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In Re: Patent Term Extension
Application for
U.S. Patent No. 5,811,447

FINAL DETERMINATION DENYING PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156 FOR U.S. PATENT NO. 5,811,447

This is in response to the Request for Reconsideration (Request for Recon) filed on November 16, 2015, of the denial of patent term extension mailed October 16, 2015, regarding the patent term extension application for U.S. Patent No. 5,811,447 (the '447 patent). The Request for Recon is in support of an application for extension of the patent term (PTE application) of the '447 patent under 35 U.S.C. § 156 that was filed in the United States Patent and Trademark Office on December 7, 2012. The PTE application was filed by Angiotech Pharmaceuticals Inc. (Applicant), on behalf of Boston Scientific Scimed, Inc., the patent owner of record. Extension is sought based upon the premarket review under section 515 of the Federal Food, Drug, and Cosmetic Act (FFDCA) of a medical device known by the tradename ZILVER® PTX Drug Eluting Peripheral Stent. The ZILVER® PTX Drug Eluting Peripheral Stent was approved for commercial use and sale by the Food and Drug Administration (FDA) on November 14, 2012.

A determination has been made that the '447 patent is **NOT** eligible for patent term extension under 35 U.S.C. § 156 based upon the regulatory review period of ZILVER® PTX Drug Eluting Peripheral Stent. Therefore, Applicant's PTE application is **DENIED**.

A. PROCEDURAL BACKGROUND

(1) On September 22, 1998, the USPTO issued the '447 patent to Lawrence L. Kunz et al. The '447 patent was originally assigned to NeoRx Corporation.

(2) On November 14, 2012, FDA approved Premarket Approval Application (PMA) No. P100022, thereby granting permission for commercial marketing or use of the ZILVER® PTX Drug Eluting Peripheral Stent.

(3) On December 7, 2012, Applicant filed a PTE Application under 35 U.S.C. § 156(d)(1) to extend the term of the '447 patent based on FDA regulatory review of ZILVER® PTX Drug Eluting Peripheral Stent.

(4) On February 28, 2013, Applicant filed a supplement to its PTE application.

(5) On June 11, 2013, USPTO sent a Requirement for Information to the Applicant pursuant to 37 C.F.R. § 1.750 seeking evidence that Boston Scientific Scimed Inc., through its

agent Angiotech Pharmaceutical, was authorized by Cook Medical Technologies, Inc., the marketing applicant before the FDA, to rely upon the premarket regulatory review activities of Cook Medical Technologies in seeking extension of the '447 patent.

(6) On January 10, 2014, Applicant provided a response to the Requirement for Information including an express authorization from Cook.

(7) On March 13, 2015, pursuant to the Memorandum of Understanding Between the USPTO and the FDA, see 52 Fed. Reg. 17830, May 12, 1987, the USPTO requested assistance from the FDA ("USPTO Letter to FDA") in determining eligibility of the '447 patent for patent term extension based on the regulatory review period of ZILVER® PTX Drug Eluting Peripheral Stent.

(8) On March 23, 2015, USPTO sent a Requirement for Information (RFI) to Applicant seeking information about (1) how the '447 patent claims a method of using the medical device subject to regulatory review under section 515 of the FFDCA, and consequently, (2) whether the amount of paclitaxel present in the ZILVER® PTX Drug Eluting Peripheral Stent is administered "in an amount and for a period of time effective to inhibit the contraction or migration of vascular smooth muscle cells" to achieve the recited "method of biological stenting."

(9) On May 11, 2015, the FDA communicated its findings to the USPTO. The FDA indicated that ZILVER® PTX Drug Eluting Peripheral Stent had been subject to regulatory review under PMA P100022 in accordance with section 515 of the FFDCA, and confirmed that approval of PMA P100022 did represent the first permitted commercial marketing or use of the product subject to regulatory review.

(10) On June 19, 2015, the Applicant timely filed the Response-RFI arguing that at least claim 12 of the '447 patent claims a method of using the approved product.

(11) On June 19, 2015, Applicant timely filed a request for interim extension under 35 U.S.C. § 156(e)(2).

(12) On September 17, 2015, USPTO granted an interim extension for a period of three months from the original expiration date of the '447 patent.

(13) On October 16, 2015, USPTO issued a denial of Applicant's PTE application, the entire contents of which are expressly incorporated herein.

(14) During a follow-up call with Applicant's representative, Applicant inquired whether, pursuant to 37 C.F.R. 1.750, a Request for Reconsideration of the denial of October 16, 2015, would be permitted. The USPTO explained that, in accordance with the guidance set forth in the MPEP 2755, such a request would be considered. However, the USPTO

informed Applicant that unless the PTE application were found eligible, no additional interim extensions under 35 U.S.C. 156(e)(2) would be available. Therefore, the decision of October 16, 2015 was a final agency decision such that judicial review could have been sought prior to patent expiry.

(14) On November 16, 2015, Applicant submitted the Request for Recon, a request for a second interim extension and a request that the patent term extension be granted.

B. DECISION

The USPTO has considered the arguments made by Applicant in the Request for Recon and finds that, contrary thereto, the '447 patent does not claim a method of using the ZILVER® PTX Drug Eluting Peripheral Stent, the device subject to regulatory review under PMA P100022, where the term "device" is as defined in section 201(h) of the FFDCA. This present decision incorporates the USPTO's previous decision of October 16, 2015. Therefore, the PTE application for the '447 patent is **DENIED**.

At the outset, it appears that Applicant attempts to recharacterize the approved product, ZILVER® PTX Drug Eluting Peripheral Stent, as a "drug product" rather than a "medical device" by referring to it throughout the Request for Recon as the "ZILVER controlled-delivery system." Request for Recon at 2 *et seq.* But referring to the approved product as a "controlled delivery system" does not change the nature of the product. FDA reviewed and approved the ZILVER® PTX Drug Eluting Peripheral Stent as a "medical device" under section 515 of the FFDCA; FDA did not consider the stent a "drug product" under section 505 of the FFDCA. Thus, the approved "medical device" is a drug-eluting stent, not a "controlled delivery system" for paxlitaxel. And FDA has indicated that drug-eluting stents, which comprise both a device component and a drug component, are "medical devices" to be reviewed under section 515 of the FFDCA. FDA has made this determination because, as they reasoned, "the uncoated stent functions to physically maintain vessel lumen patency, while the drug component has played a secondary role in preventing restenosis, augmenting the safety and/or effectiveness of the uncoated stent."[1]

There are several bases for the conclusion that the approved product is a stent, and in particular a drug-eluting stent that acts to impart an outward radial force upon the inner lumen of an affected vessel to establish patency.[2] First, as disclosed by Applicant in its original PTE application, the product is a drug-eluting stent that is "a flexible, slotted tube made of nitinol, *i.e.*,

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[1]See http://www.fda.gov/combinationproducts/jurisdictionalinformation/jurisdictionalupdates/ucm106552.htm (copy attached-Exhibit 1).

[2]Page 3 of product labeling as included in decision of October 16, 2015.

nickel titanium, and coated with paclitaxel." PTE application at page 2.

Second, as discussed in the decision of October 16, 2015, which is expressly incorporated by reference, the FDA-approved labeling for the ZILVER® PTX Drug Eluting Peripheral Stent describes the medical device as:

> The ZILVER PTX-Drug Eluting Peripheral Stent is a self-expanding stent made of nitinol and coated with the drug paclitaxel. It is a flexible, slotted tube that is designed to provide support while maintaining flexibility in the vessel upon deployment. Post-deployment, **the stent is designed to impart an outward radial force upon the inner lumen of the vessel, establishing patency in the stented region**.

