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Review Article

Corroboration Development and Regulatory approval of Fibrin Sealant

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Abstract

Objective

Finding the relation between scientific evidence development and regulatory approval of medical devices in existing markets, USA (United states of America) and EU (European Union)

Design

To understand this relation, we used evidence development of fibrin sealant as a case study. In general fibrin sealant is a good case study because there is a lot of information available about it.

A systematic review method based on the Cochrane handbook was used to find the evidence development regarding fibrin sealant. We investigated different indications of fibrin sealant, the year of publication, and the phases in clinical trials. To find the procedures and requirements of the approval for fibrin sealant, we searched the government website of their regulatory agencies FDA (Food and Drug Administration), EMA (European Medicine Agency), and CFDA (China Food and Drug Administration).

Results

The relation between evidence development and approval, we found that the cumulative publications of fibrin sealant increased almost in a straight line from 1998 to 2019. Regarding the applications of fibrin sealant, in the first four years after 1998, no new applications were approved, the next four years, two applications were approved, in the four years after that, there were four new applications.

Conclusions

In the first years, the amount of new approved applications is very low, compared to the amount of new publications, but afterwards it goes much faster. Even though fibrin sealant seems to be a Medical Device, the regulatory approval takes time to catch up. For the future research, it would be interesting to also include sales data of fibrin sealant to analyse how sales data influences the medical device companies' strategies for publication and market approval.

Keywords: Regulatory approval, Fibrin sealant, FDA, EMA, CFDA, Medical Device

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1. Introduction

1.1 Trends in Medical Device Development and Approval

The process of developing and approving medical devices has changed in the past decades, as it becomes more difficult to get medical devices approved. First there are new hurdles for medical devices development and approval. Second, medical device companies invest more on R&D, but only fewer medical devices were approved. However, there are also emerging markets that present new opportunities. We first explain the hurdles and then the opportunities.

First, there are new hurdles for the medical device approval. Traditionally, safety, efficacy, and quality of manufacture are the first three hurdles. When the medical device had passed these three hurdles it would be approved for market access. (1) However, the regulatory approval requirements have changed. New guidelines for conducting clinical trials have been published, the regulatory requirements of future medical device development have increased, achievement for regulatory marketing approval becomes longer and more resources are needed. (2) For example, in the US, the FDA (CDRH) has made the regulatory approval stricter with the FDA Amendments Act of 20017 and introduced

mandatory risk evaluation and mitigation strategies (REMS). One reason why the FDA became stricter is because of incidents such as Implantable cardioverter defibrillator (non-CRT), that experience rapid battery depletion due to a low resistance path developing within the circuit component. There have been seven confirmed failures (9%). (3)

Second, to meet the high standard of approval requirements, medical device companies have to do more research. The current situation is that medical device companies invested a lot of money in R&D, but fewer medical devices were approved by FDA. However, the cost of international industry on R&D increased from 60 billion USD to 154 billion USD per year from 2009 to 2019; however, the approved new medical devices were decreasing from 40 per year to 26 per year. (4) Thus there is a problem with cost effectiveness of R&D of medical device companies; more cost must be earned back by fewer medical devices.

Third, because of the rising costs, medical devices reimbursement is becoming another hurdle for development and commercialization. In the past it was sufficient to pass only three regulatory hurdles: safety, efficacy, and quality of manufacture. However, health care purchasers and budget holders have faced a great deal of pressure because of changing demographics, availability of innovation and new technology, and the increasing patient expectations. For instance, the number of aging people is increasing gradually, and health care purchasers have more opportunities to choose new technologies. (1) Also because of the economic crisis, governments around the world are trying to find solutions for their health account deficits, for instance restricting reimbursements of medical devices. For example, in France, the government has introduced a new reimbursement strategy, the reimbursement rates of 110 medical devices of low therapeutic value were cut from 35% to 10-20. In Germany, reimbursement decisions are affected by a cost-effectiveness analysis, and the reimbursement becomes more difficult. (5)

Fourth, emerging markets present new opportunities for the medical device industry. (Medical devices & Biotech Industry Global Report., 2019) Medical device manufacturers nowadays can turn their business into developing countries, such as China, Brazil, Russia, and India. The business of the medical device industry in emerging markets has increased two-fold. (6) China and India are considered to be leading the emerging markets. (7) There is a rising demand for medical devices to treat chronic diseases, the Chinese government spending on healthcare, medical device market increased 20% in 20019. The size of China's medical device market has doubled to 80 billion USD by 2018.

