



TITLE: Taxol-Based Drug-Eluting Stents as an Alternative to Traditional Stenting for Coronary Atherosclerotic Heart Disease

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TAXOL-BASED DRUG-ELUTING STENTS AS AN ALTERNATIVE TO TRADITIONAL STENTING FOR CORONARY ATHEROSCLEROTIC HEART DISEASE (CAD)

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of Taxol-based drug-eluting stents as an alternative to traditional stenting for coronary atherosclerotic heart disease (CAD).

BACKGROUND

Coronary atherosclerotic heart disease (CAD) is the most common cause of cardiovascular disability and death in the United States. In addition, it has major impacts on quality of life including chronic pain, disability and unemployment. Men are more often affected than women with an overall ratio of 4:1, but beyond age 70 the ratio is 1:1 (Massie and Amidon, 2003). Risk factors for coronary artery disease include a positive family history, age, male gender, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity and elevated blood levels of homocysteine and C-reactive protein. Clinical trials have shown that interventions aimed at modifying some of these risk factors (e.g. smoking cessation, lipid reduction and treatment of hypertension) can both prevent CAD and delay its progression and complications.

In addition to risk modification, patients with CAD who develop angina pectoris are treated with a variety of medications (nitrates, beta-blockers, platelet inhibiting agents and calcium blocking agents) or may be offered coronary artery revascularization. The two main revascularization procedures are coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) usually with stenting. The indications for coronary artery revascularization are often debated, but the trend toward using more aggressive interventions has increased as a result of the growing use of coronary angioplasty and stenting (Massie and Amidon, 2003). It is estimated that there will be approximately 2.5 million coronary interventions performed worldwide in 2005 (Kleiman *et al.*, 2003)

Coronary artery stenosis can be effectively dilated by inflation of a balloon under high pressure. The mechanism of dilation involves both rupture of the plaque and remodeling of the vessel. This procedure, once reserved for proximal single vessel disease, is now widely used for patients with multiple lesions and with multi-vessel disease. Although usually initially successful, PCI can be complicated by re-narrowing of the stenosis (restenosis) in 33% of patients (Chong and Cheng, 2004; Garas *et al.*, 2001), often necessitating a repeat procedure. Patients often present with symptoms of recurrent angina, but may be asymptomatic (Kleiman *et al.*, 2003).

This complication has led to the widespread use of intracoronary stents. A review of 150,000 procedures performed at 139 hospitals in the National Cardiovascular Data Registry between 1998 and 2000 found that overall stents were used in 77% of cases, with significant interhospital variability (Anderson *et al.*, 2002). Potential indications for stenting include: 1) prevention of restenosis after PTCA, 2) following direct percutaneous coronary intervention performed for the treatment of an acute MI, 3) for the management of saphenous vein thrombosis, and 4) for the treatment of acute or threatened closure (Holmes *et al.*, 1998). Coronary stents have significantly reduced the rate of restenosis by about half, down to 10%-20% in focal lesions and in vessels > 3.0 mm in diameter. However, in-stent restenosis (ISR) occurs in over 30%-60% of patients with diabetes, in diffuse lesions, in vessels less than 3 mm diameter and in bifurcation lesions (Hiatt *et al* 2002). About 50%-75% of patients with restenosis will experience recurrent ischemic symptoms (Leon and Wong, 1994).

The major factor responsible for in-stent restenosis is thought to be neo-intimal hyperplasia. Neointimal hyperplasia is provoked as a result of mechanical arterial injury and foreign body response to the stent that incites acute and chronic inflammation in the vessel wall. The subsequent elaboration of cytokines and growth factors activates smooth muscle cell migration and proliferation (Hoffman *et al.*, 1996). The majority of restenoses following stenting develop within the first three to four months after the procedure.

DRUG ELUTING STENTS

Stents coated with biocompatible materials (such as gold and carbon), anticoagulants (such as heparin), corticosteroids, and anti-mitotic agents have all been studied in humans or animals for the prevention of restenosis. With the exception of drug-eluting stents, for the most part, the results have been disappointing (Babapulle and Eisenberg 2002). Drug-eluting coronary stents are designed to inhibit growth of new tissue resulting from neo-intimal hyperplasia. Biocompatible polymer stent coatings can be used as a base for binding drugs and other compounds to a stent. Placement of a drug onto a stent with a special polymer coating or positioning a drug-eluting sleeve around a metal stent allows slow drug release over a period of 15-45 days. This delivery method allows for minimal systemic drug release and may reduce the risk of toxicity (Sheiban *et al*2002).

