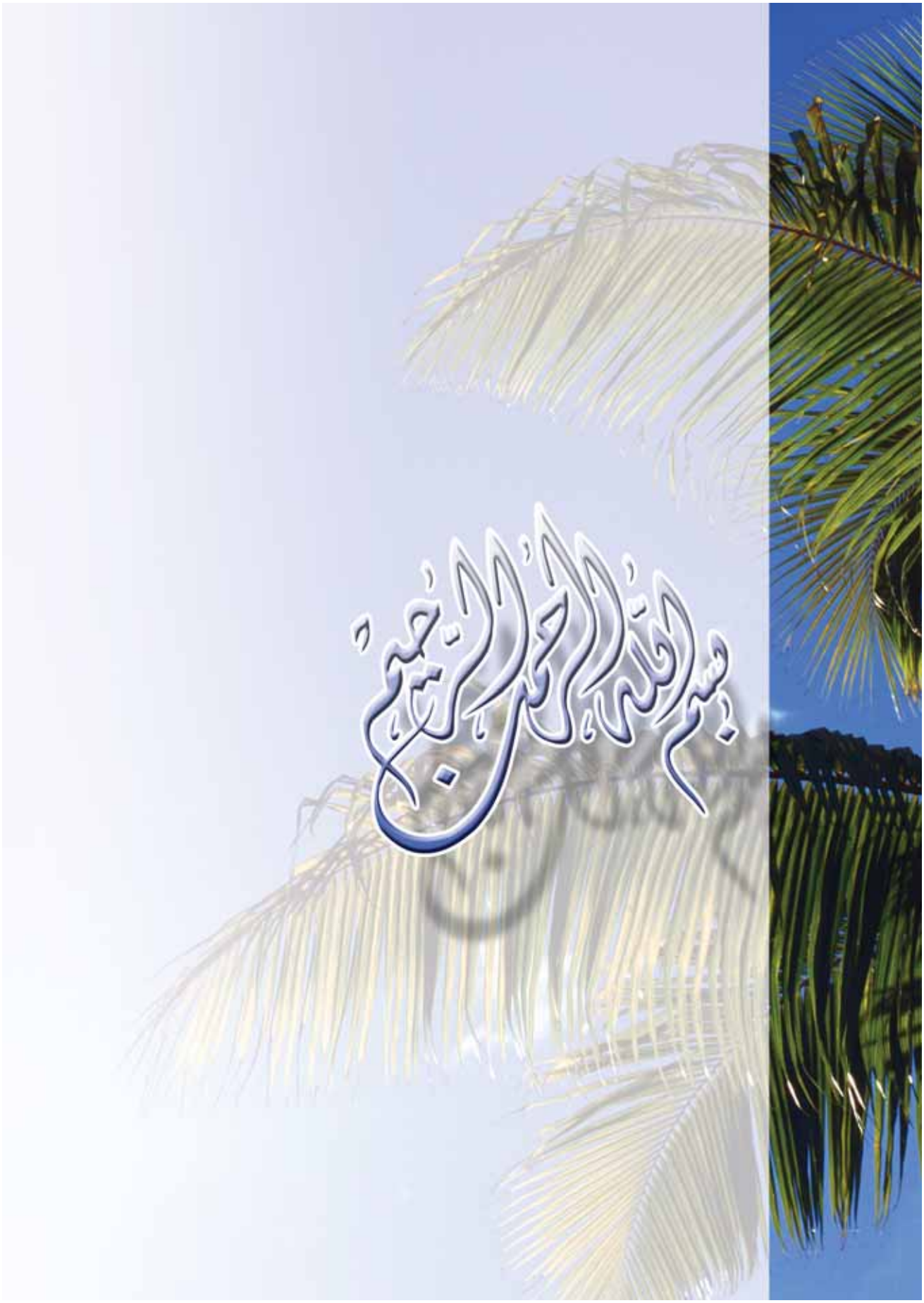
الدواء العربي

نشرة علمية ثقافية نصف سنوية تصدر عن شركة أكديما

السنة الثلاثون ـ العددان 59 . 60 حزيران 2011 م ـ رجب 1432 هـ


بسم الله الرحمن الرحيم

الدواء العربي

نشرة علمية ثقافية نصف سنوية تصدر عن شركة أكديما

المراسلات

ص.ب ٩٢٥١٦١ عمان ١١١٩٠ الاردن

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الدواء العربي

6-8 ounces of water with it. Then gradually add more calcium each week.

Summary

Most studies show that low calcium intake is associated with low bone density, bone loss and higher numbers of broken bones. Getting enough calcium is one of the many things you can do to help reduce bone loss. People who get plenty of calcium may still be at risk for bone loss and osteoporosis due to a variety of factors. These include vitamin D deficiency, family history, physical inactivity, smoking, alcohol abuse and certain medications and medical disorders known to cause bone loss.

References

1) www.nof.org

or less. This is the case when we eat calcium rich foods or take supplements. Taking your calcium all at once, however, is better than not taking it at all. Because the average daily diet contains about 600 mg of calcium from foods, most people only need about 600 mg of calcium from supplements.

Try to get your calcium-rich foods and/or supplements in smaller amounts throughout the day, preferably with a meal. You should take most calcium supplements with food. Eating food produces stomach acid that helps your body absorb the calcium. The body can absorb supplements of cal cium citrate at anytime. You can take calcium citrate supplements either with or without food depending on your preference.

Side Effects

Side effects from calcium supplements, such as gas or constipation may occur. If increasing fluids in your diet does not solve the problem, try another type or brand of calcium. It may require trial and error, but fortunately there are many choices.

When starting a new calcium supplement, it may be tolerated better if you start with a smaller amount. For example, start with 200-300 mg of calcium every day for a week, and drink an extra

* Calcium supplements should not be taken at the same time as iron supplements.

* Thyroid hormones should not be taken within four hours of calcium supplements to prevent interactions (unless directed otherwise by a healthcare provider or pharmacist).

* Medications that need to be taken on an empty stomach should not be taken at the same time as a calcium supplement.

