Direct-to-Consumer-Advertising (DTCA) of Angioplasty and Stents For Chronic Angina:

Public Statement for the Record

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Over 12 million Americans (and hundreds of millions worldwide) suffer from chronic angina pectoris (chest discomfort) due to the progressive "hardening of the arteries process", known as atherosclerosis, that either gradually restricts blood flow to heart muscle causing angina or, in its more malignant expression, abruptly blocks flow to a portion of heart muscle, resulting in a myocardial infarction (MI), or heart attack. Three treatment approaches exist to treat both angina and MI: medical therapy (agents such as aspirin, beta-blockers, statins, and blood pressure-lowering treatments like ACE inhibitors); coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI), more commonly known as coronary angioplasty with stents to prop (and keep) open narrowed coronary arteries. PCI is life-saving when used emergently for acute MI; medical therapy for heart attack (often using blood clot-busting drugs known as thrombolytics) is less effective, while CABG surgery acutely is rarely employed and is probably more dangerous in an emergent heart attack situation. Thus, for the treatment of acute MI, PCI has become the accepted and preferred approach to management.

By contrast, about one-half of all patients with atherosclerosis have more chronic forms of angina that are not emergent indications for PCI or CABG surgery. Because PCI and stents can be performed both safely and effectively in heart attack patients and in the larger population of patients with so-called "stable coronary artery disease" who typically manifest chest pain symptoms of angina with exertion, there has been a prevalent belief among both physicians (cardiologists, internists, primary care physicians) and patients (including lay public health consumers without known heart disease) that PCI is equally effective for reducing death, recurrent heart attack and recurrent hospitalizations for chest pain in both heart attack and angina patients.

PCI represents a multi-billion dollar industry that supports significantly both hospital and physician revenues. In a competitive marketplace, stent manufacturers and the device industry now appear poised to bring the marketing and advertising of such interventions into the living rooms of Americans through television-based direct-to-consumer-advertising (DTCA) to the lay public.

Background and History of DTCA

DTCA is generally described as any promotional effort by pharmaceutical companies to present prescription drug information to the general public through the lay media.[1] Such ads, which may appear in newspapers, magazines, non-medical journals, pharmacy brochures, direct mail letters, and on television, radio and Internet websites, usually fall into one of three categories:[2]

1. "Product-claim" ads that include a product's name and a therapeutic claim (typically of benefit) about the product.
2. "Help-seeking" ads that promote public health education and discuss a particular disease or health condition, and advise the consumer to "see your doctor", but do not explicitly mention a product's name.
3. "Reminder" ads that call attention to a product's name but make no reference to the health condition the drug is used to treat.

Of these three categories, U.S. Food and Drug Administration (FDA) has the authority to directly regulate only product-claim ads. The regulations require that therapeutic claims not be "false or misleading". For 70 years, Congress has overseen, through the FDA, the

authority to regulate prescription drug advertising which, at that time, consisted primarily of print advertisements in medical journals directed largely toward physicians. The statutory authority for current regulation of DTCA to the consumer public emanated from congressional legislation in 1938, during which the Federal Food, Drug, and Cosmetic Act (FFDCA) outlined the requirements that pharmaceuticals must meet before they could be approved for marketing in the United States.[3] Section 201 of the Act gives the FDA broad authority to consider drugs "misbranded" if their labeling or advertising is false or misleading in any way. In 1962, Congress added Section 502(n) to the Act in order to give the FDA statutory authority to regulate prescription drug labeling and advertising, including DTCA.[4] In effect, the FDA was charged with regulating pharmaceutical effectiveness in addition to regulating safety. Moreover, responsibility for prescription drug advertising was transferred from the Federal Trade Commission, which still regulates advertising for over-the-counter drugs, medical devices, in addition to hospitals, clinics and physicians) to the FDA. Importantly, in the same section of the amendment, Congress ***prohibited*** FDA from "issuing any regulations that would require prior approval of the content of any advertisement," presumably because this would violate constitutional First Amendment rights.

In 1969, FDA issued final regulations governing drug advertising at 21 C.F.R § 202/1.[5] Under these regulations, advertisements must meet four basic attributes: 1) they cannot be false or misleading; 2) they must present a "fair balance" of information about the risks and benefits of using the drug; 3) they must contain "facts" that are "material" to the product's advertised uses; and 4) in general, the advertisement's "brief summary" of the drug must include **every** risk from the product's approved labeling.