Labeling at 3 (Copy in October 16, 2015 decision, emphasis added). Clearly the label for the ZILVER® PTX Drug Eluting Peripheral Stent indicates that the stent, after expanding in the vessel, achieves patency.

Third, part of the brief overview of the information related to the FDA's approval of PMA P1000022, found at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm330293.htm (copy attached as Exhibit 2), describes how the ZILVER® PTX Drug Eluting Peripheral Stent works. Specifically, the information states, "[t]he ZILVER® PTX stent remains in the artery permanently acting as a support (scaffold) to hold the artery open so blood can flow through the artery." The overview also describes the role of paclitaxel in preventing restenosis by stating, "[t]he paclitaxel coating helps prevent the artery from narrowing again."

Fourth, Cook Medical, the sponsor of the PMA for the ZILVER® PTX Drug Eluting Peripheral Stent, in its own Patient Guide (copy attached as Exhibit 3) describes the procedure for surgical placement of the ZILVER® PTX Drug Eluting Peripheral Stent. That Patient Guide describes deployment of the ZILVER® PTX Drug Eluting Peripheral Stent to an affected vessel and states that the "stent expands and stays in place to keep the artery open after the catheter is withdrawn." Patient Guide at page 6.

Thus, it is clear, not only from Applicant's description of the product, but also from the Patient Guide and the overview of the approval from FDA, that the approved product is a drug-eluting stent ("medical device") that acts to open an occluded vessel by physically expanding in the affected area.

I. Claim 12 of the '447 patent does not claim a method of using the ZILVER® PTX Drug Eluting Peripheral Stent

A predicate to finding a patent eligible for patent term extension based on FDA review of

a product subject to premarket regulatory review ("a regulated product") requires that the patent claim the product, a method of using the product or a method of manufacturing the product. Here, the regulatory review period was conducted under section 515 of the FFDCA. Where FDA reviews a regulated product under section 515 of the FFDCA, the regulated product is a medical device.[3] Therefore, substituting that term into 35 U.S.C. § 156(a) yields, "(a) [t]he term of a patent which claims a [medical device], a method of using a [medical device], or a method of manufacturing a [medical device] shall be extended . . . ." Because claim 12 is directed to a method of biologically stenting a mammalian blood vessel, Applicant and USPTO agree that eligibility rests on whether claim 12 of the '447 patent claims a method of using the approved medical device. In other words, it is undisputed that claim 12 does not claim the approved medical device itself or a method of manufacturing the approved medical device.

Because the review of the ZILVER® PTX Drug Eluting Peripheral Stent was under section 515 of the FFDCA and not section 505 of the FFDCA, the method of using the approved product (medical device) must be a method of using:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, **and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes**.

See section 201(h) of the FFDCA (emphasis added).

Applicant asserts that the '447 patent claims a method of using the ZILVER® PTX Drug Eluting Peripheral Stent. Applicant asserts that the USPTO inappropriately ignores paclitaxel

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[3]See http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm (copy attached-Exhibit 4) indicating that "[p]remarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance." (Copy attached).

administration by the device and focuses solely on the structural features of the ZILVER® PTX Drug Eluting Peripheral Stent. Specifically, Applicant states that the USPTO has pointed to no authority for requiring that the structural features of the stent be positively recited in claim 12. Request for Recon at 8-9.

The USPTO responds that the proper inquiry of whether the '447 patent claims a method of using the ZILVER® PTX Drug Eluting Peripheral Stent must focus on whether claim 12 recites a method of using a "medical device" as statutorily defined. And the statutory definition of a "medical device," as found in section 201(h) of the FFDCA focuses on the structural features of the device (*i.e.*, "an instrument, apparatus . . .") and specifically excludes a medical device that would "**achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is dependent upon being metabolized for the achievement of any of its primary intended purposes**." .

Claim 12 of the '447 patent recites:

> A method for biologically stenting a mammalian blood vessel, which method comprises administering to the blood vessel of a mammal a cytoskeletal inhibitor in an amount and for a period of time effective to inhibit the contraction or migration of the vascular smooth muscle cells.

Applicant points out that it is clear from the written description of the '447 patent that claim 12 encompasses the local administration of drugs to the blood vessel wall. Request for Recon at 4. The USPTO agrees with this statement. However, that claim 12 encompasses local administration of drugs to the blood vessel wall does not answer the question of whether claim 12 claims a method of using a medical device. The complete inquiry must ask whether claim 12 claims a method of using a drug-eluting stent, such as the ZILVER® PTX Drug Eluting Peripheral Stent, because the product subject to regulatory review was a medical device. A medical device is defined under section 201(h) of the FFDCA, *see infra*. And here, claim 12 does not recite any structural features of a medical device. And claim 12 recites a method whereby the primary purpose ("biological stenting") is achieved via chemical action. Thus, based on the definition of medical device at section 201(h) of the FFDCA and the requirement that such an approved product "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes," the USPTO does not find sufficient support in the claim language of claim 12 or the written description of the '447 patent to find that claim 12 claims a method of using a drug-eluting stent, such as the ZILVER® PTX Drug Eluting Peripheral Stent.

Turning to construction of the term "comprising" as that term is used in claim 12, Applicant states that the term "comprising" indicates that other steps may be included. The USPTO does not disagree with this statement. However, a method of biologically stenting, which fails to describe a method of using a drug-eluting stent in any instance, does not claim a

method of using the ZILVER® PTX Drug Eluting Peripheral Stent. At most, claim 12 encompasses a method of using paclitaxel. But the approval of the ZILVER® PTX Drug Eluting Peripheral Stent was not under section 505 of the FFDCA as a "drug product" that administered paclitaxel. Instead, as pointed out above, and in the previous decision from October 16, 2015, the approval of ZILVER® PTX Drug Eluting Peripheral Stent was pursuant to section 515 of the FFDCA, which means that the approved product is a medical device and as such, "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Applicant states that claim 12 expressly encompasses biological stenting by administering paclitaxel. Request for Recon at 9. Applicant's argument as to the term "comprising" would have the USPTO consider that even though no single mention of a drug-eluting stent is described in the entire written description of the '447 patent, somehow claim 12, because it uses "comprising" which is construed as "open language," includes physical stenting in addition to biological stenting. As previously pointed out in the decision from October 16, 2015, there is no written description of a drug-eluting stent found within the written description of the '447 patent document, and therefore no evidence that the inventors of the subject matter described in the '447 patent actually invented or had possession of a drug-eluting stent.

Applicant asserts that claim 12 "clearly contemplates" the local and sustained administration of the cytoskeletal inhibitor in conjunction with a physical angioplasty procedure that "can include placement of a physical stent." The USPTO does not agree that the claim "clearly contemplates" the placement of a physical stent. The only recitation of "stent" in the entire specification (aside from the term "biological stenting") defines the patient population that may benefit from a method of biological stenting. Applicant relies on that language. Specifically, Applicant cites to column 30, lines 36-44, which states:

> In a preferred aspect, the infusion catheter may be conveniently a double balloon or quadruple balloon catheter with a permeable membrane. In one representative embodiment, a therapeutically effective dosage of a therapeutic conjugate or dosage form is useful in treating vascular trauma resulting from disease (e.g., atherosclerosis, aneurysm, or the like) or vascular surgical procedures such as angioplasty, atheroectomy, placement of a stent (e.g., in a vessel), thrombectomy, and grafting.