* Consider calcium citrate supplements over other calcium supplements if you take proton pump inhibitors (PPIs) such as Prevacid, Prilosec and Nexium. Because these medications block stomach acid, our body may better absorb calcium citrate which does not need stomach acid for absorption.

Calcium Absorption

The body easily absorbs most brand name calcium products. Calcium supplements need to dissolve in the stomach for calcium to be absorbed. Chewable and liquid supplements dissolve well because they break down before entering the stomach. The USP symbol on the label also lets you know that the supplement will break down and dissolve so that the body can use it.

Calcium is absorbed best when taken in amounts of 500 - 600 mg

sium, phosphorus and vitamin K are also important for bone health, but are usually obtained by eating a well-balanced diet. Most experts recommend that people take multivitamins or supplements only when they are not able to get enough nutrients from foods.

Safety

Calcium supplements made from unrefined oyster shell, bone meal or dolomite may contain lead or other toxic metals. Choose supplements that are made by known brand names with proven reliability for these types of supplements.

If you are not familiar with the brand, look for labels that state (purified) or have the USP (United States Pharmacopeia) symbol. The USP Verified Mark on the supplement label means that the USP has tested and found the calcium supplement to meet certain standards for purity and quality. Because applying for the USP symbol is voluntary, many fine products may not display this symbol. The USP symbol is helpful when you don't know the brand.

Here are a few examples on drug interactions between calcium supplement and other drugs:

* Calcium supplements may reduce the absorption of the antibiotic tetracycline.

Vitamin D (Daily)
19 through 49 years
1,000 mg
400-800 IU
50 years and over
1,200 mg
800-1000 IU
Pregnant & Breastfeeding Women
Calcium (Daily)
Vitamin D (Daily)
18 years and under
1,300 mg
400-800 IU
19 years and over
1,000 mg
400-800 IU

*NOF does not have specific vitamin D recommendations for these age groups. These are the recommendations of the American Academy of Pediatrics.

A Simple Way to Add Calcium to Many Foods

A single tablespoon of nonfat powdered milk contains about 50 mg of calcium. Try adding some to:

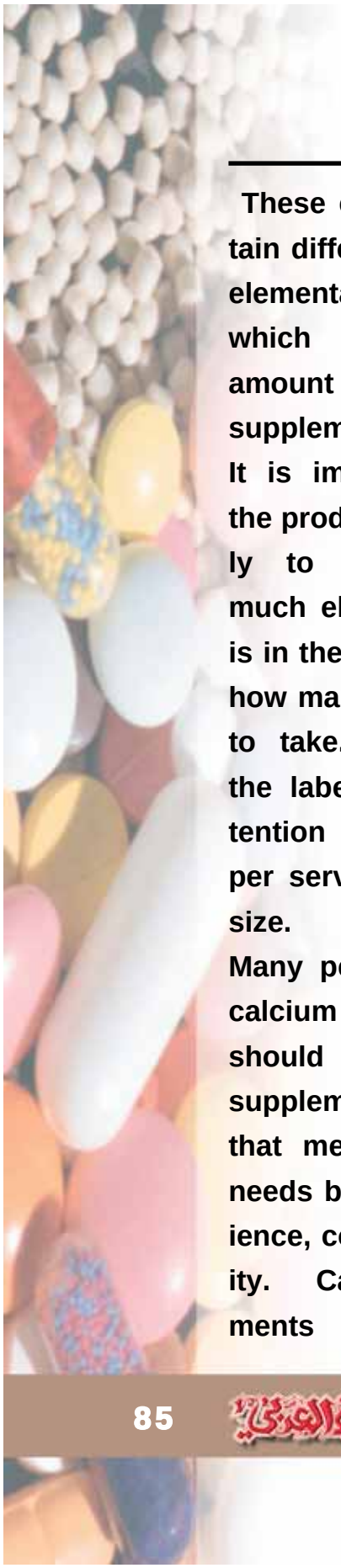
* Puddings
* Homemade cookies
* Breads or muffins
* Soups or gravy
* Casseroles

About two-to-four tablespoons can be added to most recipes!

Other Vitamins and Minerals

Calcium supplements are also available in combination with vitamins and other minerals. Although vitamin D is necessary for the absorption of calcium, it does not need to be taken at the same time as a calcium supplement.

Minerals such as magne



These compounds contain different amounts of elemental calcium, which is the actual amount of calcium in the supplement.

It is important to read the product label carefully to determine how much elemental calcium is in the supplement and how many doses or pills to take. When reading the label, pay close attention to the amount per serving and serving size.

Many people ask which calcium supplement they should take. The best supplement is the one that meets a person's needs based on convenience, cost and availability. Calcium supplements are available without a prescription in a wide range of preparations (including chewable and liquid) and in different amounts.

NOF Calcium and Vitamin D Recommendations

Children & Adolescents	
Calcium (Daily)	
Vitamin D (Daily)	
1 through 3 years	
500 mg	
400 IU*	
4 through 8 years	
800 mg	
400 IU*	
9 through 18 years	
1,300 mg	
400 IU*	
Adult Women & Men	
Calcium (Daily)	

foods we eat, then we don?t need to take a supplement. Taking more calcium than we need in supplements does not have added benefits and can even have some risks. We shouldn't take supplements that we don't need.

Calcium exists in nature only in combination with other substances called compounds. Several different calcium compounds are used in supplements, including calcium carbonate, calcium citrate, calcium lactate and calcium phosphate.

mendations

According to NOF recommendations:

*** Adults age 50 and older need a total of 1,200 milligrams (mg) of calcium from all sources* and 800-1,000 international units (IUs) of vitamin D every day.**

*** Adults under age 50 need a total of 1,000 milligrams (mg) of calcium from all sources* and 400-800 international units (IUs) of vitamin D every.**

***This includes the total amount of calcium you get from both food and supplements.**

People who get the recommended amount of calcium from foods do not need to take a calcium supplement. Some people, however, may still need to take a vitamin D supplement. There are two types of vitamin D supplements. They are vitamin D3 and vitamin D2.

Getting too much calcium from supplements may increase the chance of developing kidney stones and other health problems in some people. According to most experts, the safe upper limit for total daily calcium intake from all sources is 2,000 - 2,500 mg.