In 1985, the FDA emphasized that DTCA must meet the same standards as those aimed at medical professionals. Importantly, the agency regulations differentiated between print and broadcast DTCA product-claim ads. In the former, all risk information, including major side effects, contraindications, and precautions that is contained in the drug's FDA label, must be explicitly divulged. In the latter, only "major risk information" must be directly stated, but such broadcast ads must further direct viewers and listeners to other sources from which they can access complete risk information. This regulatory distinction between print and broadcast ads emanates from the more practical consideration that the latter are exquisitely time-limited (typically 30-60 seconds in duration). Thus, broadcast ads would have to include a much shorter but nonetheless lengthy "major statement" of risks, while also making "adequate provision" for viewers to obtain full FDA-prescribing information.[6]

In 1997, the FDA issued a preliminary "Guidance for Industry" that re-interpreted FDA regulations without actually changing any regulations. Reiterating traditional requirements, the Guidance stated that in addition to be non-deceptive, prescription drug advertising must:

- Present a fair balance between information about effectiveness and information about risk.
- Include a thorough, major statement conveying "all of the product's most important risk information in consumer-friendly language".
- Communicate all information relevant to the product's indication (including limitations to use) in consumer-friendly language.[6]

The new interpretation made clear, however, that the "major statement" in radio and TV ads could be far simpler than what had been previously required. "adequate provision" of required information could be achieved by including a very concise summary of risks and related information (often via voice-over), while identifying sources for more complete information (e.g., an 800 number, an Internet website address, either concurrent print ads or information about specific, publicly accessible locations such as pharmacies; plus a statement that all information is available from all physicians and pharmacists.[6] In the wake of the August 1997 policy change, DTCA continued to accelerate, reaching $1.31 billion in 1998, $1.9 billion in 1999, $2.5 billion in 2000 and $2.7 million in 2001.

DTCA of the Cypher® Stent

On November 22, 2007, during the Dallas Cowboys-New York Jets nationally-televised Thanksgiving Day National Football League game, the first direct-to-consumer advertising (DTCA) campaign of a drug-eluting coronary stent was launched by a device manufacturer. Cordis/Johnson & Johnson, Inc. initiated a 60-second advertisement of their sirolimus stent (known as Cypher™) in a featured segment boldly entitled "Life Wide Open". This marked the dawn of a new era in DTCA within the medical industry which, heretofore, has witnessed a virtual explosion in television advertising of branded pharmaceutical agents to the lay public over the past decade. Such an advertisement may have not seemed surprising or out of place to many consumers regularly exposed to a plethora of DTCA initiatives by way of network and cable broadcasts; yet, it marked a

virtually unprecedented transition of this practice from pharmaceuticals to medical devices. On the surface, the provocative "Life Wide Open" advertisement touting the benefits of the Cypher™ drug-eluting stent (DES) seemed no different from similar television ads espousing the virtues of various prescription-brand drugs directed at acute coronary syndromes, arthritis, depression, prostatic enlargement, restless leg syndrome and, of course, erectile dysfunction. In comparison, however, the "Life Wide Open" DTCA campaign raises new, important questions regarding the net societal benefit of medical advertising to the lay public. Even if there is a general benefit to the unfettered transmission of information in a free society with precedent First Amendment protection, has the medical industry crossed the line in promoting this particular device to millions of individuals who are unable to discern many of the subtle and complex therapeutic issues that even specialists continue to debate?

The Distinction of Drug vs. Device DTCA

Unlike drugs that merely require a physician office visit and an explicit prescription by a provider (physician or physician-extender) that can then be filled by the patient at a pharmacy, a specialized medical device such as the Cypher® stent requires a very sophisticated medical understanding that few individuals in the lay public could realistically expect to gain from a DTCA campaign. During a diagnostic coronary angiogram that might result in a potential PCI procedure, a cardiac patient may likely be in significant pain, medicated with sedatives or analgesics, potentially acutely overwhelmed with the recent disclosure of obstructive coronary artery disease and, thus,

unable to comprehend fully all of the therapeutic implications of which type of stent would be best for him or her in the setting of an operative procedure. It seems difficult, if not impossible, to imagine that a patient would, in the above clinical context, attempt to challenge an interventional cardiologist's judgment and clinical acumen by calling into question which particular stent type (bare metal stent or drug-eluting stent [DES] and, in the latter instance, Cypher® versus Taxus®) should be used. Moreover, many hospitals have explicit vendor agreements and volume incentives that may restrict stent inventory to one particular type of DES or, depending on lesional characteristics, limit the choice of DES to one that fits the appropriate coronary anatomic considerations. It seems highly unlikely that an interventional cardiologist would accede to a patient's request for a particular stent type, based solely on the patient's very limited information derived from a DTCA that touts that one particular DES. Accordingly, it is hard to understand what impact, if any, the DTCA campaign directed at the lay public could, in a meaningful way, influence Cypher® stent usage at the patient level.

