your symptoms are troublesome enough for you to start taking BETAPACE AF.

Clinical studies using BETAPACE AF have shown that the most important way to decrease your chance of getting this different type of dangerous abnormal heartbeat is for you to take the dose of BETAPACE AF that is right for you. If this abnormal heartbeat occurs, it usually happens during the first few days of treatment. This is why you should be started on BETAPACE AF in a hospital or another place where your heartbeat can be watched closely by health care professionals for the first few days. They can help you if problems occur. When BETAPACE AF is started this way, this different type of abnormal heartbeat is rare and the hospital staff is there to treat it.

It is important that when you go home, you take the exact dose the doctor prescribed for you. At any time while you are taking BETAPACE AF, watch for signs that you may be getting this different type of abnormal heartbeat and call your doctor if they occur. Call your doctor right away if you:

- faint,
- become dizzy, or
- have fast heartbeats.

If you cannot reach your doctor, go to the nearest hospital emergency room. Take your BETAPACE AF tablets with you and show them to the doctor or nurse.

Also, call your doctor right away if you have any of the following conditions:

- severe diarrhea
- unusual sweating
- vomiting
- less appetite than normal, or
- more thirst than normal.

These are conditions that will make you more likely to get the different type of abnormal heartbeat.

If you take BETAPACE AF with certain other medicines, you will increase your chance of getting this different type of abnormal heartbeat. These medicines are listed below under **"Who should not take BETAPACE AF?"**.

Once your doctor finds the right dose for you, always take that exact amount of BETAPACE AF. Never take an extra dose and never skip a dose of BETAPACE AF.

What is BETAPACE AF?

BETAPACE AF is a medicine that is given to patients with atrial fibrillation (irregular heartbeats). Atrial fibrillation happens when certain parts of the heart (the chambers known as atria) beat too fast or irregularly. When this happens, your heart cannot pump blood through your body as well as it should. This may make you feel weak and tired, or get out of breath easily. You may get an uncomfortable feeling in your chest and "fluttering" or "palpitations." Atrial fibrillation can be changed back (converted) to normal heart rhythm by an electric shock or by using certain medicines. However, atrial fibrillation can return. BETAPACE AF may help your heart stay beating regularly for a longer period of time.

This information about BETAPACE AF was developed to ensure that you and your doctor get the right information about your type of irregular heartbeats. Consult your doctor before you accept any other sotalol product that does not provide this patient information.

Who should not take BETAPACE AF?

BETAPACE AF is not for everyone with irregular heartbeats (atrial fibrillation). This is why you and your doctor need to discuss the benefits and risks of BETAPACE AF and whether your symptoms are troublesome enough for you to start taking BETAPACE AF.

Do not take BETAPACE AF if you:

- have serious kidney problems or are on kidney dialysis;
- have lung disease causing shortness of breath (such as asthma, chronic bronchitis or emphysema);
- have symptoms of heart failure (such as shortness of breath when you exercise or are physically active and swelling of the ankles or legs);
- have a very slow heart beat and do not have an implanted artificial pacemaker;

Taking certain other medicines with BETAPACE AF can increase the chance that you will get the dangerous abnormal heartbeat discussed in **"What is the most important information I should know about BETAPACE AF?"**. These include medicines used to treat abnormal heart rhythms and some other heart problems as well as medicines used to treat depression, and other mental problems, night-time heartburn, asthma and infections. Therefore, you should be sure to tell your health care provider about all prescription and non-prescription medicines you are taking, as well as vitamins, dietary supplements, and any natural or herbal remedies. In addition, tell your doctor about any problems you have with your heart or kidneys.

If you are pregnant, you should know that there is no information about the safety of BETAPACE AF in pregnant women. Some reports indicate that BETAPACE AF is passed into the breast milk. Women who are taking BETAPACE AF should not breast feed a child.

How should I take BETAPACE AF?

Your doctor will start you on BETAPACE AF in the hospital and will check your heart rhythm for the first 2 or more days of treatment. This will allow your doctor to find the right dose for you. Always take the exact amount your doctor prescribes. Never change your BETAPACE AF™ dose unless your doctor tells you to. Your doctor will do regular

tests to check that the amount you're taking is still right for you.

Keep taking your BETAPACE AF™ until your doctor tells you to stop. Keep taking it even if you feel fine. However, never take an extra dose of BETAPACE AF even if you do not feel well. When it is time to stop taking BETAPACE AF, your doctor will give you instructions on how to gradually reduce your dose over a period of 1 to 2 weeks.

You may take BETAPACE AF with or without food. However, it is important to take BETAPACE AF at the same time every day. This gives your heart a steady supply of the medicine. It might be helpful to take BETAPACE AF at the same time as something you regularly do every day.

If you are taking an antacid containing aluminum or magnesium to treat heartburn or upset stomach wait at least 2 hours after your dose of BETAPACE AF before you take the antacid.

Never try to make up for a missed dose of BETAPACE AF. You could increase your chance of getting the different type of abnormal heartbeat. If you miss taking a dose of BETAPACE AF, just take your normal amount at the next scheduled time.

If you take more BETAPACE AF than you should have, call your doctor right away. If you cannot reach your doctor, go to the nearest hospital emergency room. Take your BETAPACE AF tablets with you to show to the doctor or nurse.

What should I avoid while taking BETAPACE AF?

Certain other medicines taken with BETAPACE AF may increase the chance that you will get the dangerous abnormal heartbeat (see **"Who should not take BETAPACE AF?"**). Do not take BETAPACE AF with these medicines. Before you start taking BETAPACE AF tell your doctor about all prescription and non-prescription medicines you are taking (see also **"Who should not take BETAPACE AF?"**). Once you begin taking BETAPACE AF, do not start taking any new medicines until you check with your doctor.

Carry a list of all the medicines and supplements you take. If you have to go to the hospital or are treated by new or different health care providers, tell them you are taking BETAPACE AF and show them the list of other medicines you take. They need this information to make sure your medicines are safe to take at the same time.

Tell your doctor or dentist you are taking BETAPACE AF before you have an operation or dental surgery. BETAPACE AF can affect how well some anesthetics work.

What are the possible side effects of BETAPACE AF?

BETAPACE AF's most serious side effect, a different type of dangerous abnormal heartbeat, is discussed in **"What is the most important information I should know about BETAPACE AF?"**. Dangerous abnormal heartbeats happen rarely. But they can be serious and, in rare instances, can even cause death.