Calcium Supplements

The amount of calcium needed from a supplement depends on the amount of calcium we get from foods. If we get enough calcium from the

messages, muscles contract and other body functions.

Each day, you lose calcium through your skin, nails, hair, sweat, urine and feces. Our bodies cannot produce calcium. That's why it's important to try to get enough calcium through the foods we eat. When we don't get enough calcium for our body's needs, calcium is taken from our bones.

Sources of Calcium

Food is the best source of calcium. Dairy products, such as low-fat and non-fat milk, yogurt and cheese are high in calcium. Certain green vegetables and other foods contain calcium in smaller amounts. For people who have trouble digesting dairy products because of lactose intolerance, lactose-free dairy products and lactase enzyme pills are also available.

Calcium-fortified foods and calcium supplements are helpful for people who are unable to get enough calcium in their diets. Some juices, breakfast foods, soymilk, cereals, snacks, breads and bottled water have calcium that has been added. If you drink soymilk or another liquid that is fortified with calcium, be sure to shake the container well as calcium can settle to the bottom.

Daily Calcium Recom-

you need from food. Foods that have vitamin D include fatty fish (examples are wild-caught mackerel, salmon and tuna). Vitamin D is also added to milk and to some brands of other dairy products, orange juice, soymilk and cereals.

Check the food label to see if vitamin D has been added to a particular product. One glass of milk usually has 25% of the daily value (DV) of vitamin D. The DV is based on a total daily intake of 400 IU of vitamin D. Therefore a serving of milk with 25% of the DV of vitamin D contains 100 IU of the vitamin.

Supplements and Medications

Vitamin D supplements can be taken with or without food. While our body needs vitamin D to absorb calcium, we do not need to take vitamin D at the same time as a calcium supplement.

Calcium:

What You Should Know

Why Is Calcium Important?

Calcium is important to build stronger, denser bones early in life and to keep bones strong and healthy later in life.

About 99 percent of the calcium in our bodies is in our bones and teeth. In addition to building bones and keeping them healthy, calcium helps blood clot, nerves send

protect their skin.

Probably the most important factor which limits the ability of the skin to make vitamin D is the use of sunscreen and sun-block. Even an SPF (sun protection factor) of 8 reduces the production of vitamin D by 95 percent. These products help protect the skin from the harmful effects of the sun. Because of the cancer risk from staying in the sun, many people need to get vitamin D from other sources.

Food

Vitamin D is naturally available in only a few foods. It is very difficult to get all the vitamin D

called ergocalciferol.

Sources of Vitamin D

There are three ways to get vitamin D:

Sunlight

* Food

* Supplements and medications

Our skin makes vitamin D from the ultra-violet light (UVB rays) in sunlight. Our body is able to store the vitamin and use it later. The amount of vitamin D our skin makes depends on time of day, season, latitude, skin pigmentation and other factors. Depending on where we live, vitamin D production may decrease or be completely absent during the winter. It is difficult to measure the amount of vitamin D that our skin makes.

People with fair skin make more vitamin D than people with darker skin. People who live in higher latitudes such as New York, as opposed to lower latitudes such as Florida, may get less vitamin D from sunlight. Window glass and air pollution also decrease the amount of vitamin D that our skin can make.

People who are housebound and do not get outside are unable to make vitamin D from the sun. As adults age, the ability to make vitamin D also decreases.

Because of concerns about skin cancer, many people stay out of the sun, cover up with clothing and use either sunscreen or sun-block to

enough vitamin D, they can lose bone. Studies show that people with low levels of vitamin D have lower bone density or bone mass. They are also more likely to break bones when they are older.

Severe vitamin D deficiency can cause a disease known as osteomalacia where the bones become soft. In children, this is known as rickets. These two conditions are different from osteoporosis.

National Osteoporosis Foundation (NOF) Recommendations for Vitamin D

The National Osteoporosis Foundation (NOF) recommends that adults under age 50 get 400 - 800 International Units (IU) of vitamin D every day, and that adults age 50 and older get 800 - 1,000 IU of vitamin D every day. Some people may need more vitamin D. According to the Institute of Medicine (IOM), the safe upper limit of vitamin D is 4,000 IU per day for most adults.

There are two types of vitamin D supplements. They are vitamin D2 and vitamin D3. Previous research suggested that vitamin D3 was a better choice than vitamin D2. However, more recent studies show that vitamin D3 and vitamin D2 are equally good for bone health. Vitamin D3 is also called cholecalciferol. Vitamin D2 is also

bones.

Coffee and tea. These drinks naturally contain caffeine. Caffeine appears to decrease calcium absorption by a small amount. Drinking more than three cups of coffee every day may be harmful to bone health. If someone enjoys drinking coffee and tea, he/she can help to make up for any calcium loss by getting enough calcium to meet his/her body's needs.

Soft drinks. Some studies suggest that colas, but not other soft drinks, are associated with bone loss. While more research will help us to better understand the link between soft drinks and bone health, here is what we know:

The carbonation in soft drinks does not cause any harm to bone. The caffeine and phosphorous commonly found in colas may contribute to bone loss. Like calcium, phosphorous is a part of the bones. It is listed as an ingredient in colas, some other soft drinks and processed foods as phosphoric acid.

Vitamin D and Bone Health

Vitamin D plays an important role in protecting our bones. Our body requires vitamin D to absorb calcium. Children need vitamin D to build strong bones, and adults need it to keep bones strong and healthy. When people do not get

just shouldn't be counted as sources of calcium.

Wheat bran. Wheat bran contains high levels of phytates which can prevent our body from absorbing calcium. 100% wheat bran is the only food that appears to reduce the absorption of calcium in other foods eaten at the same time. For example, when we have milk and wheat bran cereal together, our body can absorb some, but not all, of the calcium from the milk.

We do not know exactly how much calcium is lost when you have 100% wheat bran and calcium together. If you take calcium supplements, you may want to take them two or more hours before or after eating 100% wheat bran. It's still important to eat fiber-rich foods, many of which do not interfere with calcium absorption.

Drinks and Bone Health Alcohol.