FDA Regulatory Authority of DTCA

While extant law and FFDCA regulations do not give FDA prior approval authority for prescription drug advertising, the law does give FDA authority to review the accuracy of claims in a prescription drug's promotion.[7] If the FDA feels that an advertisement for a drug that is before the public does not contain the required information or is "false of misleading", it can respond through a variety of enforcement actions. In most cases, the FDA asks the company to withdraw the violative ad. It can

initiate correspondence to the company (known as an "untitled letter" by the agency), which warns that the advertisement violates the FFDCA. Often, the letter states that the ad is "misleading" because it overstates or guarantees the product's effectiveness, expands the population approved for treatment, or minimizes the risks of the product. The letter typically asks that the ad be stopped immediately.

A more stern correspondence that the FDA can initiate is a "Warning Letter" to the company directed at more serious violations. Warning Letters state that, in addition to stopping the violative activity, the company must take corrective steps by disseminating corrective information to the audience of the violative promotional materials such as physicians, pharmacists, and patients. At times, companies may be required to run ads in the same media to correct misleading information or impressions. Usually, companies respond immediately to both "untitled" and "warning" letters, in part, because companies recognize that not only does FDA act as a watchdog to promote fair balance and content in DTCA, but that manufacturers know that the FDA approves all their new products, their manufacturing methods and facilities, and other essential operations such as clinical trials.

Thus, given that pharmaceutical firms invariably accede to FDA requests to alter or halt advertising claims, the FDA possesses an enormous capacity to resolve difficulties to its satisfaction (i.e., the prompt cessation or alteration of a questioned advertising claim or campaign) without proceeding with litigation or a court challenge, even though the FTC has, for decades, been forced to articulate and defend empirically based standards that can withstand scrutiny in the courts, including First Amendment challenges. While the FDA has never had to defend it policies in court, it is likely that the Supreme Court

would probably provide First Amendment protection to DTCA, given its longstanding support for upholding commercial free speech decisions that are pragmatically based.

As noted previously, while the law explicitly prohibits FDA from requiring pre-publication review and approval of ads, most manufacturers voluntarily choose to submit proposed ads to FDA prior to their public release in order to avoid the expense of pulling an already launched ad campaign. Thus, the voluntary pre-review and after-the-fact system of post-publication review by FDA, absent any new legislative change, provides the FDA with statutory authority to impose requirements on the content of advertisements to ensure that ads provide accurate and unbiased information.

Additionally, Congress could investigate (and potentially replicate) the experience in New Zealand, the only other developed nation that permits DTCA of prescription drugs. In that country, all ads making therapeutic claims for advertised products must first be pre-approved by the Association of New Zealand Advertisers, Therapeutic Advertising Pre-Vetting Service, which promotes an industry-based, self-regulatory advertising framework or code of conduct that encourages fair balance of advertising content. Through Congress' encouragement, FDA could establish an advisory panel under the Federal Advisory Committee Act which could either itself recommend standards for prescription drug ads, or encourage industry to develop a new set of standards for self-regulation.

Alternatively, additional regulatory activity by FDA would require new statutory authority, should Congress decide that there is a need for greater enforcement of standards for DTCA. Such new regulatory authority could include an increase compliance and enforcement tools such that Congress could authorize FDA to impose

punitive sanctions against companies that violate the law, an explicit requirement of re-release review of all DTCA before ads are released to the general public, set limits on the timing and placement of ads such that the long-term risk-to-benefit ratio for new prescription drugs could be more completely defined before millions of people are put at risk or, finally, to ban all DTCA to the lay public. As noted, however, such a complete ban would likely trigger court challenges to First Amendment and commercial speech protections. Alternative possibilities might include a time-limited ban of DTCA of 1-2 years after a new drug has been approved in order to collect additional drug/device safety data, or to explicitly require more prominent disclosures in the ads about the safety of prescription drugs, especially the inherent risks of potential safety concerns of new drugs.

