HealthTech Activator

Medical Device Access to the US Market

TRANSITIONING FROM CE MARK TO 510(K) REGULATORY REQUIREMENTS

TOTAL ANKLE REPLACEMENT DEVICE – IMPLANT CASE STUDY

An early-stage NZ medical device company wants to sell a total ankle replacement device for primary or revision surgery in the US market. The company previously achieved CE mark in Europe for the same product. The next step in commercialisation is to obtain 510(k) clearance to market the product in the US. As with the European regulators, the US FDA considers the total ankle replacement product a medical device when it is used in primary or revision surgeries. Even though the company obtained a European CE mark, it finds the US FDA premarket approval requirements complex.

The client's product development and clinical teams recognise the need for a regulatory strategy that balances timelines and cost against the delivery of a marketable product. The strategy establishes requirements to obtain clearance from the FDA, by identifying:

1. Product classification for the subject device
2. International standards and recommended guidance documents i.e. how the existing CE mark data package can be repurposed to meet FDA requirements
3. Selecting a comparator product (called a predicate device)
4. Performance test requirements (laboratory and other testing)
5. Timeline, i.e. how and when testing should be undertaken.

The company is considering whether to confirm with the FDA the appropriate classification of its total ankle replacement device (using the 513(g) submission process) but is not wanting to delay the product launch as it has identified a new competitor that is likely to launch a similar product this year. The company has identified the closest comparison product currently on the US market (on the basis of intended use and technology) to be the Hintermann Series H2™ Total Ankle Replacement – a semi-constrained cemented prosthesis for primary or revision surgery, which is a Class II device.

The development team have been informed that while there is not a FDA Special Controls guidance document available for the testing and regulatory submission process, there is a guidance of industry document (published in 2000) that applies specifically: *'Testing of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements'*. To demonstrate substantial equivalence, a head-to-head test data package needs to be generated (comparing the subject and predicate device characteristics). Additionally, testing as specified in the above-referenced guidance must be conducted.

To achieve the fastest path to product launch through the US FDA regulatory system, the company has engaged a regulatory expert in NZ to answer the following questions:

1. Can you confirm the FDA classification of our device?
2. Can you advise on the impact of identifying market clearance requirements, i.e. the use of standards and scope of testing?
3. How can we be sure we have chosen the right comparator product (predicate device) for our application?
4. How do we identify the right testing to undertake on our product so that our product launch date is not delayed by needing to do further testing after our application has been submitted?
5. Are the evidence requirements similar to what we have already developed for the CE mark, or do we need to undertake new tests?

ANSWERS TO THE COMPANY'S QUESTIONS

Despite the differences, CE and FDA have one common goal, i.e. ensuring that medical device manufacturers produce and market safe products that comply with the applicable regulations while ensuring adherence to good manufacturing practices and design control requirements.

1. Device Classification

The first step toward obtaining FDA clearance for marketing the new product is to determine the device's classification. Although it's sometimes helpful to ask the FDA to identify the classification of a product (using a 513(g) process), in this case it was not advisable for the following reasons:

- The 513(g) process takes 60 days to get a response from the FDA, while a qualified consultant can make the same determination in less than a day.
- Hiring a consultant typically costs less than the 513(g) fee (i.e. the FDA fee is $4,195 for large companies and $2,098 for small businesses).

- The FDA's classification determination is non-binding and the accuracy of the FDA's response is highly dependent upon the quality of information provided by the company.

Once the predicate device is identified, a regulatory consultant would be able to locate a three-letter product code to confirm the class of device (in this case 'HSN', which is a Class II device requiring premarket notification via a 510(k) submission).

Refer to:

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevi ce/default.htm

2. (a) File Requirements

In the absence of a Special Controls guidance document (i.e. a FDA issued product specific guidance), there are other guidance documents and/or FDA recognised consensus standards (e.g. ISO Standards) that define the performance requirements for a medical device in the product classification.

Given the above, the company is required to submit a Traditional 510(k) submission. The 510(k) submission should provide sufficient detail for the FDA to be able to determine that the device is substantially equivalent (SE) to another similar legally marketed device(s), i.e. the predicate device.

A Traditional 510(k) submission contains summaries of all the test methods and results. Test requirements for the proposed device are defined by the testing that the primary predicate device completed. The FDA recognises many ISO standards for inclusion in the 510k applications. A description of the tests and the results obtained are essential for submission.

The FDA reviewer has to confirm that the performance testing identified by the company is acceptable, as well as verify that the performance testing has been completed and acceptance criteria have been met. The FDA performance target for making a decision regarding clearance is 90 days for a Traditional 510(k) application.