Drinking heavily can lead to bone loss. Many people who drink too much do not get enough calcium. Drinking may also lower our body's calcium supply. Drinking too much alcohol is bad for our overall health and can make us more likely to fall and break bones.

Coffee, tea and soft drinks (sodas). Some people are concerned that certain nutrients and substances in these drinks are harmful to

for several hours and then cooking them in fresh water. In addition to calcium, beans contain magnesium, fiber and other nutrients.

Meat and other high protein foods.

Getting enough protein is important for bone health and overall health. The amount of protein needed each day is about 5 ounces for women and 5’ ounces for men. However, special high protein diets can cause the body to lose calcium. We can make up for this loss by getting enough calcium for our body’s needs. For example dairy products, although high in protein, also contain calcium that is important for healthy bones.

Salty foods. Eating foods that have a lot of salt (sodium) causes our body to lose calcium and can lead to bone loss. Try to limit the amount of processed foods, canned foods and salt added to the foods you eat each day. To learn if a food is high in sodium, look at the Nutrition Facts label.

Spinach and other foods with oxalates.

Our body doesn’t absorb calcium well from foods that are high in oxalates (oxalic acid) such as spinach. Other foods with oxalates are rhubarb, beet greens and certain beans. These foods contain other healthy nutrients; they

trients. If not, we may need to take multivitamins or supplements. we cannot get all of the vitamins and minerals our body needs by taking supplements, which is why it's important to eat at least 1' cups of fruits and two cups of vegetables every day.

More research studies will help us to better understand the link between eating fruits and vegetables and bone health.

Beans (legumes).

Pinto beans, navy beans, peas and other beans are high in substances called phytates. Phytates interfere with our body's ability to absorb the calcium that is contained in beans. We can reduce the phytate level by soaking beans in water

Fruits and vegetables.

Several studies have linked higher intakes of fruits and vegetables with better bone health. It is not entirely clear why fruits and vegetables promote healthy bones. Some scientists believe that fruits and vegetables contain certain nutrients that are beneficial for bones. Some examples of these nutrients are:

Calcium. Sources include collard greens, turnip greens, kale, okra, Chinese cabbage, dandelion greens, mustard greens and broccoli.

Magnesium. Sources include spinach, beet greens, okra, tomato products, artichokes, plantains, potatoes, sweet potatoes, collard greens and raisins.

Potassium. Sources include tomato products, raisins, potatoes, spinach, sweet potatoes, papaya, oranges, orange juice, bananas, plantains and prunes.

Vitamin C. Sources include red peppers, green peppers, oranges, grapefruits, broccoli, strawberries, brussels sprouts, papaya and pineapples.

Vitamin K. Sources include certain dark green leafy vegetables such as kale, collard greens, spinach, mustard greens, turnip greens and brussels sprouts.

If we eat a well-balanced diet, we should be getting enough of these nu-

cery store usually has vitamin D added to it. This means it's fortified with vitamin D. Some other dairy products are fortified with vitamin D, but many of them are not.

Fish. Canned sardines and salmon (with bones) are good ways to get calcium. You can also get calcium from eating canned shrimp. Fatty fish such as salmon, mackerel, tuna and sardines are other ways to get vitamin D.

Fortified foods. Calcium and vitamin D are sometimes added to certain brands of juices, breakfast foods, soy milk, rice milk, cereals, snacks and breads. These foods can help us get more calcium and vitamin D in our diet.

How food affect your bone health

Certain foods can affect our bones.

Dr. Eman Rebhi

Learning about these foods can help us make healthier food choices every day.

Dairy products

Dairy products are high in calcium. Low-fat and non-fat milk, yogurt and cheese are good choices. If someone like these foods, it's an easy way to get calcium. It's important to try to get enough calcium from the foods you eat. When our diet does not have enough calcium for our body's needs, calcium is taken from our bones.

Vitamin D is also important because it helps our body use calcium. The milk we buy in the gro-

that may have changed the regulatory status of the issues discussed in the letter.

The Freedom of Information Act (FOIA) requires publicly accessible "electronic reading rooms" with agency FOIA response materials and other information to be routinely available to the public, with electronic search and indexing features.

References

1-FDA: Regulatory Procedures Manual, "Exhibit 4-1 Procedures for Clearing FDA Warning Letters and Untitled Letters" Accessed 06 July 2010.

2-FDA: Inspections, Compliance, Enforcement, and Criminal Investigations, "Warning Letter Close-Out Letter Program" Accessed 06 July 2010.

3-FDA: Freedom of Information Accessed 06 July 2010.

Warning Letter. For example:

1. The product is adulterated under Section 402 (a)(3) or 402(a)(4) of the Act;
2. There is a violation of cGMP;
3. The product contains illegal pesticide residues; or
4. The product shows short contents, sub-potency, or super-potency.

Warning Letter close-out letter

After the FDA has completed an evaluation of corrective actions via follow-up inspection, it may issue a Warning Letter close-out letter ("close-out letter"). This procedure applies to Warning Letters issued on or after September 1, 2009.

Public access to Warning Letters

Warning Letters are made available under the Freedom of Information (FOI) Office. Published letters are redacted or edited to remove confidential information. Redacted copies will not include "bcc" information, or the "credit page" related to drafting sequence, etc.

It is important to third parties reading Warning Letters to understand that matters described in FDA Warning Letters may have been subject to subsequent interaction between FDA and the recipient of the letter

tives

As there is no legal requirement for the FDA to warn individuals or firms that they or their products are in violation of the law before taking enforcement action, a Warning Letter is not a required prerequisite to taking enforcement action. The FDA further asserts that there are egregious circumstances when issuing a Warning Letter is not appropriate, and it will then take immediate enforcement action. These include:

1. The violation reflects a pattern of conduct of a substantially similar nature during which time the individual and/or firm has been notified of violation;
2. The violation is intentional or flagrant;
3. The violation presents a reasonable possibility of injury or death;
4. The violations are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters; and,
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing.