BETAPACE AF's most common side effects are tiredness, slow rate, shortness of breath, and dizziness. BETAPACE AF can also cause other side effects. If you are concerned about these or any other side effects, ask your doctor.

Important points about BETAPACE AF

BETAPACE AF can help you best if you take it as your doctor has prescribed it.

- Take your medicine every day as prescribed.
- Do not miss doses or take extra doses.
- Call your doctor right away if you feel new fast heartbeats with lightheadedness and fainting. These can be serious and in rare instances can even cause death.
- Do not take BETAPACE AF if you have serious kidney problems, lung disease causing shortness of breath, symptoms of heart failure.
- Tell your doctor and pharmacist the name of all medications (prescription, non-prescription, and natural/herbal remedies) you are taking.
- Do not start taking any other medicines without telling your doctor.
- Go for all your regular checkups.
- Get your refills on time.
- Do not stop taking BETAPACE AF until your doctor tells you to stop.

This leaflet provides a summary of information about BETAPACE AF. Your doctor or pharmacist has a longer leaflet written for healthcare professionals that you can ask to read. BETAPACE AF was prescribed for your particular condition. Do not use it for another condition or give it to others.

Manufactured by:
BERLEX® Laboratories, Wayne, NJ 07470

6072300/6071800 02/00

TIKOSYN™
(Dofetilide)
Capsules

PATIENT INFORMATION ABOUT
TIKOSYN™ (Tee' ko sin)
(generic name: dofetilide)

This leaflet includes information about Tikosyn™ that is important for you to know. Read *this information carefully before you start taking Tikosyn. Also read it each time you get a* refill of Tikosyn to see whether any information regarding your condition has changed. Talk with your doctor or pharmacist if you have any questions. The information in this leaflet cannot take the place of discussions with your health care provider.

What is the most important information I should know about Tikosyn?
Because you have irregular heartbeats (atrial fibrillation) that are troublesome to you, Tikosyn has been prescribed to help your heart to beat in a more normal way. However, in some patients Tikosyn can cause a different type of abnormal heartbeat, that can be dangerous, and in rare instances can even cause death. You may feel this different type of *abnormal heartbeat as a fast beating of the heart with lightheadedness and fainting. The* possibility of this different type of abnormal heartbeat is the reason you and your doctor have discussed whether your symptoms are troublesome enough for you to start taking Tikosyn.

Clinical studies using Tikosyn have shown that the most important way to decrease your chance of getting this different type of dangerous abnormal heartbeat is for you to take the dose of Tikosyn that is right for you. If this abnormal heartbeat occurs, it usually happens *during the first few days of treatment. This is why you should be started on Tikosyn in a* hospital or another place where your heartbeat can be watched closely by health care professionals for the first few days. They can help you if problems occur. When Tikosyn is started this way, this different type of abnormal heartbeat is rare and the hospital staff are there to treat it.

It is important that when you go home, you take the exact dose the doctor prescribed for you. At any time while you are taking Tikosyn, watch for signs that you may be getting this different type of abnormal heartbeat and call your doctor if they occur.
Call your doctor right away if you:
- faint,
- become dizzy, or
- have fast heartbeats.

If you cannot reach your doctor, go to the nearest hospital emergency room. Take your Tikosyn capsules with you and show them to the doctor or nurse.

Also, call your doctor right away if you have any of the following conditions:
- severe diarrhea,
- unusual sweating,
- vomiting,
- less appetite than normal, or
- more thirst than normal.

These are conditions that will make you more likely to get the different type of abnormal heartbeat.

If you take Tikosyn with certain other medicines, you will increase your chance of getting *this different type of abnormal heartbeat. These medicines are listed below under "Who* should not take Tikosyn?".

Once your doctor finds the right dose for you, always take that exact amount of Tikosyn. Never take an extra dose and never skip a dose of Tikosyn.

What is Tikosyn?
Tikosyn is a medicine that is given to patients with atrial fibrillation (irregular heartbeats). Atrial fibrillation happens when certain parts of the heart (the chambers known as atria) beat too fast or irregularly. When this happens, your heart cannot pump blood through your body as well as it should. This may make you feel weak and tired, or get out of breath easily. You may get an uncomfortable feeling in your chest and "fluttering" or "palpitations." Atrial fibrillation can be changed back (converted) to normal heart rhythm by an electric shock or by using certain medicines. However, atrial fibrillation can return. Tikosyn may help your heart to beat more regularly and stay beating regularly for a longer period of time.

Who should not take Tikosyn?
Tikosyn is not for everyone with irregular heartbeats (atrial fibrillation). This is why you and your doctor need to discuss the benefits and risks of Tikosyn and whether your symptoms are troublesome enough for you to start taking Tikosyn.

Do not take Tikosyn if you:
- are taking certain other medicines, including
  - cimetidine (TAGAMET, TAGAMET HB)*, used to treat heartburn, upset stomach, and stomach ulcers, available both by prescription and without a prescription
  - verapamil (CALAN, CALAN SR, COVERA-HS, ISOPTIN, ISOPTIN SR, VERELAN, VERELAN PM)*, used to treat high blood pressure and certain heart problems
  - ketoconazole (NIZORAL)*, used to treat certain fungus infections
  - *trimethoprim alone (PROLOPRIM, TRIMPEX)* or the combination of trimethoprim* and sulfamethoxazole (BACTRIM, SEPTRA)*, used to treat certain bacterial infections
  - prochlorperazine (COMPAZINE)*, used to treat nausea and vomiting
  - megestrol (MEGACE)*, used to treat certain types of cancer or loss of appetite and weight loss associated with AIDS
- *have serious kidney problems or are on kidney dialysis.*

Taking certain other medicines with Tikosyn can increase the chance that you will get the dangerous abnormal heartbeat discussed in "What is the most important information I should know about Tikosyn?". These include medicines used to treat heart conditions, high blood pressure, depression and other mental problems, asthma, allergies, hay fever, skin p[illegible]d infections. Therefore, you should be sure to tell your health care provider about all prescription and non-prescription medicines you are taking, as well as vitamins, dietary supplements, and any natural or herbal remedies.

In addition, tell your doctor about any problems you have with your heart, kidneys or liver.

If you are pregnant, you should know there is no information about the safety of Tikosyn in pregnant women or whether Tikosyn is passed into breast milk. Women who are taking Tikosyn should not breast feed a child.

Tikosyn is not recommended for children.