Two drug-eluting stents have now been FDA approved: the sirolimus-eluting stent (CYPHER™, Cordis, a Johnson and Johnson Co.) and a paclitaxel-eluting stent (TAXUS, Boston Scientific). Sirolimus is a potent immunosuppressive agent with anti-inflammatory and anti-proliferative effects. It is a natural fermentation product produced by the fungus *Streptomyces hygroscopicus*, originally found on Easter Island (Degertekin *et al* 2002). The sirolimus-eluting stent utilizes a nonerodable methacrylate copolymer matrix for controlled endovascular delivery of the drug to the arterial tissue. This stent-based drug delivery system provides controlled release of sirolimus over a period of four weeks

(Hiatt *et al* 2002). The sirolimus-eluting stent was reviewed at the CTAF meeting on June 11, 2003 and found to meet CTAF technology assessment review criteria.

PACLITAXEL-ELUTING STENTS

Paclitaxel (Taxol) is a trace compound derived from the Pacific Yew tree (*Taxus brevifolia*) found in the Pacific Northwest and Canada (Sonoda *et al.*, 2003). Paclitaxel and its derivatives are microtubule inhibitors that prevent cell migration and proliferation, thereby interrupting the restenotic cascade at multiple levels (Grube *et al.*, 2002). As a chemotherapeutic agent, paclitaxel is administered at doses more than 3,000 times greater than used for stent delivery.

There are several different paclitaxel-eluting stents in current or past clinical trials or in development (e.g. Honda *et al.*, 2001; Hong *et al.*, 2003; Park *et al.*, 2003), but only the TAXUS™ paclitaxel-eluting stent (Boston Scientific, Natick, MA) is currently FDA approved. This stent utilizes a copolymer carrier system developed to provide homogeneous coverage of the stent platform after deployment (Silber, 2003). The polymer provides controlled biphasic release with an initial burst of paclitaxel followed by lower level release through 10 days. Two release formulations have been studied (slow release and moderate release); both carry the same total dose of 1.0 µg/mm² but the moderate release stent has an 8-fold higher release over the first 10 days than does the slow release (Silber, 2003). The TAXUS™ paclitaxel-eluting stent (Boston Scientific, Natick, MA) is the subject of this review.

TA Criterion 1: The technology must have the appropriate regulatory approval.

The TAXUS™ Express²™ Paclitaxel-Eluting Stent System (Boston Scientific, Natick, MA) received FDA premarket approval on March 4, 2004. The device is indicated for improving luminal diameter for the treatment of de novo lesions <28 mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter. Post market reporting is required on an annual basis.

TA criterion 1 is met

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The published peer reviewed literature examining the use of TAXUS™ paclitaxel-eluting stent to prevent restenosis in humans consists of three randomized clinical trials (Stone *et al.*, 2004; Colombo *et al.*, 2003; Grube *et al* 2002). In

addition, Tanabe *et al.* (2004) and Serruys *et al.* (2004) have reported on findings from serial intravascular ultrasound from patients enrolled in the TAXUS II trial.

Outcomes assessed in these trials include baseline angiographic and intravascular ultrasound evaluation prior to stent placement and at one month, six months and 12 months. Quantitative coronary angiographic end-points include:

- Minimal lumen diameter of the stented segment plus the 5 mm segments proximal and distal to the stent.
- Late lumen loss -- the difference between the post-intervention minimum lumen diameter (MLD) and the MLD at follow-up.
- Restenosis -- stenosis of 50% or more of the luminal diameter.
- Late loss index -- late lumen loss divided by gain in luminal diameter achieved by the procedure.

Angiographic measurements are not always predictive of a patient's symptoms or prognosis. Clinical end-points include major adverse cardiac events (MACE) such as myocardial infarction, death and revascularization of the target lesion or vessel including coronary artery bypass grafting.