In certain situations, the agency may also take other actions as an alternative to, or concurrently with, the issuance of a

During any subsequent inspection, FDA investigators are expected to verify overall completeness and effectiveness of corrective actions. The timing of a subsequent investigation may be expedited or routine, as determined by the issuing office. Should violations be observed during a subsequent inspection or through other means, enforcement action(s) may be taken without further notice. Additional enforcement actions (sequential or concurrent) available to the FDA to achieve correction are product recall, seizure, injunction, administrative detention, civil money penalties and/or prosecution.

Special types of Warning Letters

Joint Warning Letters

The FDA and the Federal Trade Commission (FTC) issued their first joint Warning Letter on October 15, 2009. It was issued to a web site marketing fraudulent supplements.

Cyber Warning Letters

"Cyber" Warning Letters are Warning Letters sent via the Internet to web sites that offer to sell online prescription drugs that may be illegal. These letters warn that they may be engaged in illegal activities and informs them of the laws that govern prescription drug sales.

Warning Letter alterna

Counsel (OCC). The lead center is responsible for bringing the Warning Letter through the review process, including the review and incorporation of comments as appropriate from the other involved entities.

Office of the Chief Council (OCC) review

Deputy Secretary of the Department of Health and Human Services directed on November 29, 2001, that the FDA submits all Warning Letters to the OCC prior to their issuance so that they can be reviewed for legal sufficiency and consistency with Agency policy. The OCC has 15 working days to complete its review. If the OCC fails to make a timely response to Direct Reference Warning Letters and those issued as a result of foreign inspections, the District or Center can presume concurrence and may send the Warning Letter out without additional input from the OCC.

Follow up inspections

For a CBER Warning Letter, a follow-up inspection will be scheduled to occur approximately 30 days after the response to the Warning Letter is received to determine the adequacy of the reported corrective actions. If corrective action has not been made or the firm has failed to respond, the district will consider suitable follow-up.

3. Bioresearch Monitoring Program violations; and
4. Product advertising violations."

CDER requires their review for additional types of violations, which are:

1. "New drug charges - including unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements;
2. Adverse drug experience reporting violations;
3. Novel and unusual tamper-evident packaging violations;
4. Prescription Drug Marketing Act violations;
5. Investigational drug use violations;
6. CGMP charges involving active pharmaceutical ingredients and other drug component manufacturing deficiencies;
7. CGMP charges involving all dosage forms, including medical gases;
8. CGMP charges involving inspections of facilities for therapeutic biologic products regulated by CDER; and
9. Pharmacy compounding issues."

Lead center

When the issues in a Warning Letter require review by more than one center, a "lead center" is designated. The lead center is responsible for communication with the other involved center(s), the district, and the FDA's Office of Chief

tions. In the case of Warning Letters being considered for products offered for sale through internet web sites, corrective action to remove claims or inactivate the website is easily reversible, and should be carefully considered, along with the other factors above, in determining whether or not to issue a Warning Letter. Warning Letters for, or involving, internet web sites should be issued in as close proximity as possible to the time when the claims were last observed, and reference to the date on which the claims were observed should be included in the letter."

Also, a Warning Letter usually will not be issued if the agency finds that corrective actions are implemented, adequate, and that the violations that would have supported the Warning Letter have been corrected.

Center review

Warning letters with the following violations are required to be reviewed by their respective FDA Center (e.g. Center for Drug Evaluation and Research (CDER) :

1. "All labeling violations - except where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guides, and Drug Health Fraud Bulletins;
2. Computer application and software violations;

although a written promise to take prompt corrective action, in the right context, can result in a decision to not issue a Warning Letter. The potentially influencing factors are:

* "The firm's compliance history, e.g., a history of serious violations, or failure to prevent the recurrence of violations;
* "The nature of the violation, e.g., a violation that the firm was aware of (was evident or discovered) but failed to correct;
* "The risk associated with the product and the impact of the violations on such risk;
* "The overall adequacy of the firm's corrective action and whether the corrective action addresses the specific violations, related violations, related products or facilities, and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence;
* "Whether documentation of the corrective action was provided to enable the agency to undertake an informed evaluation;
* "Whether the timeframe for the corrective action is appropriate and whether actual progress has been made in accordance with the timeframe; and,
* "Whether the corrective action taken ensures sustained compliance with the law or regula

tion, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. [If cGMP Violations are cited: Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a [supplier or manufacturer] until the above violations are corrected. A re-inspection may be necessary.]

"Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. [If you no longer manufacture or market ____, your response should so indicate, including the reasons that, and the date on which, you ceased production"

Avoiding a Warning Letter

Ongoing or promised corrective actions generally do not prevent receiving a Warning Letter,

sponse recipient

The Warning Letter will specify a designated district or center official to whom the response should be addressed

Issuer

The entity issuing the Warning Letter will be identified, whether the district director, division director, or higher agency official.

Standardized closing text

For drug Warning Letters, the information in the above sections will be in closing paragraphs as follows (bold type indicates optional/alternative language to be used as appropriate):

"The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist [at your facility/in connection with your product(s)]. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that [you/your firm] comply[ies] with all requirements of federal law and FDA regulations.

"You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limita

vestigators, sponsors, and monitors involved in clinical trials) that, "Federal agencies are advised of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.

And for device Warning Letters that include cGMP violations:

"Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the viola tions related to the subject devices have been corrected.

Instructions for the response

Instructions, as appropriate, will be provided stating that the response includes: "each step that has been or will be taken to completely correct the current violations and to prevent similar violations;

1. the time within which correction will be completed;

2. any reason the corrective action has not been completed within the response time; and

3. any documentation necessary to show that correction has been achieved

Identification of the re

request corrections and a written response within a specific period after receipt of the letter, usually fifteen (15) working days. At the district's discretion, the recipient may be offered an opportunity to discuss the letter with district officials or, when appropriate, with center officials.

Warning statement

There will be a warning statement that failure to achieve prompt correction may result in enforcement action without further notice. While examples of such actions may be included, there will not be any commitment that enforcement action will be taken.