How should I take Tikosyn?
Your doctor will start you on Tikosyn in the hospital and will check your heart rhythm for the first 3 days of treatment. This will allow your doctor to find the right dose for you. Always take the exact amount your doctor prescribes. Never change your Tikosyn dose *unless your doctor tells you to. Your doctor will do regular tests to check that the amount* you're taking is still right for you.

Keep taking your Tikosyn until your doctor tells you to stop. Keep taking it even if you feel fine. However, never take an extra dose of Tikosyn, even if you do not feel well.

You may take Tikosyn with or without food. However, it is important to take Tikosyn at the same time every day. This gives your heart a steady supply of the medicine. It might be helpful to take Tikosyn at the same time as something you regularly do every day.

Never try to make up for a missed dose of Tikosyn. You could increase your chance of getting the different type of abnormal heartbeat. If you miss taking a dose of Tikosyn, just take your normal amount at the next scheduled time.

If you take more Tikosyn than you should have, call your doctor right away. If you cannot reach your doctor, go to the nearest hospital emergency room. Take your Tikosyn capsules with you to show to the doctor or nurse.

What should I avoid while taking Tikosyn?
Certain other medicines can increase the amount of Tikosyn in your body (see "Who should not take Tikosyn?"). This can increase your chance of getting the different type of abnormal heartbeat. Do not take Tikosyn with these medicines. Before you start taking Tikosyn tell your doctor about all prescription and non-prescription medicines you are taking (see also "Who should not take Tikosyn?"). Once you begin taking Tikosyn, do not start taking any new medicines until you check with your doctor.

Carry a list of all the medicines and supplements you take. If you have to go to the hospital or are treated by new or different health care providers, tell them you are taking Tikosyn and show them the list of other medicines you take. They need this information to make sure your medicines are safe to take at the same time.

What are the possible side effects of Tikosyn?
Tikosyn's most serious side effect, a different type of dangerous abnormal heartbeat, is *discussed in "What is the most important information I should know about Tikosyn?".* Dangerous abnormal heartbeats happen rarely. But they can be serious and, in rare instances, can even cause death.

Tikosyn's most common side effects are headache, chest pain, and dizziness. Tikosyn can also cause other side effects. If you are concerned about these or any other side effects, ask your doctor.

Important points about Tikosyn
Tikosyn can help you best if you take it as your doctor has prescribed it.
- Take your medicine every day as prescribed
- *Do not miss doses or take extra doses*
- Call your doctor right away if you feel new fast heartbeats with lightheadedness and fainting. These can be serious and in rare instances can even cause death.
- Tell your doctor and pharmacist the names of all medications (prescription, non-prescription, and natural/herbal remedies) you are taking
- Do not start taking any other medicines without telling your doctor
- Do not take cimetidine (TAGAMET, TAGAMET HB)*, verapamil (CALAN, CALAN SR, COVERA-HS, ISOPTIN, ISOPTIN SR or VERELAN, VERELAN PM)* or ketoconazole (NIZORAL)*, trimethoprim alone (PROLOPRIM, TRIMPEX)* or in combination with sulfamethoxazole (BACTRIM, SEPTRA)*, prochlorperazine (COMPAZINE)* or megestrol (MEGACE)*
- Go for all your regular checkups
- *Get your refills on time*
- Do not stop taking Tikosyn until your doctor tells you to stop.

This leaflet provides a summary of information about Tikosyn. Your doctor or pharmacist has a longer leaflet written for health care professionals that you can ask to read. Tikosyn was prescribed for your particular condition. Do not use it for another condition or give it to others.

* Listed trademarks are the property of their respective owners.

Pfizer

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MEDICATION GUIDES

Preamble to the Final Fule and Regulations

federal register

Tuesday
December 1, 1998

Part V

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 201 et al.
Prescription Drug Product Labeling; Medication Guide Requirements; Final Rule

PREAMBLE ONLY

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 208, 314, 601, and 610

[Docket No. 93N-0371]

RIN 0910-AA37

Prescription Drug Product Labeling; Medication Guide Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is establishing requirements for the distribution of patient labeling for selected prescription human drug and biological products used primarily on an outpatient basis. The agency is requiring the distribution of patient labeling, called Medication Guides, for certain products that pose a serious and significant public health concern requiring distribution of FDA-approved patient medication information. The intent of this action is to improve public health by providing information necessary for patients to use their medications safely and effectively. FDA believes that this program will result in direct improvements in the safe and effective use of prescription medications.

DATES: This regulation is effective June 1, 1999. Written comments on the information collection requirements should be submitted by February 1, 1999.

ADDRESSES: Submit written comments on the information collection requirements to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Nancy M. Ostrove, Center for Drug Evaluation and Research (HFD-40), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2828, (Ostrove@CDER.FDA.GOV).

Toni M. Stifano, Center for Biologics Evaluations and Research (HFM-20), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-827-3028, (Stifano@A1.CBER.FDA.GOV).

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of August 24, 1995 (60 FR 44182), FDA published a proposed rule entitled, "Prescription Drug Product Labeling; Medication Guide Requirements," under which the agency would encourage development and distribution of written patient medication information by the private sector. This information was intended to supplement oral counseling from health care professionals. The agency proposed distribution goals and performance standards for this information. The agency proposed to survey the marketplace in the years 2000 and 2006 to determine how much patient medication information is being distributed and whether it is useful. The 1995 proposal sought comment on two approaches FDA could take if the private sector's voluntary program failed to reach the predetermined goals.

The proposal also included provisions that would permit the agency to require FDA-approved written patient information (Medication Guides) for distribution with prescription drug and biological products that pose a "serious and significant public health concern requiring immediate distribution of FDA-approved patient medication information." (For the purposes of this document, the shorter term "serious and significant concern" will be used to refer to those drug products that FDA determines require Medication Guides for safe and effective use by the public.) The agency indicated that it would use this authority only on limited occasions.

In the proposal, FDA stated its position that patient information about the risks and benefits of prescription drug and biological products is necessary for patients to use these products safely and effectively. The overall patient medication information program was proposed to provide patients with the information needed to improve their use of prescription drug and biological products. Furthermore, FDA demonstrated in the preamble to the proposed rule that the program could result in substantial health care cost savings by reducing the harm caused by inappropriate drug use and enhancing the benefits of drugs by facilitating their proper use.

FDA originally provided 90 days for public comment, and, in response to requests, extended the comment period for an additional 30 days until December 22, 1995 in the Federal Register of November 24, 1995 (60 FR 58025). In the Federal Register of January 30, 1996 (61 FR 2971), the agency announced a public workshop to be held on February 14 and 15, 1996, to discuss issues related to defining the useful information that would be provided in the voluntary program. The agency also sought written comments on issues raised at the workshop. Comments were accepted until March 6, 1996.