1.2 Impact on Medical device and Evidence Development

Given these trends, medical device companies can follow different strategies:

1. Approve more products in emerging markets

2. Continue to get approval for products existing markets (the US and EU)

First, we already mentioned that emerging markets are becoming the essential growing elements for medical device industries. So maybe they will approve more medical devices in emerging markets, not only in the US, EU, but also in countries such as in China, India and Brazil. Different countries have different medical device approval process and requirements. In practice, there are three major medical device approval agencies: CDRH (UCFDA), MDD (EU).and CFDA, the FDA decides about the US, MDD about EU and CFDA about China. Approval procedures and requirements are different in these countries. Most medical device companies are from the US which also is a large market. Therefore, it is logical for these companies to apply first in the US, then in EU, and finally in developing markets such as in India and China. However, the regulatory agencies in India and China might work faster or be less strict.

Second, companies can focus on getting existing medical devices approved for new purposes. The US (and also the EU) is still a large market. Forty percent of the global medical device market is still in the US 8). There are on-label and off-label indications of medical devices. On-label indications of medical devices are FDA-approved indications. These medical devices are widely used in the US. Off-label indications of medical devices are non FDA-approved indications. However, off-label indications are also popularly used in clinical trials. Once a medical device is approved for one indication, it may be used for off-label indications, which can be used for different doses, different conditions, or different population. Off-label indications of a medical device are generally legal, however, promotion of off-label indications by medical device manufacturers are illegal, because they have not been approved for market access. (9) Off-label indications markets are limited, as promote sales by medical device companies are illegal, otherwise medical device companies would be fined seriously. (10) However, off-label promotion still happens, maybe medical device companies can invest more on off-label indications of medical devices, which can be approved by FDA in the future.

Because of these choices, it is not clear what the influence is on the medical device approval and evidence development. Companies can follow two strategies:

a) Strategy S1: companies focus on emerging markets

As emerging markets are essential growing elements for medical device companies, they have to follow rules in these markets and will publish only studies that help sell in these markets.

b) Strategy S2: companies focus on the US and EU

Forty percent of the global medical device market is still in the US and EU. Medical device companies can continue to publish papers for the US market to meet the high standard requirements for medical device approval. Medical device companies can publish more off-label studies of existing medical devices

2. Objective

Our objective is to investigate the evidence development and the regulatory approval of medical devices in different countries and to understand the effect of existing trends on the approval process. We will choose one specific product to answer these questions. We do this with a case study on fibrin sealant, with a systematic review for several reasons. One reason is that fibrin sealant already has developed for a long time. The first commercial fibrin sealant was available in EU in 1970s, but it took until 1998 for fibrin sealant to be approved by FDA in the US. Thus, there is a lot of evidence and many companies already filed for approval. Also, fibrin sealant is developing over time for new indications, and it has several off-label indications, some of them can be approved by FDA in the near future. Finally, fibrin sealant is also used in emerging markets, such as in India, China and Brazil. Thus, the main research question is:

What is the relation between scientific evidence development and regulatory approval of fibrin sealants in the US and EU?

The sub research questions are:

1. How has the Evidence Developed about Fibrin Sealants from Pre-Clinical Trials to Clinical Trials from 1998 until 2019? 2. How do Regulatory Hurdles Affect the Approval of Fibrin Sealant? 3. What is the Relation between the Scientific Evidence on Fibrin Sealants and Regulatory Approval? 4. Which of these two Strategies S1 and S2 is Favoured by Companies Based on the Results of Q1, Q2 and Q3?