There is sufficient evidence to evaluate the safety and efficacy of TAXUS™ paclitaxel-eluting stents.

TA criterion 2 is met

Levels of Evidence: 1, 5.

TA Criterion 3: The technology must improve the net health outcomes.

RANDOMIZED TRIALS: TAXUS™ PACLITAXEL-ELUTING STENTS FOR DE NOVO NATIVE CORONARY LESIONS

Patient Benefits

TAXUS I (Grube *et al* 2002) was a prospective, double-blind, three center study of 61 patients in Germany that compared the safety and feasibility of the TAXUS NIRx™ stent system (n=31) compared with bare NIR™ stents (n=30) (Boston Scientific Corp) for the treatment of de novo or restenotic coronary lesions. Inclusion criteria included lesion lengths ≤ 12 mm, stenosis diameter of 50%-99%, and vessel diameter between 3.0 and 3.5 mm. All patients

were treated with aspirin for 12 months and clopidogrel for 12 months. Clinical evaluation was scheduled at 1, 6, 9 and 12 months after implantation. Angiographic and IVUS imaging was performed before and after the procedure and at six months. The primary end-point was MACE at 30 days. Of the 61 patients enrolled, 2 had restenotic lesions. The six month MACE rate was 0% in the TAXUS group compared with 7% in the control group (P=NS). At 12 months the difference in the MACE rate between the control and TAXUS group was also not significant (3% vs. 10%). At six months, the in-stent binary restenosis rate was 10% (3 of 29 patients) for the control group and 0% (0 of 30) for the TAXUS stent (p=NS). Late lumen loss and IVUS assessment of neointimal hyperplasia significantly favored the TAXUS group. The authors conclude that the inability of the study to identify significant differences between the paclitaxel DES and the control stent may have been due to the small numbers and excellent clinical and angiographic outcomes in the control group.

TAXUS II (Colombo *et al.*, 2003) was a randomized, double-blind trial of 536 patients at 38 medical centers that compared the efficacy and safety of the TAXUS slow-release (SR) and moderate-release (MR) stents with uncoated stents. Two sequential cohorts were randomized 1:1 to either the SR or MR stent or an uncoated stent. The primary end-point was six-month percent in-stent net volume obstruction as measured by intravascular ultrasound (IVUS). Secondary end-points were six-month angiographic restenosis and six and 12-month incidence of major adverse cardiac events (MACE). Angiographic inclusion criteria specified a single de-novo target lesion with estimated stenosis $\geq 50\%$ and $\leq 99\%$, estimated length ≤ 12 mm, and location in a native coronary vessel ≥ 3.0 mm and ≤ 3.5 mm in diameter. Exclusion criteria included coronary intervention within 30 days, LVEF $< 30\%$, evolving myocardial infarction, unprotected left main disease and prespecified need to implant more than one 15 mm stent for full lesion coverage. Mean patient age was around 60 years in all groups and about 15% of control and TAXUS patients were diabetic. At six months, percent net volume obstruction within the stent per IVUS was significantly lower for TAXUS stents (7.9% for SR and 7.8% for MR) compared with respective controls (23.2% and 20.5%; $P < 0.0001$). Angiographic restenosis was also significantly improved in the paclitaxel stent groups. At six months, binary restenosis rates were significantly improved in the TAXUS-SR (20.1% to 5.5%; $p = 0.0001$) and TAXUS-MR (23.8% to 8.6%; $p = 0.001$) groups compared with the control group. Peri-procedural and in-hospital MACE rates were comparable in all groups. MACE rates at six months were significantly lower in the TAXUS-SR (8.5%; $P = 0.0035$) and TAXUS-MR (7.8%; $P = 0.0019$) groups than in the control groups (around 20% in both groups). This reduction in MACE was attributable to lower rates of target-lesion revascularization in the TAXUS groups.