Impact

For drug Warning Letters (except those issued to Institutional Review Board (IRBs), clinical investigators, sponsors, and monitors involved in clinical trials), there will be a statement regarding the implications for the award of federal contracts. If current Good Manufacturing Practice (cGMP) violations are cited, the statement will be regarding the potential impact on requests for approval of export certificates and drug applications

Additional impact for device manufacturers

There will be a statement in device Warning Letters (except those issued to IRBs, clinical in

Addressees

The Warning Letter should be addressed to the highest known official in the firm that includes the facility that was inspected, and a copy should be sent to the highest known official at the specific facility that was inspected. If a separate response from other officials is expected by the FDA, they may be included as addressees. Districts will routinely provide copies of Warning Letters to appropriate state agencies. Suitable notations (e.g., cc, or copy sent to) should be used in the letter and identify each person by name, title, and, if appropriate, address.

Inspection details

The dates of the inspection and a description of the violative condition practice, or product in brief but sufficient detail to provide the respondent the opportunity to take appropriate corrective actions, include citation of the section of the law and, where applicable, the regulation violated. Unlike the Form FDA 483, the Warning Letter will cite regulatory references for each violation.

Promised corrections

The Warning Letter should acknowledge corrections promised during the inspection or provided to the district in a written response.

Response request

The Warning Letter will

lishments will voluntarily comply with the law. When departures are observed the FDA gives an organization an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. A step in this process, depending on the nature of the violation, is to issue a Warning Letter, which also serves to establish "prior notice."

The agency has a computer application called the Compliance Management System (CMS) that is used for electronically submitting Warning Letter recommendations from district offices to FDA Centers. All recommendations by the district offices must use the CMS for submitting the proposed Warning Letter, the Form FDA 483 that supports the alleged violations, the Establishment Inspection Report (EIR), and any written response by the firm.

Warning Letter content

The elements listed below are common to Warning Letters:

Title

The Warning Letter will have the words "WARNING LETTER" at the top.

Delivery

Warning Letters should be sent to ensure overnight delivery and receipt of delivery (e.g., return receipt requested, FedEx) should be documented. The mode of delivery will be stated upon the Warning Letter.

i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency?s principal means of achieving prompt voluntary compliance with the Act.

While violations are generally determined through the FDA's own inspections, they can also be issued based upon evidence obtained by state personnel. A Warning Letter is considered by the agency to be informal and advisory. While it communicates the agency's position on a matter, it does not commit the FDA to taking enforcement action. For these reasons, the FDA does not consider Warning Letters to be final actions on which it can be sued.

The US FDA expects that most individuals, firms, and government estab

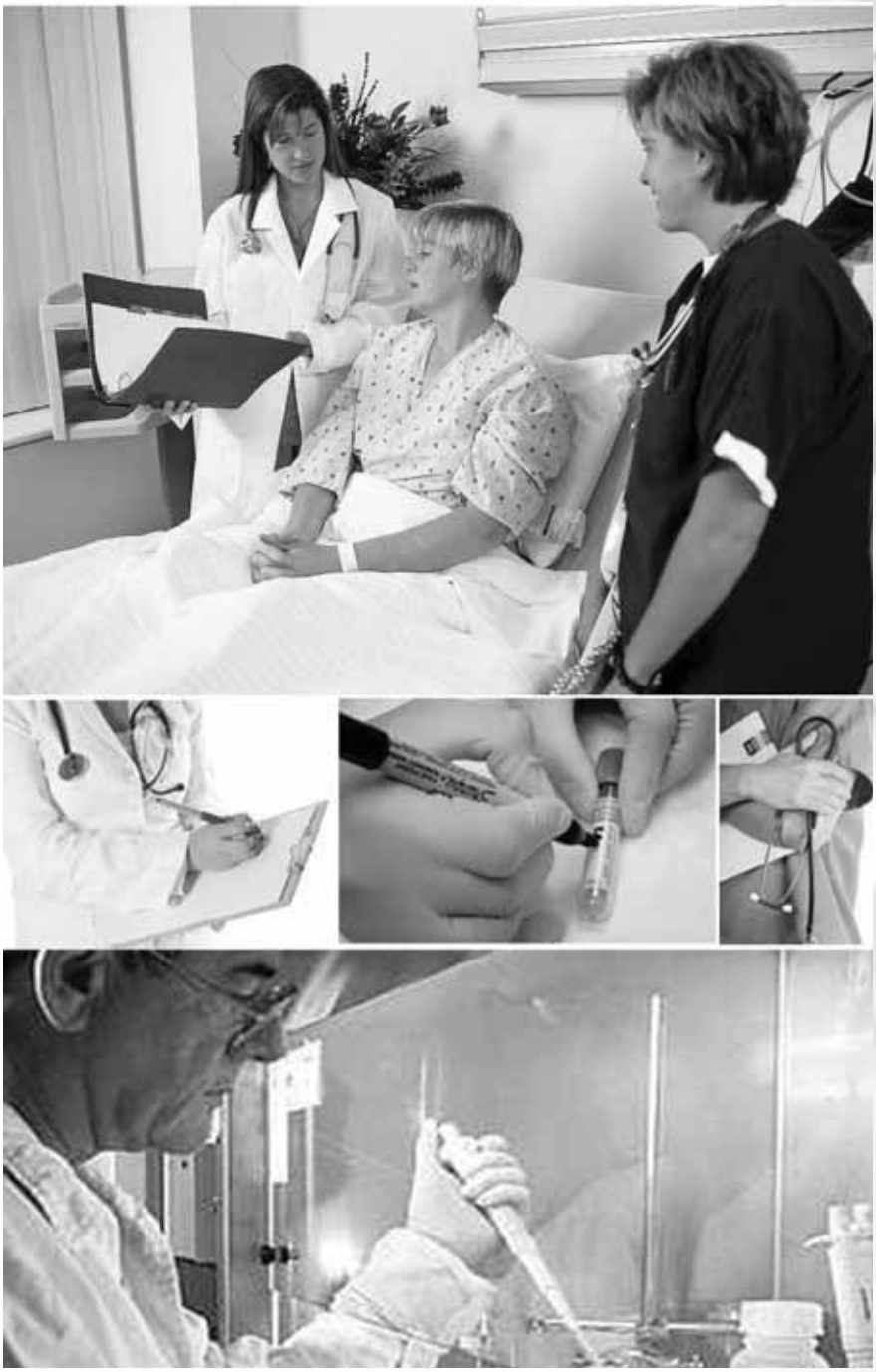
FDA

Warning Letter

Eng. Bassam Qaisieh
Acdima

Introduction

The US FDA defines a Warning Letter as "a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations." Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act, its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance,



tation of any benefit. In most other trials, however, patients are not paid, in order to ensure that their motivation for participating is the hope of getting better or contributing to medical knowledge, without their judgment being skewed by financial considerations. However, they are often given small payments for study-related expenses like travel or as compensation for their time in providing follow-up information about their health after they are discharged from medical care.