This information can be used in the following ways: First, patients, doctors, hospitals, governments will learn more about the safety, efficacy and cost- effectiveness of fibrin sealant. As patients they would consider how safe and effective of the medical devices are. Because costs in hospitals are increasing significantly, doctors and hospitals have to think of cost-effectiveness, cost-savings of using new medical devices. Second, governments also take more consideration of cost-savings of using new medical devices. The medical device companies can improve their development and marketing strategy for fibrin sealant in different countries with this information. Third, the case study results can be generalized to other products; understanding of trends in the medical device market sector can help governments to improve regulation and reduce costs.

We now present the evidence accumulation for different indications, hemostats, tissue sealants, adhesives, and face-lifts. For each of the indications approved by FDA, we will collect the scientific evidence development of on-label indications from 1998 to 2019. The evidence development of on-label indications will be shown from pre-clinical trials to clinical trials.

3. Methods

Systematic reviews

A systematic review collects all the best available evidence from literature regarding a specific research question by using definite, systematic. (11, 12) We will discuss two methods, one is Cochrane Handbook for Systematic Reviews, and the other is Standards for Systematic Review.

Cochrane Handbook for Systematic Reviews of Interventions

One specific method for doing a systematic review is described in the Cochrane handbook. This is written by the Cochrane Collaboration. The Cochrane Collaboration is an international organization and its mission is to help the general public, healthcare providers, policy makers, and patients make definite decisions by providing the best evidence. They use systematic review to collect the best evidence. (13)

The Cochrane Handbook for Systematic Reviews of Interventions presents advances of systematic review methodology with the latest information. (14)

The second part of this handbook indicates the general methodologies of a systematic review, including eight steps:

- Defining the review question and developing criteria for including studies
- Searching for studies
- Selecting studies and collecting data
- Assessing risk of bias in included studies
- Analysing data and undertaking meta-analyses
- Addressing reporting biases
- Presenting results and 'Summary of findings' tables
- Interpreting results and drawing conclusions
- We explain these steps in more detail:

The first step for a systematic review is to define the research question and develop criteria for data inclusion. A systematic review should start with a research question, which has to specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes (also known as PICO: Participants, Interventions, Comparisons, and Outcomes). The process of review begins with well-defined research questions that help to ensure the criteria of data inclusion and exclusion, decide about the search strategies, data collection and analysis. (15) Eligibility criteria are the pre-specification of criteria for data inclusion and exclusion in systematic review. This is the key point to recognize a systematic review from a narrative review. They are developed by considering PICO in systematic review. (16)

The second step is searching for studies. The handbook recommends several databases: MEDLINE, EMBASE, and CENTRAL (The Cochrane Central Register of Controlled Trials). These three are the most important sources to search in systematic review. MEDLINE and EMBASE can be searched by using words in the title or abstract and the standardized indexing terms. CENTRAL offers the most widely used source of studies of

controlled trials. PubMed, a free version of MEDLINE. (17), is also popularly used. MeSH (Medical Subject Headings) is a vocabulary thesaurus that is used for indexing studies for PubMed, which is managed by the US National Library (U.S. National Library of Medicine, 2012). Both MeSH terms and free-text are combined together by using AND or for searching. Some national and regional databases are not available in MEDLINE and EMBASE. For example, the Chinese Biomedical Literature Database (CBM), and PASCAL used in Europe searching are not included. (17)

The third step is selecting studies and collecting data. The selected data has to meet the eligibility criteria for inclusion. Reference management software can be used to remove overlapped information in the same study, or examine titles, abstracts, or full-text articles to meet the inclusion criteria. The date collection forms are also used for data selection. After