TAXUS IV (Stone *et al.*, 2004) was a prospective, randomized, double-blind, multi-center trial of the TAXUS SR stent compared to a bare metal stent. They enrolled 1314 patients at 73 centers in the U.S. who were receiving a stent in a single, previously untreated coronary artery stenosis. Clinical exclusion criteria included previous or planned use of intravascular brachytherapy in the target vessel or of any drug-eluting stent; myocardial infarction within 72 hours

before enrollment; a left ventricular ejection fraction of less than 25 percent; a serum creatinine level of more than 2.0 mg per deciliter (177 μ mol per liter), a leukocyte count of less than 3500 per cubic millimeter, or a platelet count of less than 100,000 per cubic millimeter. On angiography, patients had to have a single target lesion with a reference-vessel diameter on visual examination of 2.5 to 3.75 mm and a lesion length of 10 to 28 mm that could be covered by a single study stent (though additional study stents could be implanted in the event of edge dissections). Angiographic exclusion criteria included a left main or ostial target lesion, moderate or severe calcification of the target vessel or lesion, tortuosity or angulation, bifurcation of the target lesion (defined by a side branch measuring more than 2.0 mm in diameter with more than 50 percent stenosis), an occluded target lesion or thrombus. The primary end point was the nine-month incidence of ischemia-driven target-vessel revascularization and major adverse cardiac events (MACE). The principal secondary end point was the extent of stenosis of the target lesion at nine months. The average age was about 63 years and about 1/4 of the patients in each cohort were diabetic. The number of stents implanted per patient, the mean length and diameter of the stents, and other deployment and implantation variables were similar in the two groups. At the end of the nine-month follow-up period, the rates of target-vessel failure and major adverse cardiac events were significantly lower in the patients who received a paclitaxel-eluting stent than in those who received a bare-metal stent. The rate of ischemia-driven target-vessel revascularization at nine months was reduced from 12.0 percent with the implantation of a bare-metal stent to 4.7 percent with the implantation of a paclitaxel-eluting stent (relative risk, 0.39; 95 percent confidence interval, 0.26 to 0.59; $p < 0.001$). Target-lesion revascularization was required in 3.0 percent of the group that received a paclitaxel-eluting stent, as compared with 11.3 percent of the group that received a bare-metal stent (relative risk, 0.27; 95 percent confidence interval, 0.16 to 0.43; $p < 0.001$). The rate of angiographic restenosis was reduced from 26.6 percent to 7.9 percent with the paclitaxel-eluting stent (relative risk, 0.30; 95 percent confidence interval, 0.19 to 0.46; $p < 0.001$). Significantly, the risk of restenosis was reduced by more than 80 percent among patients with diabetes who received a paclitaxel-eluting stent, so that these patients and patients without diabetes had similar rates of angiographic recurrence. At nine months, there were no significant differences in death from cardiac causes (1.4% in the paclitaxel stent group vs. 1.1% in the bare-metal stent; $p = \text{NS}$); myocardial infarction (3.5% vs. 3.7%; $p = \text{NS}$); or stent thrombosis (0.6% vs. 0.8%; $p = \text{NS}$).

Pending Trials

TAXUS V is a randomized, multisite trial studying the slow-release formulation in higher risk patients, including patients with smaller vessels and longer lesions requiring multiple stents. In addition, one arm of the trial will compare the TAXUS SR with intracoronary brachytherapy for the treatment of in-stent restenosis. Enrollment began in June 2003. TAXUS VI is an international trial designed to test the safety and efficacy of the MR stent in the treatment of longer lesions, including the use of multiple stents (<http://www.bostonscientific.com>).

Patient Risks

There are a number of potential risks to patients with the use of stents in general and drug-eluting stents in particular. Stenting is now performed in the majority of percutaneous coronary interventions and increasingly in more complex and older patients (Anderson *et al.*, 2002). In spite of the growing uses of stents, the success rate has actually increased. The rate of emergent CABG has fallen to 1.9%; the rate of in-hospital Q-wave MI is 0.4%; and overall mortality is 1.4% (Anderson *et al*2002).

There are a number of early complications of bare-metal stents that may also occur with the drug-eluting stents. These complications include failed delivery with potential stent embolization, stent thrombosis, myocardial infarction (typically non-Q wave), side branch occlusion, bleeding, and death. Failed delivery (or failed stent deployment) is a potentially serious problem, but is infrequent. In a recent review, failed delivery occurred in 0.4-2% of cases (Bolte *et al.*, 2001). Stent thrombosis usually occurs within the first 24 hours (acute) or within 1-4 weeks (subacute) after stent placement (Leon *et al.*, 1994). With second- generation stents and antithrombotic regimens the reported incidence has ranged from 0.9% to 2.5%.