Participating in a clinical trial:

Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. Depending on the kind of participants required, sponsors of clinical trials use various recruitment strategies, including patient databases, newspaper and radio advertisements, flyers, posters in places the patients might go (such as doctor's offices), and personal recruitment of subjects/ patients by investigators.

such as the U.S. National Institutes of Health offer grants to investigators who design clinical trials that attempt to answer research questions that interest the agency. In these cases, the investigator who writes the grant and administers the study acts as the sponsor, and coordinates data collection from any other sites. These other sites may or may not be paid for participating in the study, depending on the amount of the grant and the amount of effort expected from them.

Investigators:

Many clinical trials do not involve any money. However, when the sponsor is a private company or a national health agency, investigators are almost always paid to participate. These amounts can be small, just covering a partial salary for research assistants and the cost of any supplies (usually the case with national health agency studies), or be substantial and include 'overhead' that allows the investigator to pay the research staff during times in between clinical trials.

Subjects/Patients:

In Phase I drug trials; participants are paid because they give up their time (sometimes away from their homes) and are exposed to unknown risks, without the expec

proved for medical use. Clinical trials follow a standardized process.

The costs to a pharmaceutical company of administering a Phase III or IV clinical trial may include, among others:

* Manufacturing the drug(s)/device(s) tested.
* Staff salaries for the designers and administrators of the trial.
* Payments to the contract research organization, the site management organization (if used) and any outside consultants.
* Payments to local researchers (and their staffs) for their time and effort in recruiting patients and collecting data for the sponsor.
* Study materials and shipping.
* Communication with the local researchers, including onsite monitoring by the CRO before and (in some cases) multiple times during the study.
* One or more investigator training meetings.
* Costs incurred by the local researchers such as pharmacy fees, IRB fees and postage.
* Any payments to patients enrolled in the trial (all payments are strictly overseen by the IRBs to ensure that patients do not feel coerced to take part in the trial by overly attractive payments)

These costs are incurred over several years.

National health agencies

*** If a clinical trial concerns a new regulated drug or medical device (or an existing drug for a new purpose), the appropriate regulatory agency for each country where the sponsor wishes to sell the drug or device is supposed to review all study data before allowing the drug/device to proceed to the next phase, or to be marketed. However, if the sponsor withholds negative data, or misrepresents data it has acquired from clinical trials, the regulatory agency may make the wrong decision.**

*** In the U.S., the FDA can audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data). Different countries have different regulatory requirements and enforcement abilities. An estimated 40 percent of all clinical trials now take place in Asia, Eastern Europe, central and south America.**

Economics:

Sponsor:

The cost of a study depends on many factors, especially the number of sites that are conducting the study, the number of patients required, and whether the study treatment is already ap

study staff at all locations is responsible for informing the coordinating investigator of anything unexpected.

* The local investigator is responsible for being truthful to the local IRB in all communications relating to the study.

IRB:

Approval by an IRB, or ethics board, is necessary before all but the most informal medical research can begin.

* In commercial clinical trials, the study protocol is not approved by an IRB before the sponsor recruits sites to conduct the trial. However, the study protocol and procedures have been tailored to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol, the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in-house IRBs.

* The IRB scrutinizes the study for both medical safety and protection of the subjects/patients involved in the study, before it allows the researcher to begin the study. It may require changes in study procedures or in the explanations given to the subjects/patient.

Regulatory agencies:

cian investigator believes that the study treatment may be harming subjects in the study, the investigator can stop participating at any time.

* The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study.

* The local investigator or his/her study staff are responsible for ensuring that potential subjects in the study understand the risks and potential benefits of participating in the study; in other words, that they (or their legally authorized representatives) give truly informed consent.

* The local investigators are responsible for reviewing all adverse event reports sent by the sponsor. (These adverse event reports contain the opinion of both the investigator at the site where the adverse event occurred, and the sponsor, regarding the relationship of the adverse event to the study treatments). The local investigators are responsible for making an independent judgment of these reports, and promptly informing the local IRB of all serious and study-treatment-related adverse events.

* When a local investigator is the sponsor, there may not be formal adverse event reports, but

seems to be causing unexpected and study-related serious adverse events.

* The sponsor is responsible for collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment. This is an area where sponsors can slant their judgment to favor the study treatment.

* The sponsor and the local site investigators are jointly responsible for writing a site-specific informed consent that accurately informs the potential subjects of the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language. FDA regulations and ICH guidelines both require that " the information that is given to the subject or the representative shall be in language understandable to the subject or the representative." If the participant's native language is not English, the sponsor must translate the informed consent into the participant language.

Local site investigators:

* A physician's first duty is to his/her subjects/ patients, and if a physi

women, and/or women who become pregnant during the study. In some cases the male partners of these women are also excluded or required to take birth control measures.

* Throughout the clinical trial, the sponsor is responsible for accurately informing the local site investigators of the true historical safety record of the drug, device or other medical treatments to be tested, and of any potential interactions of the study treatment(s) with already approved medical treatments. This allows the local investigators to make an informed judgment on whether to participate in the study or not.

* The sponsor is responsible for monitoring the results of the study as they come in from the various sites, as the trial proceeds. In larger clinical trials, a sponsor will use the services of a Data Monitoring Committee (DMC, known in the U.S. as a Data Safety Monitoring Board). This is an independent group of clinicians and statisticians. The DMC meets periodically to review the unblinded data that the sponsor has received so far. The DMC has the power to recommend termination of the study based on their review, for example if the study treatment is causing more deaths than the standard treatment, or

main functions is ensuring that potential subjects/patients are adequately informed about the clinical trial. If the patient is unable to consent for him/herself, researchers can seek consent from the subject/patient's legally authorized representative.