The fourth step is about the bias. A bias is an error or a deviation from the truth in results or inferences in a systematic review. Type of bias includes selection bias, performance bias, attrition bias, detection bias, and reporting bias. In a Cochrane review, the evaluation process is called the assessment of risk of bias in included studies. In clinical trials, the sources of bias are from sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, or selective outcome reporting. Domain-based evaluation is the tool recommended by Cochrane Collaboration to evaluate risk of bias. (18)

The fifth step is about data analysis and meta-analysis method. Meta-analysis is the statistical method to combine the results from different studies. A special software tool called RevMan can be used for the types of meta-analyses performance. (19)

The sixth step is addressing reporting biases. Reporting biases include publication bias, time lag bias, multiple (duplicate) publication bias, location bias, citation bias, language bias, and outcome reporting bias. Two specific ways to reduce or avoid reporting bias are: the inclusion of unpublished studies in systematic. Funnel plots methods are used for detecting reporting biases. (20)

The seventh step is about results and conclusions. A system has been developed by the GRADE Working Group (GRADE stands for Grades of Recommendation, Assessment, Development and Evaluations). This system is used for evaluating the quality of evidence in systematic review. It was divided into four levels by the GRADE approach: high, moderate, low, and very low levels. The highest level is based on randomized trials. Results can be presented by ways of statistical analysis, dichotomous outcomes, and continuous outcomes. Conclusions are specified to implications for practice and implications for research. (21)

Standards for Systematic Review

Another publication about systematic review is the "Standards for Systematic Reviews", which published by the Institute of Medicine of the National Academic in 2019. (22) It gives several standards for systematic reviews:

a. Standards for Initiating a Systematic Review

   To start a systematic review, a team with expertise should be built. Expertise can be in the pertinent clinical content areas, in systematic review methods, in searching for relevant evidence, and in quantitative methods.

b. Standards for Finding and Assessing Individual Studies

   The first step is to conduct a comprehensive systematic search for evidence. The next steps are to take action to address potentially biased reporting of research results, screen and select studies. These are followed by the next steps: document the search, manage data collection, and critically appraise each study.

c. Standards for Synthesizing the Body of Evidence

   First, using a pre-specified method to evaluate the body of evidence, conduct a qualitative synthesis, and a qualitative analysis, the systematic review will include a quantitative analysis (meta-analysis).

d. Standards for Reporting Systematic Reviews

   Prepare final report using a structured format, peer review the draft report.

4. Literature Selection Criteria

The search terms are finalized on the basis of common name, material, intended use and indications The suitability of article for inclusion/exclusion was performed as per following criteria;

Screening

a. Once the search terms are finalized, literature are searched using them.

b. The results of each search terms shall be filtered as requirement and further screening is performed.

c. The Tittles and abstracts are studied on-line to take and overview of the literature. The article is reviewed for its relevance to performance and safety of product.

d. Repeated articles shall be excluded during screening.

e. Literatures found relevant are further downloaded for selection.

Inclusion Criteria

a. Data which is most comprehensive and up-to-date available.

b. The Literature provides data of equivalent device addressing its generic name/brand name,

c. Literature selected is objective and justified the relevant data i.e. both favourable and unfavourable

d. Literature preferably come from recognized, scientific, peer-reviewed journals in the field

e. Literature provides data about risk, safety & effectiveness of the product.

f. Independent review papers describing performance/technical or non-clinical results of equivalent product.

g. The literature clearly describes and evaluates the application of equivalent device, either by describing case studies, clinical study and/or they should describe the background of its mode of action, safety, adverse event.

Exclusion Criteria

a. Literature contains information not relevant to the product/ its intended use.

b. Literature contains unsubstantiated opinions.

c. Literature contains insufficient information to analyse device performance and safety.

d. Literature that's contains information other than claimed.

e. Repeated Literature shall be excluded during screening.

Selection of Literature

a. The articles are reviewed and included/excluded as per criteria.

b. The included articles are further appraised and evaluated.