As the agency was reviewing these and other comments on the proposed rule, Congress enacted legislation regarding patient labeling. This legislation, section 601 of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, for the fiscal year ending September 30, 1997 (Pub. L. 104-180) (the Appropriations Act), established a voluntary private-sector process under which national organizations representing health care providers, consumers, pharmaceutical companies, and other interested parties were to collaborate in the development of a long-range plan to achieve the goals of FDA's proposed rule concerning patient labeling as previously described. The legislation adopted the distribution and information quality goals of the proposed rule. The law further required that the plan developed by these organizations be submitted to the Secretary of Health and Human Services (the Secretary) for acceptance, rejection, or modification before implementation. The collaborative process established by this legislation has been completed and the long-range private-sector plan has been accepted by the Secretary.

While section 601 of the Appropriations Act limits the authority of the Secretary to implement FDA's proposed rule regarding written information voluntarily provided to consumers, there is specific legislative history that makes it clear that section 601 does not preclude FDA from using its existing authority to implement a mandatory program for the small number of products that pose a "serious and significant concern" and require distribution of patient information. That legislative history states that section 601:

> [i]s not to be construed as prohibiting the FDA from using its existing authority or regulatory authority to require as part of the manufacturers' approved product labeling the dispensing of written information inserts to consumers on a case-by-case basis with select prescription drugs to meet certain patient safety requirements.

Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Bill, 1997, S. Rept. 104-317, 104th Cong., 2d sess., p. 132, July 11, 1996.

In light of this legislation, the agency is deleting the provisions of the proposed rule that dealt with the private sector voluntary program, and is limiting this final rule to the mandatory program covering products of "serious and significant concern." Because the voluntary program is not part of this

final rule, the agency will not summarize and respond to comments relating only to those provisions. Instead, this document will focus on the comments concerning the program for products of "serious and significant concern."

The final rule incorporates most of the provisions of the proposed rule regarding the mandatory program for products of "serious and significant concern" and provides additional clarification regarding how the agency would identify products that require a Medication Guide. Additional changes have been made that reflect the narrowed focus of the final rule. Highlights of the final rule are summarized, followed by a summary and discussion of the comments.

II. Highlights of the Final Rule

The final rule establishes a patient medication information program under which Medication Guides will be required for a small number of products that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information necessary for the product's safe and effective use. FDA anticipates that an average, no more than 5 to 10 products per year would require such information.

The major provisions of the medication information program for products of "serious and significant concern" and the changes from the proposed rule follow.

A. General Provisions (Part 208, Subpart A)

1. Scope and Purpose

A number of changes have been made to the provisions in part 208 (21 CFR part 208) to reflect the narrowed focus of this final regulation in response to section 601 of the Appropriations Act, and to clarify its purpose and scope. Section 208.1(a) has been changed to indicate that the final regulation does not cover voluntarily distributed patient information for most prescription drugs, but rather covers products of "serious and significant concern." The phrase "that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information" was added to § 208.1(a) to accomplish this change.

Section 208.1(a) of the 1995 proposed rule stated that the requirements applied to products "administered primarily on an outpatient basis without direct supervision by a health professional." FDA has changed the term "administered" in this context to the term "used," because "administered" is likely to be misinterpreted as involving administration by another individual. In addition, the agency has determined that Medication Guides may, on rare occasions, be required for products of "serious and significant concern" that are used on an inpatient basis or under the supervision of a health professional. This change has been made by moving the word "primarily" to immediately follow the word "applies" in the second sentence of § 208.1(a). In light of this change, the last sentence of proposed § 208.1(a) has been deleted, because it is no longer needed.

Under the proposed rule, the patient information program applied to all new prescriptions, but only upon request by the patient for refill prescriptions. Because of the narrowed focus of this final rule and because the agency believes that the patient information that will be provided in Medication Guides is important to the safe and effective use of a product, it is necessary to require the distribution of a Medication Guide with every prescription for that product. Accordingly, § 208.1(a) has been changed so that patient information required under this part must be provided for all prescriptions of the drug, whether they are new prescriptions or refills and regardless of whether the information is requested by the patient.

Section 208.1(b) as proposed has been deleted because the final regulation no longer covers voluntarily distributed patient information. This change was made because of the enactment of section 601 of the Appropriations Act, which created a process under which national organizations representing consumers, health professionals, pharmaceutical companies, and others developed a plan for the voluntary distribution of patient information. This legislation specifically prohibits the implementation of the proposed rule if a plan acceptable to the Secretary is developed and submitted within the statutory time period. The accompanying legislative history makes it clear, however, that the agency was not precluded from requiring FDA-approved patient leaflets for drugs of serious and significant concern under its existing authority. New § 208.1(b) describes the purpose of patient labeling required under the final regulation.

The information will be required if the agency determines that it is necessary to patients' safe and effective use of the drug product. The agency added this provision to clarify the regulations when it will require Medication Guides and to reflect the agency's intention to make the decision to require a Medication Guide carefully and on a case-by-case basis. This approach to Medication Guides is consistent with the legislative history of the Appropriations Act discussed earlier in this preamble. The new language in § 208.1(b) also helps differentiate required Medication Guides from the voluntary private sector program.

Section 208.1(c) as proposed has been deleted. Its primary purpose was to provide a standard against which voluntarily distributed patient information would be evaluated. However, the voluntary program is no longer part of this regulation. The agency believes that the substance of this provision is valuable, however, and has therefore changed § 208.20, Content and format of a Medication Guide, to include all of the elements of proposed § 208.1(c). These elements are also closely related to the criteria adopted during the collaborative private-sector process.

New § 208.1(c) of the final rule describes when FDA may require a Medication Guide. Patient labeling will be required if the agency determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. FDA believes that these circumstances will apply to a very small group of products. These circumstances have been clarified to address comments that they were overly broad.

Proposed § 208.1(d) has been deleted as unnecessary because the final regulation applies only to "serious and significant" products.

2. Definitions

Section 208.3 contains definitions of important terms used in part 208. Several changes have been made in this section to help clarify the Medication Guide program. Numerous comments conveyed confusion about what constitutes a "Medication Guide," for example, whether the term refers to voluntary private sector patient information or mandated FDA-approved patient information. Therefore, in the final rule new § 208.3(h) defines "Medication Guide" to mean FDA-approved patient labeling conforming to

the specifications set forth in part 208 and other applicable regulations. This term now applies only to patient information required for products of "serious and significant concern."