The local IRB must certify researchers and their staff before they can conduct clinical trials. They must understand the local subject/patient privacy law and good clinical practice. International Conference of Harmonization Guidelines for Good Clinical Practice (ICH GCP) is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure that the "rights, safety and well being of trial subjects are protected".

Safety:

Responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study, and (in some cases, if the study involves a marketable drug or device) the regulatory agency for the country where the drug or device will be sold.

Sponsor:

* For safety reasons, many clinical trials of drugs are designed to exclude women of childbearing age, pregnant

Clinical Studies

Part 2

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Ethical considerations:

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. This committee is called the Institutional Review Board (IRB). Most IRBs are located at the local investigator's hospital or institution.

To be ethical, researchers must obtain the full and informed consent of participating human subjects. One of the IRB's

توزع (نشرة الدواء العربي) مجاناً على الجهات التالية :

- وزارات الصحة العربية.
- الجامعات وكليات الطب والصيدلة في جميع أرجاء الوطن العربي.
- المكتبات العامة في جميع الأقطار العربية.
- شركات الأدوية العربية.
- إتحادات ونقابات المهن الطبية العربية.

نموذج إشتراك مجاني
(بنشرة الدواء العربي)

السيد / رئيس هيئة التحرير المحترم ،

يرجى إدراج اسمي بقائمة المشتركين (بنشرة الدواء العربي) ، وتزويدي بصفة منتظمة بنسخة من النشرة (مجاناً) على العنوان التالي :

الاسم والشهرة : _____

المؤهل العلمي : _____ الوظيفة : _____

المؤسسة : _____

المدينة : _____ البلد : _____

رقم الهاتف : _____ رقم الفاكس : _____

العنوان الالكتروني : _____

ص.ب : _____ الرمز البريدي : _____

ملاحظة :

في حالة تغيير العنوان أو إحدى البيانات المذكورة أعلاه يرجى إشعار رئيس هيئة التحرير بذلك على عنوان النشرة:

ص.ب 925161 عمان 11190 الاردن . فاكس : 5821 649 . e-mail: acdima@go.com.jo

شروط النشر في الدواء العربي

- تقبل جميع المقالات والمواضيع العلمية المتعلقة بالدواء والصناعات الدوائية والمستلزمات الطبية إضافة الى المقالات الإقتصادية والإدارية، وتخضع جميع المواد المقدمة للنشر للتقييم من قبل المختصين وفقا لسياسة النشر.
- تقدم المقالات أو المواضيع مطبوعة على البريد الأليكتروني وتكون الصور المرفقة واضحة.
- ضرورة الإشارة الى مصادر البحث أو الدراسة وتتبع الطريقة التالية في توثيق المعلومات.

أ - الكتب:

إسم المؤلف، العنوان، مكان النشر، الناشر، تاريخ النشر.

ب - الدوريات:

إسم كاتب المقال: عنوان المقال، عنوان المجلد، المجلد، السنة، الصفحة.

- لا تلتزم النشرة برد المقالات التي لا تنشر.
- ترسل المقالات والمواضيع الى: نشرة الدواء العربي -

الشركة العربية للصناعات الدوالية والمستلزمات الطبية «أكديما»

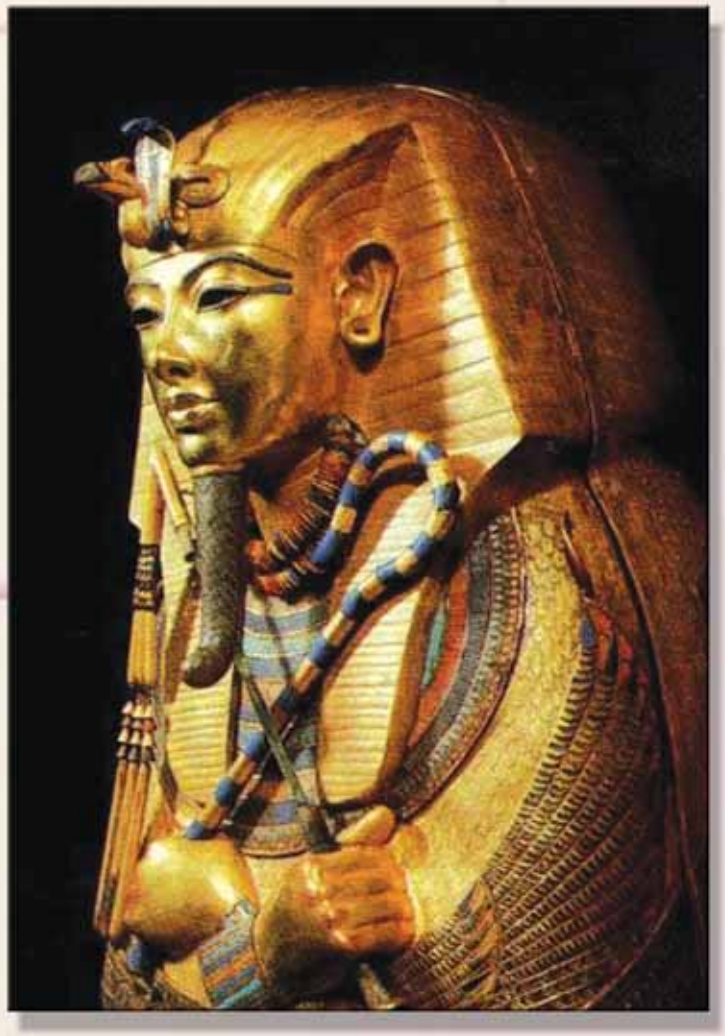
ص.ب 925161 عمان 11190 الاردن

E-mail: acdima@go.com.jo

تصرف مكافآت مالية جيدة للمقالات التي تنشر

الإشراف الفني والإخراج

سامي عبد الحليم إبراهيم



تابوت الملك توت عنخ آمون / المتحف المصري - جمهورية مصر العربية