5. Fibrin Sealant

We now explain more about the medical device that we will research in this review. TachoSil is a sponge sealant patch that is coated with the active substances human fibrinogen and human thrombin. TachoSil is used in adults during an operation, to stop bleeding and to seal the surfaces of internal organs, as support to stitching during surgery on the blood vessels, during neurological surgery to prevent leakage of the fluid surrounding the brain (called cerebrospinal fluid or CSF). TachoSil is used when standard techniques are not sufficient.

These components are fibrinogen and thrombin. When they are put together, they mimic the final stages of blood coagulation, where a stable, physiological fibrin clot is formed. During the final phase of the coagulation cascade, thrombin in the presence of calcium converts fibrinogen to insoluble, loose fibrin threads. Fibrin sealants facilitate haemostasis by mimicking this final phase of the coagulation cascade which leads to the formation of a semi-rigid clot. The manufacturing process of Fibrin sealant is shown below in figure 1. (23)

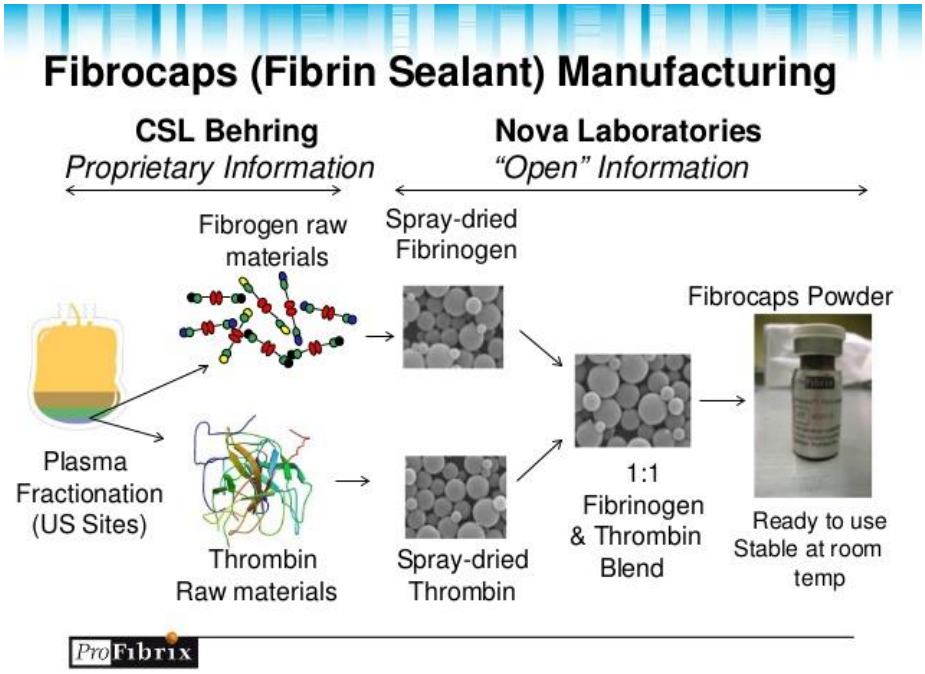

Figure 1. Manufacturing process of Fibrin sealant

Seven clinical trials were carried out on Tachosil for specific indications of use. Two of the studies looked at the effects of TachoSil in stopping bleeding. The studies compared the effects of TachoSil and an argon beamer (a device that sears the cut surface and reduces bleeding) in a total of 240 adults having liver surgery. The main measure of effectiveness was the time until the bleeding stopped. A third study compared TachoSil with standard stitching in 185 patients having kidney surgery.

Two studies were carried out to see if TachoSil could be used as a tissue sealant. The studies compared TachoSil and standard surgical techniques, such as stitching and stapling, in a total of 490 patients having lung surgery. Effectiveness was measured by looking at whether air leaked from the lungs after surgery.

A sixth study looked at the effectiveness of TachoSil in surgery on the heart or major blood vessels. The study compared TachoSil with standard materials in 120 patients, of whom around three-quarters also had surgery

on vessels with stitches and one-quarter had surgery on the heart. The main measure of effectiveness was the number of patients whose bleeding had stopped after three minutes.