Applicant concludes that this recitation means that the method of biological stenting "clearly contemplates" placement of a physical stent. But the above recitation from the specification does not describe a method of using a drug-eluting stent such as the ZILVER® PTX Drug Eluting Peripheral Stent. At most, it contemplates that **after** vascular trauma, for example, **after** placement of a stent, an infusion catheter could be used to administer a drug product to the vessel.

Thus, this portion of the specification does not support Applicant's argument that the

specification supports delivery of a cytoskeletal inhibitor to a mammalian blood vessel via a drug-eluting stent. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

II. The Federal Circuit decision in Hoeschet-Roussel Pharmaceuticals is Directly on Point

Applicant argues that the Federal Circuit decision in *Hoescht-Roussel Pharma v. Lehman*, 109 F.3d 756, 42 U.S.P.D.2d 1220 (Fed. Cir 1997) is inapplicable because the facts of *Hoescht* are "entirely different than the present facts." Request for Recon at 11. The USPTO agrees that the present facts are not *exactly* the same as those presented in *Hoescht*. But the USPTO's decision from October 16, 2015 did not rely on *Hoescht* because the present PTE application presents an exactly the same fact pattern. Rather, the USPTO relies on *Hoescht* for the Court's legal conclusion that "the concept of a 'claim' is different from the concept of infringement, and, as a result, the plain meaning of 'claims' is not the same as the plain meaning of infringement." 109 F.3d at 759.

In the present case, claim 12 does not claim a method of using a drug-eluting stent such as the ZILVER® PTX Drug Eluting Peripheral Stent. Instead claim 12 is directed to a method of biological stenting, which Applicant acknowledges is achieved by the targeted administration of a pharmacological agent. Request for Recon at 4. Applicant has failed to cite to any written description in the '447 patent which describes using a drug-eluting stent for (1) biological stenting; (2) administering paclitaxel or (3) physically stenting an occluded vessel. As has been described by several sources, *infra*, the ZILVER® PTX Drug Eluting Peripheral Stent acts to open an occluded vessel by "impart[ing] an outward radial force upon the inner lumen of an affected vessel to establish patency." Thus, even if *arguendo* the use of the ZILVER® PTX Drug Eluting Peripheral Stent might *infringe* claim 12 (because the stent delivers paclitaxil to a blood vessel), claim 12 does not *claim* a method of using ZILVER ® PTX Drug Eluting Peripheral Stent.

Applicant would have the USPTO ignore the claimed method and focus solely on a single step of claim 12. Specifically, Applicant indicates that the ZILVER® PTX Drug Eluting Peripheral Stent accomplishes "administering to the blood vessel of a mammal a cystoskeletal inhibitor." The USPTO does not disagree that the ZILVER® PTX Drug Eluting Peripheral Stent does administer paclitaxel to the blood vessel of a mammal. However, Applicant appears to ignore the preamble of the claim which is that the claim is a method of biologically stenting, which Applicant acknowledges is different from physical stenting. See Request for Recon at 9 (indicating that "comprising" means other steps may be included and that "there is nothing that precludes achieving biological stenting in conjunction with physical stenting"). As previously discussed, however, the approved product "impart[s] an outward radial force upon the inner lumen of an affected vessel to establish patency." Such an action constitutes physical stenting.

Again, the use of the ZILVER® PTX Drug Eluting Peripheral Stent might *arguendo* infringe "[a] method for biologically stenting a mammalian blood vessel, which method comprises administering to the blood vessel of a mammal a cytoskeletal inhibitor in an amount and for a period of time effective to inhibit the contraction or migration of the vascular smooth muscle cells," if the claim is read broadly enough to cover subject matter not described in the '447 patent. But infringement is unlikely because the literature, the description by Cook Medical (in the marketing applicant before FDA), the FDA, and the Applicant all indicate that the ZILVER® PTX Drug Eluting Peripheral Stent achieves stenting by acting as a support (scaffold) to hold the artery open so blood can flow through the artery and that the inclusion of paclitaxel on the stent structure acts to treat restenosis, just as FDA has concluded regarding a drug component in a drug-eluting stent in its Jurisdictional Update: Drug-Eluting Cardiovascular Stents."[4]

Thus, for the proposition that "the concept of a 'claim' is different from the concept of infringement, and, as a result, the plain meaning of 'claims' is not the same as the plain meaning of infringement," *Hoescht* is directly on point to the present case since, at most, the present claim might be infringed by the use of a drug-eluting stent such as the ZILVER® PTX Drug Eluting Peripheral Stent. Claim 12 does not, however, claim a method of using a drug-eluting stent, such as the ZILVER® PTX Drug Eluting Peripheral Stent.

III. USPTO is Consistent with Its Past Practices

At page 12 of the Request for Recon, Applicant states the following:

> The fact that a patent claim reads on products in addition to the approved product cannot be the basis for denying PTE.

The USPTO agrees with this statement. However, the USPTO is not denying an extension in the present case because claim 12 of the '447 patent reads on products in addition to the approved product. The USPTO is denying an extension of the '447 patent because claim 12 of the '447 (or any other claim of the '447 patent) does not claim a method of using the approved product, *i.e.*, a method of using a drug-eluting stent, such as the ZILVER® PTX Drug Eluting Peripheral Stent.

Applicant points out that USPTO granted an extension on U.S. Patent No. 5,041,126 (the '126 patent) for the Cook GRII Coronary Stent, where claim 1 of the patent recites:

> 1. A method for inserting a stent which comprises:
> (a) engaging a stent, having a longitudinal length, around a balloon catheter,

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[4]See also page 12 of Cook Medical's Patient Guide answering the question, "what is a stent?"

> (b) locating the catheter and stent within a passageway, and
> (c) inelastically expanding the stent, while maintaining the longitudinal length of the stent, by inflating the balloon catheter within the stent to inelastically deform the stent until the stent engages the passageway.

The approved product, the Cook GRII coronary stent, is a medical device. Thus, extension of any patent that claims a method of using such a medical device would be eligible for patent term extension. In the '126 patent, the approved product is a stent and the claim expressly states a method of using a stent. Whether claim 1 of the'126 patent would be infringed by the use of stents other than the Cook GRII stent is immaterial to a determination of eligibility for term extension. Nothing in the decision from October 16, 2015 or the present decision amounts to USPTO deviating from past practice in granting patent term extensions.

IV. Grant of Interim Extension is Predicated on Finding that the Patent is Eligible for Extension and that the Application has not Been Denied

If a patent will expire before the Director has made a determination to issue or deny an application for patent term extension, § 156(e)(2) provides for an interim patent term extension of up to one year:

> If the term of a patent for which an application has been submitted under subsection (d)(1) would expire before a certificate of extension is issued or denied under paragraph (1) respecting the application, the Director shall extend, until such determination is made, the term of the patent for periods of up to one year if he determines that the patent is eligible for extension.

§ 156(e)(2) (emphasis added).

Based on the express language of §156(e)(2), certain conditions must be satisfied in order to permit the Director to issue an interim extension. Specifically, the language "before a certificate of extension is issued or denied" in § 156(e)(2) indicates that an interim extension may be granted only during the period of time prior to the Director's determination either to issue the certificate or deny the applicant's request. Furthermore, the following language "if he determines that the patent is eligible for extension" instructs the Director to grant an interim extension only if the patent is eligible for patent term extension. If the patent is not eligible, then § 156(e)(2) explicitly prohibits the Director from granting an interim extension.