The agency on its own initiative added new § 208.3(e) to include a definition of the term "drug product." The purpose of adding this new definition is to make it clear that the term, as it is used in this final regulation, applies to the finished dosage form of both drug and biological products. Because of the addition of this definition, the subsequent provisions in § 208.3 have been renumbered.

In preparing the final rule, the agency revised the definition of the "manufacturer" of a drug product to be consistent with the definition of the "manufacturer" of a biological product. The definition of a "manufacturer" in the proposed rule inadvertently referred only to the person who actually produced the drug product, while the definition for biologicals included both the actual producer of the product as well as the person who is an applicant for a license where the applicant is responsible for complying with the product and establishment standards. This latter meaning of the term corresponds most closely to the definition of an "applicant" as that term is used in the new drug regulations in part 314 (21 CFR part 314). Therefore, FDA has included the definition of "applicant" in § 314.3(b) in the definition of a drug product manufacturer in § 208.3(g). It is important for two reasons that both meanings of "manufacturer" be included in the definition of the term for purposes of this final rule. First, FDA intends that each person potentially or actually in the chain of distribution of a product be subject to the distribution requirements in § 208.24 and for that reason both the producer of the product and the person responsible for the product application must be included. Second, for purposes of identifying the person who is responsible for the content and format requirements in § 208.20 and the requirement of obtaining FDA approval of the Medication Guide in § 208.24(a), the agency wishes to clarify that it is the person who is responsible for the product application.

The agency has also added a definition of the term "packer" in new § 208.3(i). Packers are subject to the provisions of this final rule and a definition was needed to distinguish a packer from a manufacturer or distributor.

Section 208.3(k) of this final regulation provides a definition of the terms "serious risk" and "serious adverse effect" that states that these terms mean an adverse drug experience, or the risk of such an experience, as that term is defined elsewhere in the regulations governing drug and biological products. The purpose of adding this definition is to further narrow the scope of this regulation in response to many comments complaining of the breadth of the agency's proposed criteria for identifying products of "serious and significant concern." (See previous discussion of § 208.1 (b) and (c).)

B. General Requirements for a Medication Guide (Part 208, Subpart B)

1. Content and Format of a Medication Guide

Section 208.20 now contains the requirements for both the content and format of Medication Guides. This section sets forth the specific categories of information about a product that a Medication Guide shall contain, as well as statements that shall appear on a Medication Guide. The agency has generally retained from the proposal the text and order of the headings under which the information shall appear and has also now grouped the information under the appropriate heading. This section also includes specifications for minimum letter height or type size, legibility, and presentation considerations. The combined provision is more concise and the reorganization makes the requirements clearer. The agency notes that the content and format criteria in the final rule are virtually the same as those adopted in the private sector plan discussed earlier.

The order specified in § 208.20(b) starts with a presentation of the most important information patients should know about the product to use it safely and effectively, i.e., why the product poses a serious and significant public health concern requiring distribution of FDA-approved written patient information. This section is being included in place of the summary section originally proposed by FDA. The agency made this change because it believes that it is redundant to include in such a short document a summary section containing information elaborated in other sections.

This section is followed by sections addressing the product's indications for use, contraindications, directions for use, precautions, and possible side effects. The final rule does not specify where in this order other information (e.g., storage instructions and specific instructions for using products that are not orally administered (e.g., injectables, patches)) may be placed. As reflected in § 208.20(b)(9), the rule permits the insertion of additional headings or subheadings as appropriate for specific Medication Guides.

Other changes have been made in § 208.20 of the final rule. As mentioned above, the agency believes that the criteria for determining useful information that were proposed in § 208.1(c) are important and has retained them in the final rule. All of the criteria that Medication Guides must meet, however, are now contained in a single section of this final rule (§ 208.20(a)).

The agency on its own has added language to § 208.20(a)(2) to reinforce the fact that a Medication Guide, while based on the approved labeling, should be understandable to laypersons and therefore need not use the identical language in the approved labeling.

Other small changes have been made in § 208.20 as well. Section 208.20(a)(7) and (b)(1) now require that a Medication Guide contain the established or proper name of the drug in order to recognize the terminology used for biologicals. (See 21 CFR 600.3(k)). The introductory sentence of § 208.20(b) has been changed to make it clear that only the headings that have relevance to the drug product should be included in a Medication Guide. Other changes have been made throughout § 208.20(b) to emphasize that only specific, important information about the drug product should be included in a Medication Guide. These changes are being made so that the effectiveness of the patient labeling is not reduced by its being too long or including irrelevant information.

FDA has added the following language to § 208.20(b)(3) relating to the product's indications: "In appropriate circumstances, this section may also explain the nature of the disease or condition the drug product is intended to treat, as well as the benefit(s) of treating the condition." This addition is designed to allow, when relevant, a fuller discussion that could include the benefits of treatment.

Finally, FDA has made two changes to § 208.20(b)(8). First, § 208.20(b)(8)(ii) has been changed to make it clear that a Medication Guide must contain a statement that a drug product should not be used for a condition other than that for which it is prescribed. This change is made to avoid any confusion with the statement that drugs may sometimes be prescribed for uses not described in the Medication Guide. Second, § 208.20(b)(8)(iii) has been changed to make it clear that the name and address of the dispenser may be included in a Medication Guide. The

name and address of the manufacturer, distributor, or packer of a drug product that is not also a biological product or of the manufacturer or distributor of a drug product that is also a biological product is required. This change was made to correct a drafting error in proposed § 208.20(b)(8)(iii) that would have allowed the dispenser's name alone to appear on a Medication Guide.

2. Distributing and Dispensing a Medication Guide

Section 208.24 sets forth the requirements for distributing and dispensing Medication Guides. The agency has made several changes to this section to make clear the responsibilities of each person distributing a drug product subject to this part. The agency has added new § 208.24(a) that explicitly requires the manufacturer to obtain FDA approval of the Medication Guide before it can be distributed. Although this requirement had been stated indirectly in the proposed rule regarding products of "serious and significant concern," the agency believed it should be stated clearly in the final rule. Because the majority of Medication Guides will be required at the time of approval, it is appropriate for FDA to approve the text of both patient labeling and professional labeling at the same time.