In addition to the above, drug-eluting stents raise a number of different potential risks for patients. Like radioactive stents, paclitaxel inhibits smooth muscle proliferation. Synthetic polymers are often used as carriers and biocompatibility is a concern as polymers may induce an exaggerated inflammatory reaction (Babapulle and Eisenberg 2002). Concerns have also been raised regarding incomplete vessel healing and re-endothelialization, which may lead to an increased risk of late thrombosis (Bartorelli and Trabattoni, 2002) and concerns about potential vascular cytotoxicity. However, the rate of thrombosis seen in the TAXUS and sirolimus trials has not been significantly greater than that seen with the control stents (less than 1% in all RCT's).

TA criterion 3 is met

TA Criterion 4: **The technology must be as beneficial as any established alternatives.**

Other strategies that have been used to prevent in-stent restenosis include radioactive stents (brachytherapy), systemic therapy, and stents coated with other material such as gold and heparin. Intracoronary radiation with ribbons containing gamma or beta radioactive seeds have been found to reduce neo-intimal formation and in-stent stenosis by impairing smooth muscle cell proliferation. However, the long-term efficacy of radioactive stents is uncertain as they may delay but not prevent restenosis. In one study of 40 patients, Kay *et al* (2001) found that repeat catheterization and IVUS at one year demonstrated progression of neointimal hyperplasia primarily in the mid and distal part of the stent; 23% required revascularization.

A variety of systemic pharmacological therapies have been investigated to prevent thrombosis and restenosis after PTCA and after stent implantation (Garas *et al.*, 2001). Anti-platelet agents such as aspirin and ADP receptor antagonists (ticlopidine and clopidogrel) have met with the most success for the prevention of thrombosis, but have had little impact on restenosis. For example, in the Stent Anticoagulation Restenosis Study, aspirin and ticlopidine were found to be better than aspirin alone or aspirin plus warfarin for the prevention of stent thrombosis (Leon *et al.*, 1998). These systemic therapies are likely to be used along with DES to prevent thrombosis. Which drugs and for how long is still being investigated.

Stents coated with other materials have also been studied to prevent stent restenosis. Results thus far have been disappointing. For example, one clinical trial comparing heparin-coated stents with uncoated stents for the prevention of restenosis failed to show a significant difference between the two groups (Babapulle and Eisenberg 2002). Gold-coated stents have not been found to be associated with an improved outcome and may actually increase the amount of neointimal proliferation and restenosis (Park *et al.*, 2002).

To date, TAXUS™ paclitaxel-eluting stents and sirolimus-eluting stents have been shown to safely and effectively improve clinical outcomes associated with decreased restenosis rates.

TA criterion 4 is met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Drug-eluting stents are macroscopically indistinguishable from the standard stents currently being used around the world. Unlike radioactive stents, they require no special handling and no special training is needed.

TA criterion 5 is met.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center Medical Advisory Panel had not reviewed this topic at the time of this review.

American College of Cardiology (ACC) – California Chapter

The ACC provided representation and testimony at the meeting in support of the use of this drug-eluting stent.

Centers for Medicare and Medicaid Services (CMS)

CMS has made a decision to establish a new APC for procedures that use drug-eluting stents.

Society of Cardiac Angiography and Interventions (SCAI)

The SCAI was not able to provide representation at the meeting but supplied the following comment:

In March 2003, the SCAI published a position statement on the practice and health care delivery implications of DES.

"Based on the limited available data and lack of practical experience with DES use, SCAI recommends an evidence-based adoption strategy recognizing that physicians are concerned about offering the best possible patient care. Intervention should be employed only after documentation of the clinical and/or physiologic significance of individual lesions. The patient's physician should make this assessment based on objective evidence.