The legislative history of the Hatch-Waxman Act is consistent with this interpretation. Two committee reports address § 156. The Committee on Energy and Commerce prepared a report for the House version of the Act (H.R. 3605), giving a general explanation for how the provision would operate in practice:

> It is possible that the original term of the patent for which

> extension is sought could expire before a final decision by the Commissioner to issue a certificate of extension. This might occur, for instance, because the determination of due diligence by the Secretary of HHS or Agriculture has not been completed.
>
> In such circumstances, the Commissioner is required to determine whether the patent is eligible for extension under section 156(a), *and if it is*, to issue a certificate of extension for a period of up to one year. The length of this interim extension is discretionary with the Commissioner, but is intended to provide time for the completion of any outstanding requirements. If the Commissioner determined that subsequent interim extensions were necessary, and consistent with the objectives of section 156(e)(2), they could be granted as well. In no event could these interim extensions be longer than the maximum period of extension to which the application is thought to be eligible.

H.R. Rep. No. 857(I), 98th Cong., 2d Sess. (June 21, 1981), reprinted in 1984 U.S.C.C.A.N. 2647 at 29 (emphasis added).

The Committee on the Judiciary likewise prepared a separate report on H.R. 3605 and explained even less about § 156(e)(2):

> Proposed section 156(e) provides that the Commissioner's determination that a patent is eligible for extension is to be made solely on the basis of information contained in the application. If it is determined that the patent is eligible for an extension, the Commissioner shall issue a certificate of extension, under seal, for the period determined, in accordance with procedures authorized by subsection (c). The certificate shall be recorded in official patent files and becomes a part of the original patent.
>
> In the event that the original term of the patent for which extension is sought will expire before a final decision by the Commissioner on that extension, the Commissioner may issue an interim extension certificate for a period of up to one year.

H.R. Rep. No. 857(II), 98th Cong., 2d Sess. (Aug. 1, 1984).

The Committee on Energy and Commerce's discussion supports reading § 156(e)(2) as permitting an interim extension only if the Director determines that the patent is eligible for a patent term extension. In particular, the language "and if it is" conveys that an interim extension should not be granted if a patent is not eligible for extension under § 156(a). While the

Committee on the Judiciary did not specifically state that eligibility is a prerequisite for an interim extension, such an interpretation is not inconsistent with this report.

Furthermore, the Federal Circuit has squarely addressed the issue of granting an interim extension and found that the USPTO is without authority to grant an interim extension when the underlying application is denied. *Somerset Pharms., Inc. v. Dudas*, 500 F.3d 1344, 1346 (Fed. Cir. 2007) (explaining that when the Director denies a patent term extension, "the Director has no statutory authority to issue the interim extension" under § 156(e)(2)).

Thus, because the '447 patent is not eligible for patent term extension and is denied herein, any further interim extension under § 156(e)(2) cannot be granted.

C. CONCLUSION

Thus, for the reasons above, the USPTO finds that claim 12 of the '447 patent does not cover a method of using a drug-eluting stent such as the ZILVER® PTX Drug Eluting Peripheral Stent. As such, the application for term extension of the '447 patent is **DENIED** as failing to comply with 35 U.S.C. § 156(a), because no claim of the '447 patent claims the approved product, a method of using the approved product or a method of manufacturing the approved product.

This is a **final** agency action within the meaning of 5 U.S.C. § 704 for purposes of seeking judicial review.

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

Telephone inquiries related to this determination should be directed to Mary C. Till at (571) 272-7755.

Brian E. Hanlon

Brian E. Hanlon
Director
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: ZILVER® PTX Drug Eluting Peripheral Stent
Docket No.: FDA-2013-E-0781

Combination Products

Jurisdictional Update: Drug-Eluting Cardiovascular Stents

FDA has received several Requests for Designation (RFD) for cardiovascular stents coated with a drug component intended to maintain vessel patency by minimizing the occurrence of restenosis following stent implantation. Some of the drug components are active ingredients in drug products approved for other indications, while others are as yet unapproved.

Drug-eluting stents combine drug and device components, and are therefore combination products within the meaning of section 503(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 353 (g)) (Act). Accordingly, review responsibility for these products is assigned based on the Agency's determination of the product's "primary mode of action" (Id.; 21 CFR § 3.4). FDA has determined based on the specific RFD's submitted that the uncoated stent functions to physically maintain vessel lumen patency, while the drug component has played a secondary role in preventing restenosis, augmenting the safety and/or effectiveness of the uncoated stent. In these cases, FDA has concluded that the primary mode of action for the combination product is that of the device component, and has assigned the Center for Devices and Radiological Health (CDRH) primary responsibility for premarket review and regulation. In these cases, the clinical investigations of drug-eluting cardiovascular stents have been or will be conducted under an investigational device exemptions (IDE) application in accordance with 21 CFR Part 812, and CDRH expects to review marketing applications for the products under a premarket approval application (PMA) in accordance with 21 CFR Part 814. CDRH has conducted its reviews in consultation with the Center for Drug Evaluation and Research (CDER).

Furthermore, the assignment of primary review responsibility to CDRH is consistent with Sections VII.A.2 and VIII.A.5 of the current Intercenter Agreement between CDER and CDRH, which assigns CDRH review responsibility for devices incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function. Although the agency has determined that these products are subject to premarket review and approval solely under the medical device provisions of the Act, the agency has applied human drug Current Good Manufacturing Practices to the manufacture of the drug component of the combination product, and may apply other drug requirements to the products as appropriate. The CDRH review staff have discussed application of drug requirements in the context of specific applications.

Sponsors wishing to discuss regulation of a particular drug-eluting cardiovascular stent should contact the Interventional Cardiology Branch in the Division of Cardiovascular Devices, Office of Device Evaluation, CDRH by telephone at (301) 796-5570

Page Last Updated: 05/12/2010
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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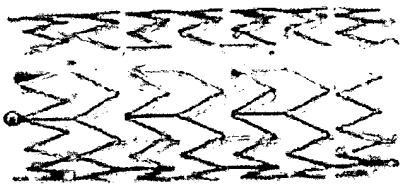
Zilver® PTX® Drug-Eluting Peripheral Stent - P100022

This is a brief overview of information related to FDA's approval to market this product. See the links below to the Summary of Safety and Effectiveness Data (SSED) and product labeling for more complete information on this product, its indications for use, and the basis for FDA's approval.



Product Name: Zilver® PTX Drug-Eluting Peripheral Stent
PMA Applicant: Cook, Inc.
Address: 750 Daniels Way, P.O. Box 489, Bloomington, IN 47402-0489
Approval Date: November 14, 2012
Approval Letter: http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100022a.pdf (http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100022a.pdf)

What is it? The Zilver® PTX Drug-Eluting Peripheral Stent (Zilver® PTX Stent) is a self-expanding, small metal, mesh tube (stent) with the outer surface coated with the drug Paclitaxel that can be implanted in an artery in the thigh (femoropopliteal (http://www.merriam-webster.com/medlineplus/femoropopliteal) artery). The Paclitaxel (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) coating helps prevent the artery from narrowing again (restenosis (http://www.radiologyinfo.org/en/info.cfm?pg=angioplasty)).

How does it work?