Section 208.24(b) states the manufacturer's basic responsibility for ensuring that Medication Guides are available for distribution to patients. Under § 208.24(b), a manufacturer shall provide to distributors, packers, or authorized dispensers to which it ships the drug product, either Medication Guides in sufficient numbers, or the means to produce Medication Guides in sufficient numbers, to permit the authorized dispenser to provide a Medication Guide to each patient who receives a prescription for the drug product. The agency generally expects that the "means to produce" shall include a computer file of the Medication Guide for use with a computerized patient medication information program. Section 208.24(c) states the responsibility of the distributor or packer that receives Medication Guides, or the means to produce Medication Guides, to provide them to each authorized dispenser to whom it ships a container of drug product.

FDA has changed § 208.24 in several places to make it clear that packers are covered by this final regulation. It appears that packers had been inadvertently omitted from the proposal. The change is intended to make it clear that, in situations where a Medication Guide is distributed with the product, each person in the distribution chain has the responsibility of ensuring that the Medication Guide remains with the product so that it can reach the authorized dispenser.

FDA has also deleted the phrase "finished dosage form" from several places in § 208.24 of this rule. This phrase is no longer needed because the agency has added a definition of "drug product" in § 208.3(e) that clarifies that the term refers to products in finished dosage form.

Section 208.24 has been changed in several places to reflect the fact that Medication Guides must be dispensed with every prescription for a drug product subject to this part, and not just with new prescriptions or if requested by a patient for a refill prescription. This change is needed because it will be necessary for patients to have the information in a Medication Guide in order to use a product of "serious and significant concern" safely and effectively. It is therefore important for patients to receive this information each time they obtain the drug product.

Some comments noted that dispensers may not know if Medication Guides are provided with the product, affixed on the container, or contained within the package. Therefore, in the final rule, a new § 208.24(d) has been created that states that the label of each container of drug product (which now, because of the added definition of drug product, includes both large volume containers of finished dosage form and unit-of-use containers) shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. This new section also requires that these statements be made in a prominent and conspicuous manner. The agency on its own initiative has amended both § 208.24(d) and the regulations governing labeling of biological products to make clear how manufacturers can comply with the requirements of § 208.24(d) if a container label is too small for the required statement. (See § 610.60(a)(7).)

Section 208.24(c) of the proposed rule required the manufacturer and distributor to provide a Medication Guide with each unit-of-use container intended to be dispensed to a patient. FDA has omitted this paragraph from the final rule. This provision is not necessary because the responsibility to provide Medication Guides to the authorized dispenser is clear from the other changes to § 208.24. Further, FDA wishes to provide manufacturers, distributors, and packers flexibility in the ways that they can meet that responsibility. If a manufacturer chooses to provide Medication Guides electronically for a product in a unit-of-use container, they may now do so because of this change.

Proposed § 208.24(d) stated that the requirements of part 208 could be met by the manufacturer, distributor, or any other person acting on behalf of the manufacturer or distributor. This section further provided that a manufacturer or distributor could satisfy the requirements of part 208 with a Medication Guide printed by a distributor or authorized dispenser. This provision was intended to enable manufacturers and distributors to make use of third-party information systems that could simplify the process of dispensing patient information leaflets to patients. The proposal envisioned that third parties would most likely both create and distribute Medication Guides to authorized dispensers under the voluntary private-sector program. Proposed § 208.24(d) has been deleted from this final rule. The agency believes that it is no longer necessary because the final rule applies only to Medication Guides for products of "serious and significant concern" that will be approved by the agency and will be part of these products' approved labeling.

Section 208.24(f) was modified in response to several comments. A change has been made to make it clear that wholesalers, as well as authorized dispensers, are not subject to section 510 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360) that requires registration of producers of drugs and listing of drugs in commercial distribution if they change the container, wrapper, or labeling of any drug product, as long as the change is due solely to an act performed under part 208.

3. Exemptions and Deferrals

Section 208.26 provides the circumstances under which there may be exemptions from, or deferrals of, content and format requirements for Medication Guides, and exemption from the distribution of Medication Guides to patients under certain circumstances.

Proposed § 208.26(b) provided, in part, that a licensed practitioner or an authorized dispenser could determine that it is not in the best interests of a patient to receive a Medication Guide. FDA has changed this provision to allow only the licensed practitioner who prescribes a drug product to direct that a Medication Guide be withheld from a patient.

Section 208.26(b) has also been modified to address concerns about

possible perceived interference by FDA in the judgments of health care professionals with respect to withholding a Medication Guide from a patient. The final rule does not contain the proposed sentence that would have required authorized dispensers to provide Medication Guides for a particular product under all circumstances. Consequently, only the patient, and not FDA, can overrule the licensed practitioner's decision to withhold a Medication Guide from that patient.

Section 208.26(c) as proposed provided that a Medication Guide was not required to be dispensed in an emergency, or where the manufacturer, distributor, or authorized dispenser did not have a Medication Guide available and could document a good faith effort to provide one. Section 208.26(d) as proposed set forth a small business exemption for certain authorized dispensers. However, this exemption only applied to the broad comprehensive program of distribution of patient information. It did not apply to Medication Guides for products of "serious and significant" concern.

The agency has deleted both proposed § 208.26(c) and (d) from this final rule. FDA does not believe that such exemptions are appropriate for Medication Guides that are required for a very small number of products of "serious and significant concern" and that provide information necessary to the safe and effective use of the product.

III. Comments on the Proposed Rule

FDA received approximately 100 comments in response to the 1995 proposed rule and the request for comments associated with the February 1996 public workshop. The comments came from individual consumers and consumer organizations, academics, individual pharmacists, physicians, and other health care professionals, health professional associations, trade associations, and prescription drug and biological product manufacturers, attorneys, and others. A number of comments submitted examples of patient information leaflets currently being distributed. Several comments misunderstood the proposed rule and commented as though FDA was seeking to immediately establish a mandatory Medication Guide program to provide patient labeling for all prescription drug and biological products.

A. Patient Information—Legal Authority

1. Some comments stated that the proposal regulates the professional practice of pharmacy, which is the purview of the State boards of pharmacy. The comments stated that FDA cannot extend its statutory authority to regulate product labeling to require that pharmacists distribute information about prescription medications that they dispense. One comment added that this initiative would set a precedent for FDA to impose other regulations on individual health care professionals.

Both the proposal and the final rule seek to assure that patients receive information necessary to the safe and effective use of prescription drug products. Federal courts have affirmed FDA's authority to require the dispensing of patient labeling for prescription drugs, and that such requirement does not interfere with the practice of medicine (*Pharmaceutical Mfr. Ass'n (PMA)* v. *FDA*, 484 F. Supp. 1179 (D. Del. 1980), *aff'd per curiam*, 634 F. 2d 106 (3d Cir. 1980)).

