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Medical Device Access to the US Market

TRANSITIONING FROM CE MARK TO 510(K) REGULATORY REQUIREMENTS

An early-stage NZ medical device company wants to sell a topical adhesive (cyanoacrylate) in the US market as a consumer skin/wound adhesive. The company previously achieved a 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 cyanoacrylate a medical device when it is used as a topical adhesive. 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
2. Applicable international standards and recommended guidance documents
3. Selecting a comparator product (called a primary predicate device)
4. Performance test requirements (laboratory and other testing)
5. How and when testing should be undertaken.

The company is considering whether to confirm with the FDA the appropriate classification of its topical adhesive product (using the 513(g) submission process). However, it 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 Surgiseal™, which is a Class II device. The development team has been informed there is a FDA Special Controls guidance document available that provides recommendations for the testing and regulatory submission process, but are not sure how this information impacts the regulatory pathway they used for CE mark.

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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 having a Special Controls guidance document?
3. Are there any templates we can use to save time and ensure the right format for presenting our data?
4. How long do we anticipate regulatory clearance will take in order to start planning our US launch date?
5. How can we be sure we have chosen the right comparator product (predicate device) for our application?
6. 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?

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 towards 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., FDA fee $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 'MPN', which is a Class II device requiring premarket notification via a 510(k) submission).

Refer to:

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

2. Special Controls Guidance Documents

For some products, there are recognised consensus standards (i.e. ISO Standards) that define the performance requirements for a medical device. For others there is a Special Controls document published by the FDA that identifies which performance standards the FDA requires for a specific product classification. When there is a Special Controls guidance document available, the company may submit an Abbreviated 510(k) instead of a Traditional 510(k) submission.

An Abbreviated 510(k) submission contains summaries of all the testing results required in the Special Controls document or in an ISO Standard recognised by the US FDA. Since all the required performance testing presented in an Abbreviated 510(k) submission is in accordance with a previously accepted standard, the FDA reviewer only has to verify that the performance testing identified in the Special Controls document or the ISO Standard has been completed and acceptance criteria have been met. Therefore, the reviewer needs less time, and the FDA performance target for making a decision regarding clearance is 60 days – instead of 90 days.

3. Templates for Data Format and Presentation

The FDA has guidance documents related to 510(k) submissions, such as: '*Format for Traditional and Abbreviated 510(k)'s'*. By following this document verbatim, a company can avoid a lot of time-consuming questions from a reviewer who is having trouble finding the information they are looking for.

Additionally, a specific format for an Abbreviated 510(k) is described for some specific products (in this case for topical adhesives) that may identify some additional testing required that companies may not generally anticipate. See Performance Test Requirements section below.

4. Time to Gain Market Clearance

Most new products can only achieve initial 510(k) clearance from the US FDA by submitting a Traditional 510(k). Although the FDA has a target of this process taking 90 days, the average actual time for determination of 510(k) clearance is currently between 120 and 180 calendar days.

See also target time of 60 days for where Special Controls document exists (in section 2, above).

Refer to:

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm

5. Selection of a Primary Predicate

A unique requirement from the 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 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.

In the case of topical adhesives, the applicator is one of the primary differences between legacy products and more recent 510(k) submissions. The most recent version of Surgiseal™ has a similar applicator design and therefore Surgiseal™ is selected as the primary predicate device for this company's 510(k) submission.

Refer to:

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/P remarketSubmissions/PremarketNotification510k/ucm134571.htm

6. 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 Surgiseal™ and a sample of product made by the company. In each of these protocols, the acceptance criteria is performance 'not worse than Surgiseal™'. Where a Special Controls document exists, all the performance testing requirements are specified in this document. The guidance document also identifies several risks and their recommended mitigation measures that include testing and labelling recommendations that a company should implement:

IDENTIFIED RISK	RECOMMENDED MITIGATION MEASURES
Unintentional Bonding or Product Leaks into Eyes	Section 7 Bench Testing Section 13 Labeling
Wound Dehiscence	Section 7 Bench Testing Section 8 Shelf Life Testing Section 10 Animal Testing Section 13 Labeling
Adverse Tissue Reaction and Chemical Burns	Section 9 Bench Testing Section 10 Animal Testing
Infection	Section 7 Bench Testing Section 12 Sterifity
Applicator Malfuction	Section 7 Bench Testing
Delayed Polymerization	Section 7 Bench Testing Section 10 Animal Testing

In this case, the risks of adverse tissue reaction, chemical burns and infection have all been identified and would be addressed by biocompatibility testing and sterility testing. The company should also consider performing animal testing to identify any problems in a simulated use environment (as submitted for CE mark). Additionally, the client had not performed any testing to specifically address unintentional bonding, wound dehiscence, applicator malfunction or delayed polymerisation for CE mark, which are now specified in the Special Controls guidance document required by the US FDA. The company needs to generate verification protocols and test reports to address each of the specific risks identified.

a. 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.