- A small incision is made in the groin to insert the Zilver® PTX Stent.
- The physician then inserts and guides a catheter to the appropriate location in the artery, and deploys the stent.
- The Zilver® PTX stent remains in the artery permanently acting as a support (scaffold) to hold the artery open so blood can flow through the artery.

When is it used? The Zilver® PTX stent is used to reopen narrowed or blocked arteries in the above-the-knee femoropopliteal (in the thigh) region caused by **peripheral artery disease (http://www.nlm.nih.gov/medlineplus/ency/article/000170.htm)** (PAD). Peripheral artery disease is a common circulatory problem in which narrowed arteries reduce blood flow to limbs, usually in the legs.

What will it accomplish? The Zilver® PTX stent acts as a scaffold to:

- Hold open a narrowed artery in the thigh (femoropopliteal artery) caused by PAD.
- Improve blood flow to the extremity.

When should it not be used? The device should not be used in patients:

- with stenosis that cannot be dilated to permit passage of the catheter or proper placement of the stent
- who cannot receive recommended drug therapy due to bleeding disorders, and
- women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years.

Additional information: The **Summary of Safety and Effectiveness Data and labeling (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p100022)** are available online.

Other Resources

- **FDA News Release (/NewsEvents/Newsroom/PressAnnouncements/ucm327068.htm)**
- **NIH-MedlinePlus-Angioplasty and Stent Placement (http://www.nlm.nih.gov/medlineplus/ency/article/007393.htm)**
- **Society for Vascular Surgery – Peripheral Artery Disease (http://www.vascularweb.org/vascularhealth/pages/peripheral-artery-disease-(-pad-)-.aspx)**

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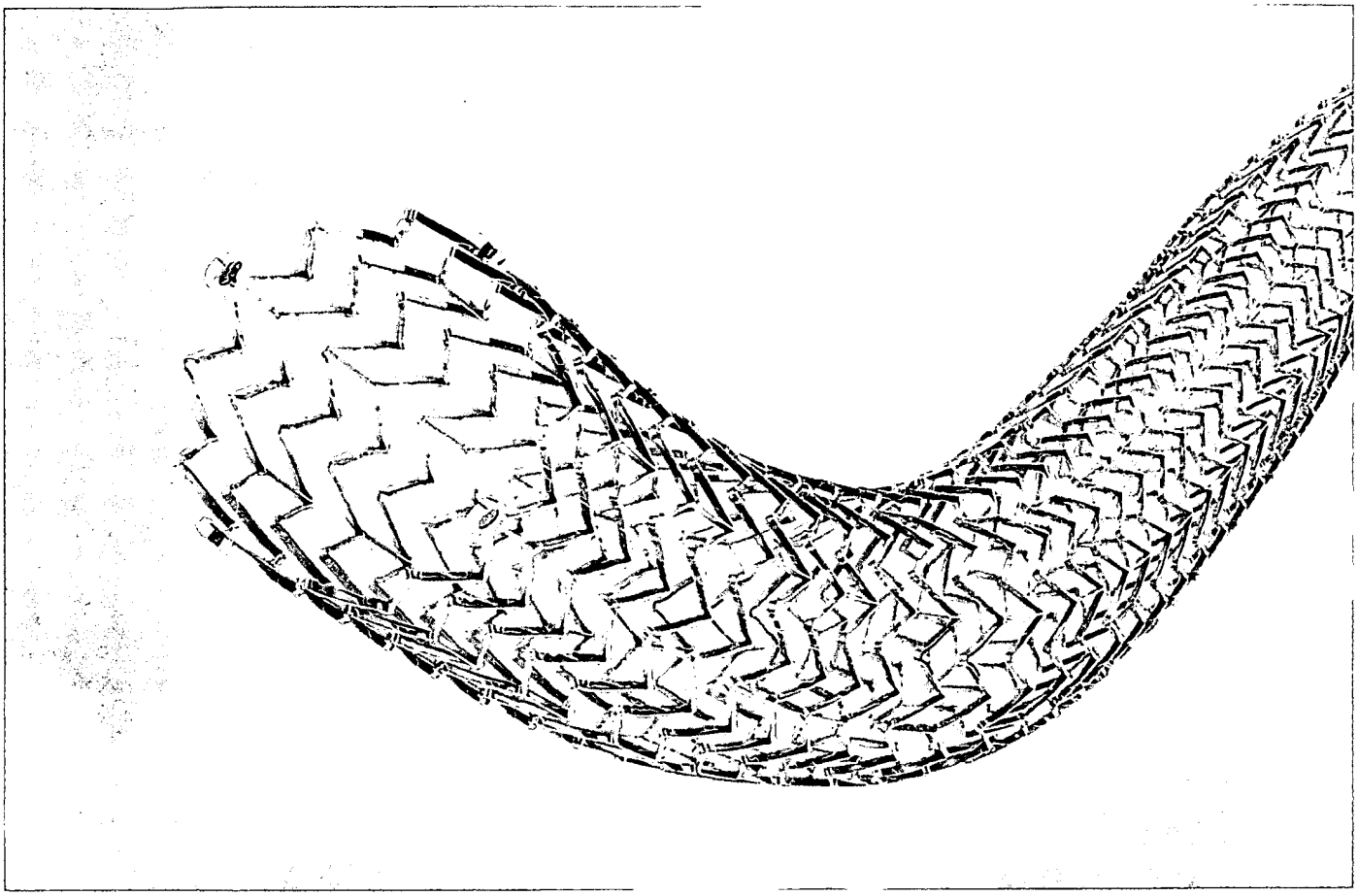
2014 Device Approvals (/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm381097.htm)

COOK MEDICAL

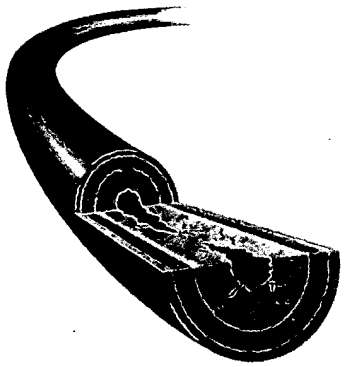
Zilver® PTX®

DRUG-ELUTING PERIPHERAL STENT



PATIENT GUIDE

CONTENTS



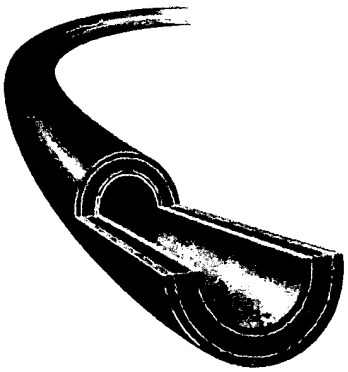
Peripheral arterial disease

PERIPHERAL ARTERIAL DISEASE

What is peripheral arterial disease?

Peripheral arterial disease, known as PAD, affects more than 30 million people worldwide every year. This serious, underdiagnosed disease is similar to coronary artery disease in that it develops when cholesterol levels and scar tissue build up, causing the arteries to narrow and restrict blood flow. The difference is that PAD affects arteries outside the heart.

Untreated, PAD can lead to difficulty in walking and, in its most severe stage, gangrene leading to leg amputation. Also, people who have PAD often have arterial blockages in other parts of the body and are therefore at greater risk of suffering a heart attack or stroke.



Healthy artery

Who is at risk?

While **peripheral arterial disease** can strike anyone, it is most common in people over the age of 65. Up to 20 percent of all adults over the age 65 are affected by PAD.