In *PMA* v. *FDA*, the court stated that "[t]he fact that the practice of medicine is an area traditionally regulated by the states does not invalidate those provisions of the act which may at times impinge on some aspect of a doctor's practice" (*Id.* at 1188). The court reasoned that the regulation at issue, which required pharmacists and dispensing physicians to distribute patient labeling with prescription drugs containing estrogens, did not forbid a physician from prescribing a prescription drug product, nor did it limit the physician's exercise of professional judgement (*Id.*). Moreover, the court stated that the regulation not only did not limit the information that a physician may provide to his or her patients, but rather it fostered open discussions between physicians and patients (*Id.*). Similarly, this final rule does not inhibit a prescriber or pharmacist from exercising his or her professional judgement, nor does it limit the information that can be given to the patient. The prescriber or pharmacist may add to the information and discuss any aspect of the product with the patient, thereby promoting better communication between health care professionals and their patients.

FDA also does not agree that it lacks statutory authority over written information about prescription drug products that is dispensed by pharmacists. The agency's authority for this final rule was set forth in the proposed rule (60 FR 44182 at 44210). In short, under section 502(a) of the act (21 U.S.C. 352), a drug product is misbranded if its labeling is false or misleading in any particular. Further, under section 505 (d) and (e) of the act (21 U.S.C. 355 (d) and (e)), FDA must refuse to approve an application and may withdraw the approval of an application if the labeling for the drug is false or misleading in any particular.

Section 201(n) of the act (21 U.S.C. 321) describes the concept of "misleading" and specifically provides that in determining whether the labeling of a drug is misleading, there shall be taken into account not only representations or suggestions made in the labeling, but also the extent to which the labeling:

> [f]ails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the [drug] * * * under the conditions of use prescribed in the labeling * * * or under such conditions of use as are customary or usual.

These provisions, along with section 701(a) of the act (21 U.S.C. 371), authorize FDA to issue regulations designed to ensure that patients using prescription drug products receive information that is material with respect to the consequences which may result from the use of these products under labeled conditions. The proposed rule also described the agency's authority for requiring Medication Guides for generic drugs and biological products.

The act authorizes FDA to regulate the marketing of drug products so that they are safe and effective for their intended uses and are properly labeled. As previously stated, FDA has determined that written patient labeling containing information on warnings, precautions, contraindications, side effects, directions for use, and other information is necessary for the safe and effective use of prescription drug products of "serious and significant concern."

2. Several comments contended that FDA lacks the legal authority to request (or require) patient labeling for prescription drug products. One comment cited section 503(b)(2) of the act (21 U.S.C. 353), which expressly exempts prescription medications from the requirement for "adequate directions for use."

FDA does not agree with these comments. As previously discussed in response to comment number 1 of this document, the agency's authority to require patient labeling for prescription drugs has been upheld by the courts (*PMA* v. *FDA*, 484 F. Supp. 1179 (D. Del. 1980), *aff'd per curiam*, 634 F. 2d 106 (3d Cir. 1980)).

Section 503(b)(2) of the act exempts dispensed prescription drugs from the "adequate directions for use" requirements under section 502(f) of the act, but does not prohibit FDA from imposing a requirement under section 502(a) that pharmacists dispense labeling directed to the patient that is

Subpart B—General Requirements for a Medication Guide

208.20 Content and format of a Medication Guide.
208.24 Distributing and dispensing a Medication Guide.
208.26 Exemptions and deferrals.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360, 371, 374; 42 U.S.C. 262.

SOURCE: 63 FR 66396, Dec. 1, 1998, unless otherwise noted.

EFFECTIVE DATE NOTE: At 63 FR 66396, Dec. 1, 1998, part 208 was added, effective June 1, 1999.

Subpart A—General Provisions

§ 208.1 Scope and purpose.

(a) This part sets forth requirements for patient labeling for human prescription drug products, including biological products, that the Food and Drug Administration (FDA) determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. It applies primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional. This part shall apply to new prescriptions and refill prescriptions.

(b) The purpose of patient labeling for human prescription drug products required under this part is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products.

(c) Patient labeling will be required if the FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

§ 208.3 Definitions.

For the purposes of this part, the following definitions shall apply:

(a) *Authorized dispenser* means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice.

(b) *Dispense to patients* means the act of delivering a prescription drug product to a patient or an agent of the patient either:

(1) By a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct supervision; or

(2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner.

(c) *Distribute* means the act of delivering, other than by dispensing, a drug product to any person.

(d) *Distributor* means a person who distributes a drug product.

(e) *Drug product* means a finished dosage form, e.g., tablet, capsule, or solution, that contains an active drug ingredient, generally, but not necessarily, in association with inactive ingredients. For purposes of this part, drug product also means biological product within the meaning of section 351(a) of the Public Health Service Act.

(f) *Licensed practitioner* means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.

(g) *Manufacturer* means for a drug product that is not also a biological product, both the manufacturer as described in §201.1 and the applicant as described in §314.3(b) of this chapter, and for a drug product that is also a biological product, the manufacturer as described in §600.3(t) of this chapter.

(h) *Medication Guide* means FDA-approved patient labeling conforming to the specifications set forth in this part and other applicable regulations.

(i) *Packer* means a person who packages a drug product.

(j) *Patient* means any individual with respect to whom a drug product is intended to be, or has been, used.

(k) *Serious risk or serious adverse effect* means an adverse drug experience, or the risk of such an experience, as that term is defined in §§ 310.305, 312.32, 314.80, and 600.80 of this chapter.

Subpart B—General Requirements for a Medication Guide

§ 208.20 Content and format of a Medication Guide.

(a) A Medication Guide shall meet all of the following conditions:

(1) The Medication Guide shall be written in English, in nontechnical, understandable language, and shall not be promotional in tone or content.

(2) The Medication Guide shall be scientifically accurate and shall be based on, and shall not conflict with, the approved professional labeling for the drug product under § 201.57 of this chapter, but the language of the Medication Guide need not be identical to the sections of approved labeling to which it corresponds.

(3) The Medication Guide shall be specific and comprehensive.

(4) The letter height or type size shall be no smaller than 10 points (1 point = 0.0138 inches) for all sections of the Medication Guide, except the manufacturer's name and address and the revision date.