Another study in 726 patients compared TachoSil with current techniques used in daily practice in preventing CSF leakage during neurological surgery. (24)

The Committee for Medicinal Products for Human Use (CHMP) decided that TachoSil's benefits are greater than its risks for supportive treatment in surgery for the improvement of haemostasis, to promote tissue sealing and for suture support in vascular surgery where standard techniques are insufficient. The Committee and recommended that TachoSil it be given marketing authorisation. The European Commission granted a marketing authorisation valid throughout the European Union for TachoSil to Nycomed Austria GmbH on 8 June 2004. The marketing authorisation was renewed on 8 June 2009.

Hemostat, sealant, and tissue adhesive were FDA approved indications of fibrin sealant. Face-lift as the new indication was approved by FDA in 2019 (FDA, 2019). Hemostat is capable of clotting blood; sealant provides a sealing block in the presence or absence of blood; adhesives bond tissues together, face-lift adhere tissue flaps in facial rhytidectomy surgery. Sealant. Marker available fibrin sealant are shown below in Table 1. (25)

Table 1 *– Hemostatic agents and tissue adhesive available in the United States.*

Component	Brand Name	Manufacturer
Hemostatic Agents		
Fibrin sealant	Tisseel VH ® Crosseal®	Baxter Healthcare Omrix
Gelatin matrix thrombin	FloSeal®	Baxter Healthcare
Thrombin	Thrombin-JMI®	Jones Pharma
Gelatin sponge	Gelfoam®	Pharmacia Upjohn
Oxidized cellulose	Surgicel®	Ethicon
Collagen sponge	Actifoam®	CR Bard
Collagen fleece	Avitene®	CR Bard
Recombinant factor VIIa	NovoSeven®	Novo Nordisk A/S
Tissue Adhesives		
Fibrin sealant	Tisseel VH ® Crosseal®	Baxter Healthcare Omrix
Polyethylene glycol	CoSeal®	Baxter Healthcare
Cyanoacrylate	Dermabond®	Ethicon

6. Development history

Fibrin sealant was first used to promote wound healing in. (26) A few years later, Grey's. (27) and Harvey's. (28) used fibrin tampons and thin fibrin plaques to bleeding surfaces. When purified thrombin was available, Cronkite et al. (29) first combined fibrinogen and thrombin to form fibrin sealant to enhance adhesion of skin grafts to burned soldiers. It was reported that because of low fibrinogen concentrations, the formation of fibrin sealant had low adhesive strength. The absence of concentrated sources of fibrinogen limited the application development of fibrin sealant for Hemostat. (30) Afterwards, the techniques of the rheological properties of fibrin sealant, such as tensile strength, elasticity and adhesiveness was improved significantly, also the fractionation methods for plasma had a great progress, and more and more concentrated fibrinogen was available. (31)

The first commercial fibrin sealant made from human fibrinogen and human thrombin was available in 1972 in Europe, and then in Canada and Japan. (32) During the late 1970s, the commercial fibrin sealant has been widely used in Europe. However, because the first commercial fibrin sealants used a concentrated source of human fibrinogen, there were concerns about the high risk of virus transmission, which limited fibrin sealant use in the United States until 1998. In 1998, TISSEEL was the first fibrin sealant approved by FDA. Since then, fibrin sealant has been approved by FDA for many indications, including hemostasis in cardiopulmonary bypass, splenic injuries, liver surgery and general surgeries, sealing in tissue anastomosis, and skin graft adhesive for burning wound. In 2019, face-lift as a new indication was approved by FDA. Fibrin sealant has been used to adhere tissue flaps during facial rhytidectomy surgery