Concerns Relating to Advertising Deception

Accordingly, it is hard to understand what impact, if any, the DTCA campaign directed at the lay public could, in a meaningful way, influence Cypher® stent usage at the patient level. Perhaps more concerning is the fact that the "Life Wide Open" television broadcast campaign implicitly promises a better life ("when you open up your heart, you open up your life") without adequately informing the public, as print ads are required to do, about the totality of possible complications and adverse clinical events that may occur. Why does the Cypher® stent patient education brochure detail all potential serious complications whereas the "Life Wide Open" campaign shows only the potential benefits? Does such a DTCA campaign using the Cypher® stent comply with FDA's existing regulatory requirements of "fair balance" or does it fall significantly short

of these stipulations? Can an unsuspecting lay public place sufficient trust in such a broadcast ad campaign to fully understand the significant risks of the Cypher® (or any) stent that are being only minimally addressed in a 60 second ad? Lastly, as FDA requires, why does the cypherusa.com website fail to adequately address important safety concerns or direct patients to a source of educational information that details comprehensively the entire spectrum of complications, risks and adverse events of the Cypher® stent in a full disclosure fashion?

Concluding Comments

We believe that the FDA should perform a critical post-release review the "Life Wide Open" DTCA in accordance with existing regulatory policy to ensure that Section 502 (n) of the FFDCA, updated and modified in 1969 and re-interpreted for broadcast usage in 1997, meets the basic requirements for non-deceptive prescription drug advertising:

- It must present a fair balance between information about effectiveness and information about risk.
- It must include a thorough, major statement conveying "all of the product's most important risk information in consumer-friendly language".
- It must communicate all information relevant to the product's indication (including limitations to use) in consumer-friendly language.

Additional Recommendations

- FDA should place drugs and devices on the same regulatory footing. DTCA should be required to reflect the evidence-based clinical data that have demonstrated only the proven clinical benefits of the drug or device being advertised. Unsubstantiated therapeutic claims or expert consensus opinion should not constitute an approved basis for DTCA to the lay public.
- Congress should authorize the FDA to adopt the model used to promote DTCA as used in New Zealand by establishing an advisory panel under the Federal Advisory Committee Act that would vet and discuss all DTCA prior to final publication. This could be a multidisciplinary committee with representative membership that would include the drug or device industry, physician specialists, and consumer union representatives. Such a Therapeutic Advertising Pre-Vetting Service would promote a self-regulatory, advertising framework or code of conduct that encourages fair balance of advertising content.
- The FDA could consider establishing a fund in which a certain percentage of "product-claim" advertising revenue would be tithed and re-directed to "help-seeking" ads that promote public health education and heighten public awareness of a particular disease state or health condition (a "see your doctor" that does not explicitly mention a product's name). This would create a methodology for promoting objective, fair, and balanced consumer health education to the lay public devoid of potential commercial bias.
- Consider enacting a ban for the first 2 years on all DTCA of drugs or devices that have been FDA-approved in order to assure that post-marketing surveillance and

Phase IV clinical data acquisition have established an appropriate safety record and profile before they are advertised broadly to the public.

References:

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Table 1A:

Potential Adverse Events Associated with Coronary Stent Placement

(From page 19; "Patient Information Guide for the Cypher Sirolimus-Eluting Coronary Stent", Cordis Corporation , 2005)

- Allergic reaction
- Aneurysm
- Arrhythmia
- Cardiac tamponade
- Death
- Dissection
- Drug reactions to antiplatelet agents, anticoagulants, or contrast media
- Emboli, distal (tissue, air, or thrombotic emboli)
- Embolization, stent
- Emergency CABG surgery
- Failue to deliver the stent to the intended site
- Fever
- Fistulization
- Hemorrhage
- Hypotension/hypertension
- Incomplete stent apposition
- Infection and pain at the intended site
- Myocardial infarction
- Myocardial ischemia
- Occlusion
- Prolonged angina
- Pseudoaneurysm
- Renal failure

- Re-stenosis of stented segment (greater than 50% obstruction)
- Rupture of native coronary artery or bypass graft
- Stent compression
- Stent migration
- Thrombosis (acute, subacute, late)
- Ventricular fibrillation
- Vessel spasm
- Vessel perforation

Table 1B:

Potential Adverse Events Related to Sirolimus

(Following Prolonged Oral Use)

- Abnormal liver function
- Anemia
- Arthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including analphylactic or anaphylactoid reactions
- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Leucopenia
- Lymphoma and other malignancies
- Thrombocytopenia