(5) The Medication Guide shall be legible and clearly presented. Where appropriate, the Medication Guide shall also use boxes, bold or underlined print, or other highlighting techniques to emphasize specific portions of the text.

(6) The words "Medication Guide" shall appear prominently at the top of the first page of a Medication Guide. The verbatim statement "This Medication Guide has been approved by the U.S. Food and Drug Administration" shall appear at the bottom of a Medication Guide.

(7) The brand and established or proper name of the drug product shall appear immediately below the words "Medication Guide." The established or proper name shall be no less than one-half the height of the brand name.

(b) A Medication Guide shall contain those of the following headings relevant to the drug product and to the need for the Medication Guide in the specified order. Each heading shall contain the specific information as follows:

(1) The brand name (e.g., the trademark or proprietary name), if any, and established or proper name. Those products not having an established or proper name shall be designated by their active ingredients. The Medication Guide shall include the phonetic spelling of either the brand name or the established name, whichever is used throughout the Medication Guide.

(2) The heading, "What is the most important information I should know about (name of drug)?" followed by a statement describing the particular serious and significant public health concern that has created the need for the Medication Guide. The statement should describe specifically what the patient should do or consider because of that concern, such as, weighing particular risks against the benefits of the drug, avoiding particular behaviors (e.g., activities, drugs), observing certain events (e.g., symptoms, signs) that could prevent or mitigate a serious adverse effect, or engaging in particular behaviors (e.g., adhering to the dosing regimen).

(3) The heading, "What is (name of drug)?" followed by a section that identifies a drug product's indications for use. The Medication Guide may not identify an indication unless the indication is identified in the indications and usage section of the professional labeling for the product required under § 201.57 of this chapter. In appropriate circumstances, this section may also explain the nature of the disease or condition the drug product is intended to treat, as well as the benefit(s) of treating the condition.

(4) The heading, "Who should not take (name of drug)?" followed by information on circumstances under which the drug product should not be used for its labeled indication (its contraindications). The Medication Guide shall contain directions regarding what to do if any of the contraindications apply to a patient, such as contacting

the licensed practitioner or discontinuing use of the drug product.

(5) The heading, "How should I take (name of drug)?" followed by information on the proper use of the drug product, such as:

(i) A statement stressing the importance of adhering to the dosing instructions, if this is particularly important;

(ii) A statement describing any special instructions on how to administer the drug product, if they are important to the drug's safety or effectiveness;

(iii) A statement of what patients should do in case of overdose of the drug product; and

(iv) A statement of what patients should do if they miss taking a scheduled dose(s) of the drug product, where there are data to support the advice, and where the wrong behavior could cause harm or lack of effect.

(6) The heading "What should I avoid while taking (name of drug)?" followed by a statement or statements of specific, important precautions patients should take to ensure proper use of the drug, including:

(i) A statement that identifies activities (such as driving or sunbathing), and drugs, foods, or other substances (such as tobacco or alcohol) that patients should avoid when using the medication;

(ii) A statement of the risks to mothers and fetuses from the use of the drug during pregnancy, if specific, important risks are known;

(iii) A statement of the risks of the drug product to nursing infants, if specific, important risks are known;

(iv) A statement about pediatric risks, if the drug product has specific hazards associated with its use in pediatric patients;

(v) A statement about geriatric risks, if the drug product has specific hazards associated with its use in geriatric patients; and

(vi) A statement of special precautions, if any, that apply to the safe and effective use of the drug product in other identifiable patient populations.

(7) The heading, "What are the possible or reasonably likely side effects of (name of drug)?" followed by:

(i) A statement of the adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently.

(ii) A statement of the risk, if there is one, of patients' developing dependence on the drug product.

(8) General information about the safe and effective use of prescription drug products, including:

(i) The verbatim statement that "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide" followed by a statement that patients should ask health professionals about any concerns, and a reference to the availability of professional labeling;

(ii) A statement that the drug product should not be used for a condition other than that for which it is prescribed, or given to other persons;

(iii) The name and place of business of the manufacturer, packer, or distributor of a drug product that is not also a biological product, or the name and place of business of the manufacturer or distributor of a drug product that is also a biological product, and in any case the name and place of business of the dispenser of the product may also be included; and

(iv) The date, identified as such, of the most recent revision of the Medication Guide placed immediately after the last section.

(9) Additional headings and subheadings may be interspersed throughout the Medication Guide, if appropriate.

§ 208.24 Distributing and dispensing a Medication Guide.

(a) The manufacturer of a drug product for which a Medication Guide is required under this part shall obtain FDA approval of the Medication Guide before the Medication Guide may be distributed.

(b) Each manufacturer who ships a container of drug product for which a Medication Guide is required under this part is responsible for ensuring that Medication Guides are available for distribution to patients by either:

(1) Providing Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to

permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product; or

(2) Providing the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.

(c) Each distributor or packer that receives Medication Guides, or the means to produce Medication Guides, from a manufacturer under paragraph (b) of this section shall provide those Medication Guides, or the means to produce Medication Guides, to each authorized dispenser to whom it ships a container of drug product.

(d) The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.

(e) Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient's agent), provide a Medication Guide directly to each patient (or to the patient's agent) unless an exemption applies under § 208.26.

(f) An authorized dispenser or wholesaler is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act, which requires the registration of producers of drugs and the listing of drugs in commercial distribution, solely because of an act performed by the authorized dispenser or wholesaler under this part.

§ 208.26 Exemptions and deferrals.

(a) FDA on its own initiative, or in response to a written request from an applicant, may exempt or defer any Medication Guide content or format requirement, except those requirements in § 208.20 (a)(2) and (a)(6), on the basis that the requirement is inapplicable, unnecessary, or contrary to patients' best interests. Requests from applicants should be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product, or for a biological product, to the application division in the office with product responsibility.

(b) If the licensed practitioner who prescribes a drug product subject to this part determines that it is not in a particular patient's best interest to receive a Medication Guide because of significant concerns about the effect of a Medication Guide, the licensed practitioner may direct that the Medication Guide not be provided to the particular patient. However, the authorized dispenser of a prescription drug product subject to this part shall provide a Medication Guide to any patient who requests information when the drug product is dispensed regardless of any such direction by the licensed practitioner.

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

Sec.

210.1 Status of current good manufacturing practice regulations.
210.2 Applicability of current good manufacturing practice regulations.
210.3 Definitions.

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374.

SOURCE: 43 FR 45076, Sept. 29, 1978, unless otherwise noted.

§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.