DES have shown significant reductions in restenosis in each group in which they have been formally tested. These include diabetics, LAD stenosis, small vessels, and both short and relatively long lesions. Some subgroups for which there are few data include patients with saphenous vein graft disease, bifurcation lesions, very small or very large arteries, prior brachytherapy, in-stent restenosis, and acute myocardial infarction. A large spectrum of the coronary disease population will have benefit from reduced recurrence rates after treatment with DES. However, there remain patients for whom this therapy requires further study."

CONCLUSION

Coronary atherosclerotic heart disease (CAD) is the most common cause of cardiovascular disability and death in the United States. Patients with CAD are often treated with a variety of medications (nitrates, beta-blockers, platelet-inhibiting agents and calcium blocking agents) and may be offered coronary artery revascularization. The two main revascularization procedures are coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) usually with stenting. While intracoronary stents have reduced the rate of stenosis following PTCA by about half, in-stent stenosis continues to be an important problem, especially for patients with diabetes, or in smaller vessels. The search for an effective method to reduce in-stent restenosis has taken on an almost religious fervor in the cardiology community, leading one paper to describe it as: “(the) quest for the Holy Grail” (Hiatt *et al* 2002).

As a result, there has been an explosion of interest in drug-eluting stents for the prevention of in-stent restenosis. Stents coated with a variety of antimitotic agents have been tested in humans or are currently in clinical trials. Each of these agents has different mechanisms of action and potential adverse effects and toxicities so will have to be evaluated in separate clinical trials and approved for use individually. Currently, the two agents that have been the most rigorously studied are sirolimus and paclitaxel. Sirolimus-eluting stents were reviewed in June 2003 and found to meet CTAF criteria.

The TAXUS trials published to date (particularly TAXUS IV) now have established the safety and efficacy of the paclitaxel eluting stent when used for a single, previously untreated coronary artery stenosis. TAXUS IV was a prospective, randomized, double-blind study; the implantation of a slow-release, polymer-based, paclitaxel-eluting stent markedly reduced the risk of clinical and angiographic restenosis as compared with the implantation of a bare-metal stent in patients with a wide range of previously untreated coronary lesions. About 1/4 of the patients in TAXUS IV were diabetic; a group that generally has high rates of stent restenosis. In addition, for patients with small coronary arteries (no more than 2.5 mm in diameter) and long lesions (longer than 20 mm) the benefits of the paclitaxel-eluting stent were particularly evident. The TAXUS paclitaxel-eluting stents have been found to be as safe as bare-metal stents in selected patients.

Patients in TAXUS IV had a single target lesion with a reference-vessel diameter on visual examination of 2.5 to 3.75 mm and a lesion length of 10 to 28 mm that could be covered by a single study stent (though additional study stents could be implanted in the event of edge dissections). Angiographic exclusion criteria included a left main or ostial target lesion, moderate or severe calcification of the target vessel or lesion, tortuosity or angulation, bifurcation of the target lesion (defined by a side branch measuring more than 2.0 mm in diameter with more than 50 percent stenosis), and an occluded target lesion or thrombus.

Patient selection for drug-eluting stents will continue to be more clearly delineated by future research. In the TAXUS IV trial, the paclitaxel-eluting stent was very effective even in traditionally high restenosis risk subgroups such as diabetics, and in vessels less than 3 mm. Further trials will be required to determine the role of these stents in patients with bifurcation disease, chronic total occlusions, saphenous vein graft disease, left main lesions and multi-vessel disease.

RECOMMENDATION

It is recommended that TAXUS™ paclitaxel-eluting stents for de novo native coronary lesions for patients with angina pectoris or silent ischemia and greater than 50 percent de novo stenosis of 10 mm – 28 mm in length, of one or more native coronary arteries with a diameter ≥ 2.5 mm and ≤ 3.75 mm meet California Technology Assessment Forum TA criteria.

TAXUS™ paclitaxel-eluting stents for treatment of stenotic lesions of the left main coronary artery; for treatment of stenotic lesions of non-coronary arteries such as saphenous vein grafts; for in-stent restenosis; for treatment of non-atherosclerotic anatomies (i.e. thrombotic lesions associated with acute MI); for bifurcation lesions; or for prior brachytherapy; and other paclitaxel drug-eluting stents do not meet California Technology Assessment Forum TA criteria.

The California Technology Assessment Forum approved the recommendation as presented.

June 9, 2004

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