The most common risk factor for PAD is smoking, which increases the risk of PAD by three to four times. On average, smokers are diagnosed with PAD 10 years earlier than nonsmokers.[1]

Diabetes is also a leading risk factor for PAD. People with type 2 diabetes have three to nearly four times the normal risk of PAD.[1] Other risk factors include:

- Obesity
- High blood pressure
- Lack of exercise
- Family history of atherosclerosis (hardening of the arteries)
- High cholesterol

What are the symptoms of PAD?

Many people with PAD do not exhibit any warning signs. In fact, only one quarter to one third of those diagnosed with PAD have any symptoms at all.[1] Those who do have severe symptoms often mistake them for signs of aging.

The most common symptom of PAD is leg pain that occurs when walking but disappears during rest. Other symptoms include:

- Numbness or weakness in the legs
- Aching pain in the feet or toes while at rest
- Ulcers or sores in the leg or foot that don't heal
- Cold legs or feet
- Skin-color changes in the legs or feet

How is PAD diagnosed?

Unfortunately, many cases of PAD go undiagnosed because the symptoms are often mistaken for signs of aging. One way to determine whether someone could be suffering from PAD is an ankle-brachial index (ABI) test. The ABI test measures the blood pressure at the ankle and at the arm. A comparison of the two blood pressure readings can point to problems. Specifically, a blood pressure that is lower in the ankle than in the arm implies a blockage in the artery between the heart and the leg. Other tests used to diagnose PAD include ultrasound, x-ray, **angiography** and magnetic resonance imaging **angiography** (MRA).

TREATMENT OF PAD

The first-line treatment for PAD consists of lifestyle changes such as smoking cessation, exercise, and lowering blood pressure and cholesterol. These changes can help to slow the progression of PAD and decrease the likelihood of a heart attack or stroke. Lifestyle changes are often made in combination with the use of certain drugs–such as antiplatelet therapy to inhibit blood clotting, statins to reduce cholesterol, and drugs to lower blood pressure. In a minority of patients, however, lifestyle changes and drug therapy are not enough to prevent PAD progression. For these patients, **angioplasty,** stenting or surgery may be necessary.

Angioplasty

Angioplasty is a nonsurgical procedure that widens narrowed or blocked peripheral arteries. In an **angioplasty** procedure, a **catheter** with a deflated balloon is inserted into the narrowed segment of the artery. The balloon is inflated to open the artery; the balloon is then deflated and the **catheter** is withdrawn.

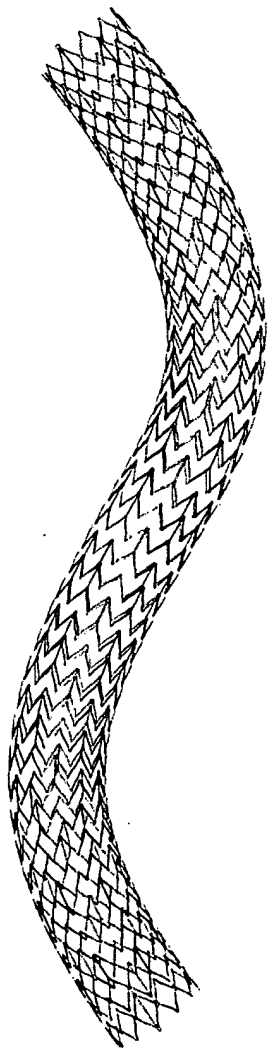
In other cases, a **stent**–a tubular metal device that acts as a scaffold–is placed in the narrowed segment of the artery. The **stent,** in an unexpanded form, is delivered via a **catheter** to the correct place. The **stent** expands and stays in place to keep the artery open after the **catheter** is withdrawn.

Restenosis

In many cases, patients who have been treated with balloon **angioplasty** and stenting experience a renarrowing, or **restenosis,** of the artery over time. This is partly because the body tries to heal the injury to the vessel that occurs when the balloon is inserted and inflated. During the healing process, excess tissue may grow over the **stent,** causing the vessel to narrow again. Up to one-third of patients will suffer from a renarrowing of arteries over time, making a repeat intervention necessary.[2]

Bypass surgery

Bypass surgery is typically reserved for patients whose anatomy is not appropriate for less invasive catheter-based treatment and for whom lifestyle changes don't work. Surgery involves sewing a vein from another part of the body or an artificial blood vessel above and below the blocked area to detour blood flow around the blockage. Surgery has additional risks, however, particularly for patients who suffer from other disorders such as heart disease, high blood pressure or diabetes.



YOUR ZILVER PTX STENT

Drug-coated stents

A **drug-coated stent** is a metal **stent** that has been coated with a drug intended to prevent renarrowing of the artery. Clinical data demonstrate that the Zilver PTX stent is effective in preventing renarrowing of the artery and can help patients who suffer from PAD.[3]

The Zilver PTX paclitaxel-eluting stent

The Zilver PTX **paclitaxel**-eluting **stent** is a nitinol **stent** coated with the drug **paclitaxel**.

What is paclitaxel?

Paclitaxel is the active component of Taxol®, a drug that is used as an anticancer agent. **Paclitaxel** is also used on **stents** used in the heart to reduce the risk of renarrowing of the artery. It is intended to limit the response of the blood vessel so excess tissue growth that could cause renarrowing of the vessel does not occur.

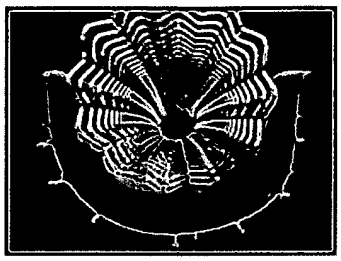
The Zilver PTX **stent** uses a very small amount of **paclitaxel**, which is applied directly to the vessel wall.

Who should not receive a Zilver PTX stent?

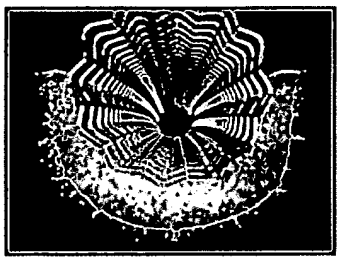
- Women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years should not receive a Zilver PTX Drug-Eluting Peripheral Stent. It is unknown whether paclitaxel will be excreted in human milk, and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.
- Patients who cannot receive recommended anti-platelet and/or anti-coagulant therapy.
- Patients judged to have a lesion that prevents proper placement of the stent or stent delivery system.

What are the potential adverse events that may be associated with a Zilver PTX stent?

- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol
- Atheroembolization (blue toe syndrome)
- Arterial **aneurysm**
- Arterial rupture
- Arterial thrombosis
- **Arteriovenous fistula**
- Death
- **Embolism**
- **Hematoma**/hemorrhage
- Hypersensitivity reactions
- Infection
- Infection/abscess formation at access site
- **Ischemia** requiring intervention (bypass or amputation of toe, foot or leg)
- **Pseudoaneurysm** formation
- Renal failure
- **Restenosis** of the stented artery
- **Stent** embolization
- Stent malapposition
- Stent migration
- Stent strut fracture
- Vessel perforation or rupture
- Worsened **claudication**/rest pain



PTX **paclitaxel**-eluting stent placed in affected vessel



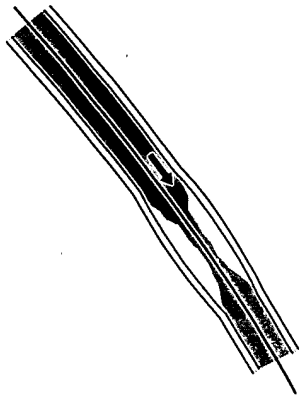
The drug **paclitaxel** is intended to keep the blood vessel from renarrowing

Potential adverse events, not described previously, may be unique to the **paclitaxel** drug coating and include:

- Allergic/immunologic reaction to the drug coating
- **Alopecia**
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- **Hematologic dyscrasia** (including leukopenia, neutropenia, thrombocytopenia)
- **Hepatic enzyme** changes
- Histologic changes in vessel wall, including inflammation, cellular damage or **necrosis**
- **Myalgia/arthralgia**
- **Myelosuppression**
- Peripheral **neuropathy**

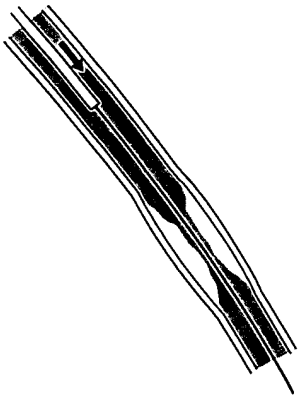
You may want to ask your physician about the potential for each of these risks in your specific situation.

THE ANGIOPLASTY AND STENTING PROCEDURE



Before the procedure

Your doctor will explain how to prepare for your **angioplasty** and **stenting** procedure before you are admitted to the hospital. You may be asked to avoid eating or drinking anything after midnight on the night before the procedure. You may also be asked to take aspirin or other medication for a few days prior to the procedure to thin your blood and prevent clots from forming.

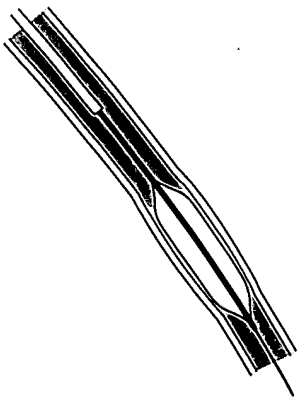


During the procedure

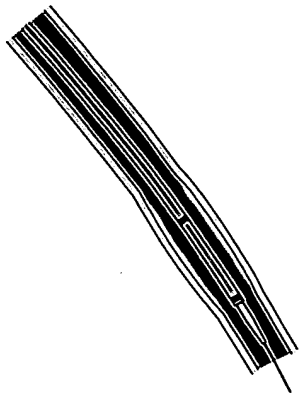
Your **angioplasty** and **stenting** procedure will take place in the hospital, your physician's office or in a catheterization lab. Although you may be given a sedative to help you relax, you will be awake during the procedure. This will allow you to follow your doctor's instructions to move, cough or breathe as needed.

Your doctor will be accessing your artery through your groin. The access area will first be shaved, swabbed with antiseptic and numbed with a local anesthetic. Your doctor will then make a small incision in your skin and gain access to your artery with a needle.

A wire guide will be inserted through the needle and advanced to the part of your artery that contains the blockage. The doctor will then insert an **introducer sheath** over the wire guide into your artery, and a balloon **catheter** will be advanced through the **introducer sheath** to the site of the blockage. The balloon will be inflated briefly, widening the blocked artery.



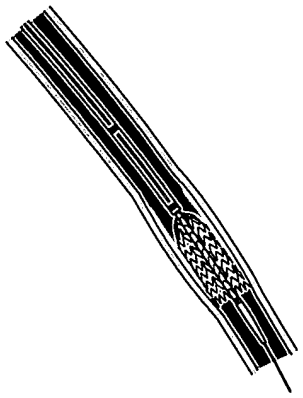
After the artery has been widened, the doctor will deflate the balloon and remove the balloon **catheter**. He or she will then advance a delivery **catheter** containing the Zilver PTX **stent** to the area of the artery where the balloon previously was. When the **stent** is positioned in the right spot, the doctor will unsheathe it, allowing it to expand against the walls of your artery. The doctor will then remove the **catheter** and wire guide, leaving the **stent** in place. The **introducer sheath** may also be left in place for a few hours while you are monitored.



After the procedure

When your procedure is finished, you will be moved to a recovery area. You may feel some discomfort, which can be relieved with pain medicine. Your blood pressure and heart rate will be monitored closely. Your doctor and the standard protocol of the facility where your procedure was performed will determine when you are allowed to go home.

FREQUENTLY ASKED QUESTIONS

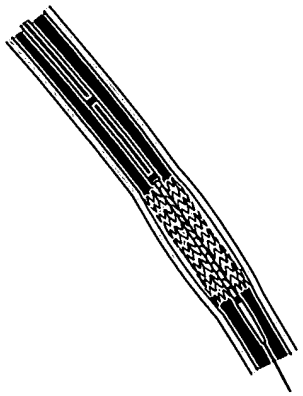


1. What is a stent?

A **stent** is a metal tube used to keep the artery open. The Zilver **stent** is made of nitinol, an alloy of nickel and titanium. This blend of metals was discovered in 1965. It has superelastic properties that help it maintain its shape, even after it is crushed many times. The **stent** is compressed into a plastic tube so that it can be passed into your artery. The **stent** is placed across the blockage, where it is released and expands to the size of your artery.

2. What is a drug-coated stent?

A **drug-coated stent** is simply a **stent** with drug on it. **Drug-coated stents** have recently become widely used for the arteries of the heart. The **drug-coated stents** have reduced the occurrence of blockages after the **stents** are in place. Zilver PTX clinical trials confirmed that **drug-coated stents** help to keep the leg arteries from becoming blocked again.[3]



3. What is paclitaxel?

Paclitaxel (păk'lĭ-tăk'səl) is a natural product that was discovered in 1967. It originally came from the bark of the Pacific yew tree. **Paclitaxel** reacts with cells in several ways. One is that it keeps cells from dividing. The cells cannot divide because **paclitaxel** keeps the microtubules (which are like muscles in your cells) from pulling the cell apart to form two new cells. Excessive cell division sometimes occurs after an artery has been treated, causing it to become blocked again. Thus, by preventing cell division, **paclitaxel** may keep your artery from becoming blocked again.

Since cancer cells divide rapidly and **paclitaxel** keeps cells from dividing, it is sometimes given to treat cancer (e.g., ovarian or breast cancer). The drug to treat cancer is called Taxol. Taxol includes **paclitaxel** and an oil to make the drug easy to inject. When Taxol is given to treat cancer, the dose is large and the drug goes throughout the entire body, which may cause side effects. The PTX **stent** was designed to reduce the chances of such side effects because the amount of **paclitaxel** on the **stent** is small, does not contain the oil found in Taxol and is given locally from the **stent** to your artery.

4. How much paclitaxel is on the stent?
The **stent** carries only 1/1,300 to 1/200 the amount of **paclitaxel** given in a single cancer treatment.

5. Where do the stent and the drug go after the doctor puts them in my body?
The doctor puts the **stent** across the blockage in the artery. The **stent** remains in that place in your artery for the rest of your life. The wall of your artery absorbs the drug from the **stent**. A small portion of the drug may get carried away by the blood flowing through your artery.

GLOSSARY

Alopecia - Baldness; absence of hair where it is normally present.

Aneurysm - A sac formed by the expansion of the wall of an artery, a vein or the heart.

Angiography - A method of taking x-rays of blood vessels after injection of contrast dye.

Angioplasty - A catheter-based treatment to open narrowed or blocked arterial vessels.

Arteriovenous fistula - An abnormal or artificial connection between an artery and vein.