2. (b) Application of Standards

FDA recognises many ISO standards for inclusion in the 510(k) applications. Conformance with recognised consensus standards supports a reasonable assurance of safety and/or effectiveness for many applicable aspects of the device. Information submitted on conformance with such standards helps establish the 'substantial equivalence' of a new device to a legally marketed predicate device. Recognition signifies that FDA is familiar with the standard and believes it is appropriate for meeting relevant premarket requirements.

Manufacturers may use FDA-recognised standards to meet 510(k) requirements in either of two ways:

1. by submitting a 'declaration of conformity'; or
2. by submitting a 'statement'.

The first approach requires manufacturers to have supporting data in their files at the time a 510(k) is submitted, while the second approach requires manufacturers to have such data before a device is marketed. Under either approach, FDA reviewers normally accept the declaration/statement in meeting relevant 510(k) requirements, and do not require the submission of information demonstrating conformity with the standard. Manufacturers may also choose to use non-recognised standards to meet relevant 510(k) requirements, though there is less assurance that these standards will be acceptable. Depending upon factors such as the FDA's familiarity with the standard and its specificity, reviewers may need information beyond a statement to support reliance on any non-recognised standards.

For US market access in this particular case study, the US FDA accepted a declaration of conformity while requiring the following non-clinical testing to be performed:

- Coating characterisation per FDA Guidance for Industry
- Range of motion analysis per ASTM F2665
- Fatigue testing per ASTM F2665
- Contact area/contact stress analysis per ASTM F2665
- Constraint testing per ASTM F2665
- Tibial Component locking mechanism testing
- Wear testing per ASTM F2665
- Endotoxin testing per FDA guidance.

2. (c) Test Requirements: US versus EU

When preparing the data package for CE mark approval, the regulatory strategy identified a number of applicable ISO standards for a device indicated for total ankle replacement. The standards include, but were not limited to: ISO 22622, ISO 22675, ISO 16955 and ISO22675. In preparation for US market access, the regulatory consultant, product[1] development engineer and quality assurance representative assigned to the team performed a gap analysis to determine similarities and differences between the test methods and specifications from the original CE mark data package that could be used to support the US FDA requirement, specifically FDA Recognised Standard Number 11-266 or ASTM F2665. Additional testing was required to meet US FDA standard requirements. Refer to Section 2(b) above for more information.

1. For this technology, the applicable FDA Guidance document is, T*esting of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements dated* 2 February 2000.

3. Selection of a Predicate Device

A unique requirement from the US FDA for a 510(k) submission is the concept of a predicate device. A predicate device is a similar product that currently has a valid 510(k). In July 2014, the US FDA released a guidance document that clarifies that companies submitting a 510(k) should clearly identify only one primary predicate – rather than identifying multiple predicates. When identifying the predicate device, a company must ensure it considers all relevant product features, including formulation/materials, clinical indication and usage advice as well as physical characteristics.

The company identified that its implants have the same intended use, indications, technological characteristics, and principles of operation as the previously cleared primary predicate, Hintermann Series H2™ Total Ankle Replacement. Through the generation of appropriate test data, the company demonstrated substantial equivalence where no new issues of safety or effectiveness (compared to predicate device) exist.

Refer to:

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134571.htm

4. Performance Test Requirements

Once a device classification and predicate device have been identified, the testing requirements are based on proving through test data that the product is no-worse than the predicate following relevant sections of 21 CFR Part 820. Quantitative comparisons between the subject device and the predicate device are not permitted by the FDA for a 510(k) submission. The subject device must be 'equivalent' or 'not worse than' the predicate device with regard to safety and efficacy.

For all the testing protocols that need to be created for this 510(k) submission, comparative testing is performed with a sample of Hintermann Series H2™ Total Ankle Replacement and a sample of product made by the company (subject device). In each of these protocols, the acceptance criteria is performance 'not worse than Hintermann'.

For this product, the company identified that mechanical testing needed to be conducted in accordance with FDA guidance applicable for the technology. Performance testing was performed to demonstrate substantial equivalence to the predicate device. Additional performance testing included tests per applicable sections of ASTM F2665, bacterial endotoxin testing and pyrogenicity testing. The FDA requires that the subject device meets or exceeds predicate device performance, and that it functions as intended to demonstrate substantial equivalence to the predicate device.

a. Timeline for the Generation of Test Data

Once the company creates a comprehensive testing list, and receives quotations for all the testing required, it would then schedule the testing, and ship samples to the testing lab, as applicable. Once testing begins, preparation of the 510(k) submission can commence. Performance testing often takes several months to complete.

It is not ideal to start preparing the 510(k) before ordering the testing, as changes may be needed to the performance testing summary multiple times. If 510(k) submission preparation commences after ordering of tests, then it is easier to create the entire performance testing summary.