Arthralgia - Pain in a joint.

Catheter - A hollow, flexible tube used to access parts of the body, such as arterial vessels.

Claudication - Condition marked by pain, tension and weakness of legs induced by walking, and the disappearance of all discomfort when at rest. This condition is caused by a narrowing of the arteries in the legs.

Drug-coated stent - A stent with a drug coating that is intended to prevent the vessel from renarrowing.

Embolism - The sudden obstruction of an artery by a clot or any foreign material formed or introduced elsewhere in the circulatory system and carried to the site of blockage by the bloodstream.

Hematologic dyscrasia - An abnormal condition in the composition of blood.

Hematoma - A collection of blood, usually clotted, in an organ, space or tissue outside a vessel.

Hepatic enzyme - A protein secreted by the liver that promotes or accelerates a chemical change in other substances.

Introducer sheath - A tube that is inserted into the body to provide access and allow delivery of other devices.

Ischemia - Lack of blood in an area of the body due to an obstruction or constriction of a blood vessel.

Myalgia - Muscular pain.

Myelosuppression - Decrease in the ability of bone marrow to produce blood cells.

Necrosis - Tissue death.

Neuropathy - Nerve damage.

Paclitaxel - A drug that prevents cell division and is derived from the Pacific yew tree.

Peripheral arterial disease - A condition that develops when cholesterol levels and scar tissue build up, causing arteries to narrow and restrict blood flow.

Pseudoaneurysm - A collection of blood from a ruptured vessel that gives the appearance of an aneurysm; also known as a false aneurysm.

Restenosis - The renarrowing of a vessel.

Stent - An expandable metal tube that is used to keep a vessel open.

REFERENCES

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2. Krankenberg H, Schlüter M, Steinkamp HJ, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). *Circulation*. 2007;116(3):285-292.
3. Refer to Instructions for Use (IFU) for full prescribing information, including indications, contraindications, warnings and precautions. See: Zilver PTX [package insert]. Bloomington, IN: Cook Medical; 2012.

NOVEMBER 2012

AORTIC INTERVENTION

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Please note: As of October 1, 2002, FDA charges a fee for review of Premarket Approvals (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048161.htm)

Overview

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance. Please note that some Class III preamendment devices may require a Class III 510(k). See "Historical Background (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm046769.htm)" for additional information.

PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

The PMA applicant is usually the person who owns the rights, or otherwise has authorized access, to the data and other information to be submitted in support of FDA approval. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. The applicant is often the inventor/developer and ultimately the manufacturer.

FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

The regulation governing premarket approval is located in Title 21 Code of Federal Regulations (CFR) Part 814 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1), Premarket Approval. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed.

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When a PMA is Required

PMA requirements apply to Class III devices, the most stringent regulatory category for medical devices. Device product classifications can be found by searching the Product Classification Database (http://www.accessda-

ta.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm). The database search provides the name of the device, classification, and a link to the Code of Federal Regulations (CFR), if any. The CFR provides the device type name, identification of the device, and classification information.

A regulation number for Class III devices marketed prior to the 1976 Medical Device Amendments is provided in the CFR. The CFR for these Class III devices that require a PMA states that the device is Class III and will provide an effective date of the requirement for PMA. If the regulation in the CFR states that "No effective date has been established of the requirement for premarket approval," a Class III 510(k) should be submitted.

Please note that PMA devices often involve new concepts and many are not of a type marketed prior to the Medical Device Amendments. Therefore, they do not have a classification regulation in the CFR. In this case, the product classification database will only cite the device type name and product code.

If it is unclear whether the unclassified device requires a PMA, use the three letter product code to search the PMA database and the Premarket Notification 510(k) database. These databases can be found by clicking on the hypertext links at the top of the product classification database web page. Enter only the three letter product code in the product code box. If there are 510(k)'s cleared by FDA and the new device is substantially equivalent to any of these cleared devices, then the applicant should submit a 510(k).

Furthermore, a new type of device may not be found in the product classification database. If the device is a high risk device (supports or sustains human life, is of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury) and has been found to be not substantially equivalent (NSE) to a Class I, II, or III [Class III requiring 510(k)] device, then the device must have an approved PMA before marketing in the U.S. Some devices that are found to be not substantially equivalent to a cleared Class I, II, or III (not requiring PMA) device, may be eligible for the de novo process as a Class I or Class II device. For additional information on the de novo process, see "**New section 513(f)(2) - Evaluation of Automatic Class III Designation: Guidance for Industry and CDRH Staff (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080195.htm)**".

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Devices Used in Blood Establishments

The Center for Biologic, Evaluation, Research (CBER) has expertise in blood, blood products, and cellular therapies as well as the integral association of certain medical devices with these biological products. To utilize this expertise marketing and investigational device submissions (Premarket Notification, Premarket Approval, and Investigational Device Exemption) for medical devices associated with the blood collection and processing procedures as well as those associated with cellular therapies are reviewed by CBER. Although these products are reviewed by CBER, the medical device laws and regulations still apply. The **list of medical devices reviewed by CBER (/BiologicsBloodVaccines/DevelopmentApprovalProcess/510kProcess/ucm133429.htm)** are available on the Internet.

In addition to CDRH guidance on Premarket Approval, **specific medical device guidance for devices reviewed by CBER (/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm)** is available at online or by contacting:

Center for Biologics Evaluation and Research
Office of Communication, Training and Manufacturers Assistance (HFM-43)
1401 Rockville Pike, Room 200N
Rockville, MD 20852-1448 U.S.A.
Telephone Number: 301-827-2000 or 800-835-4709
Fax Number: 301-827-3843

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Data Requirements

A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing

is a key to the approval of PMA application. If a PMA application lacks elements listed in the administrative checklist, FDA will refuse to file a PMA application and will not proceed with the in-depth review of scientific and clinical data. If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it will delay FDA?s review and approval. PMA applications that are incomplete, inaccurate, inconsist, omit critical information, and poorly organized have resulted in delays in approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format.

Technical Sections: The technical sections containing data and information should allow FDA to determine whether to approve or disapprove the application. These sections are usually divided into non-clinical laboratory studies and clinical investigations.

Non-clinical Laboratory Studies' Section: Non-clinical laboratory studies' section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with **21CFR Part 58 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1)** (Good Laboratory Practice for Nonclinical Laboratory Studies).

Clinical Investigations' Section: Clinical investigations' section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such.

Like other scientific reports, FDA has observed problems with study designs, study conduct, data analyses, presentations, and conclusions. Investigators should always consult all applicable FDA guidance documents, industry standards, and recommended practices. Numerous device-specific FDA **guidance documents that describe data requirements are available (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)**. Study protocols should include all applicable elements described in the device-specific guidance documents.

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References

List of references for Premarket Approvals

- **SEC. 515. [21 USC §360e] Premarket Approval; General Requirement (http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360e.htm)**
- **21 CFR 814 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1)**
- **The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm)** 1332
- **PMA Guidance Documents (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm143067.htm)**
- **CPG Sec. 300.750 Class III Devices Subject to 515(b) Requirements (/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm123766.htm)**

Other Resources

- **PMA Approvals (/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm)**

More in Premarket Approval (PMA) (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/de

PMA Definitions (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Review Process
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PMA Review Fees
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PMA Labeling
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PMA Clinical Studies
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Postapproval Requirements
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Supplements and Amendments
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Special Considerations
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Import/Export
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Frequently Asked Questions
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc

PMA Regulations
(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/uc