7. Regulatory history

Commercial fibrin sealant was first approved by the FDA in May 1998. Because of possible viral transmission diseases such as HIV, hepatitis B and C virus, the FDA delayed the approval for fibrin sealant. In 1978 the FDA withdrew the approval for use of commercial fibrinogen because of fear for the virus transmission. (32)

Because more and more clinical researches reported that fibrin sealant was safe and efficacious in clinical trials. Especially techniques of virus inactivation were developed significantly, for instance Nano filtration and heat pasteurization, which led TISSEEL as the first commercial fibrin sealant was approved by FDA on first of May 1998. These FDA-approved fibrin sealants contain human fibrinogen and human thrombin. (33) Later TachoComb, Tachosil were given approval by EU and FDA. An anti-fibrinolytic agent and bovine aprotinin

were also approved. However, the last fibrin sealant had no bovine materials because of side effects to bovine aprotinin.

Only in one case a human parvovirus transmission was suspected in Japan, out of more than four million procedures of commercial fibrin sealant that have been used word-wide for different clinical purposes. Later, techniques of virus inactivation, such as solvent detergent cleansing were improved and sensitive virus detection techniques were developed. (34) Thus, more products derived from human plasma were possible and the risk of diseases transmission became lower. (35)

On-label indications for fibrin sealant were FDA-approved indications that include Hemostat, sealant, adhesive and face-lift. Off-label indications for fibrin sealant were non-FDA approved indications, which have been used for many applications, for instance medical device delivery and tissue engineering. (36) Because we are interested in the relation between evidence development of fibrin sealant and regulatory approval, we only focused on on-label indications.

8. Results and discussion

Our main objective is to find the relation between scientific evidence development and regulatory approval of fibrin sealant.

Q1: How has the Evidence Developed about Fibrin Sealants from Pre-Clinical Trials to Clinical Trials from 1998 until 2019?

First, we investigated the evidence development of fibrin sealant by a systematic review, using 58 articles. Most of these studies were from US and EU. Our research showed that on-label indications of fibrin sealant are very efficacious and effective. We only found a few studies that showed negative results of using fibrin sealant. Hemostats are very efficacious to control the blood loss, and reduce the blood transfusion during all kinds of surgeries. Tissue sealing is used to construct a sealing in tissue anastomosis, which is effective to improve the strength of anastomosis. Adhesives are very efficacious for burned skin grafting. The skin grafting survival rate was increased slightly by adhesives. The results also showed that thin layer fibrin sealant is more effective than thick layers. Face-lift is a new indication of fibrin sealant, which is very effective to reduce hematoma for facial rhytidectomy surgeries.

Concerning the risk of bias, it was shown that the risk bias of included studies was reduced from phase I to phase II and III clinical trials. Most of these studies had low risk of bias except for the risk bias of blinding, because a large amount of studies did not mention if the studies were blinded to participants or personnel or not. Because for each indication, data appeared to be missing from our set of publications, we also looked at letters regarding regulatory approval from the FDA. These showed that the evidence (efficacy, effectiveness) from approval letters was quite similar, compared to the evidence that we found by a systematic review. This evidence met the regulatory approval requirements for marketing authorization. However, we could not uncover all evidence from all phases of the clinical trials for the indications.

Q2: How do Regulatory Hurdles Affect the Approval of Fibrin Sealant?

In general, there are two phases for the medical device regulatory approval processes: Clinical Trials (CT) and New Medical Device Application (NDA). The medical device needs to pass these two phases. The regulatory approval processes check the safety, efficacy and effectiveness of the medical device. Only if there is enough evidence to show that the medical device is safe, efficacious, and effective or it benefits outweigh its known risks, it is approved for sale. Otherwise, the medical device cannot be approved for sale.

We searched the data about the regulatory approval processes and requirements in the government websites of FDA, EMA, and CFDA. Similarly, in US and China the processes are centralized authorization procedures. The difference between US and China is that in US the approval applications should be submitted to FDA directly, however in China, the applications have to be submitted to the Provincial Medical Device Administration Authorities, and then the CFDA will take the next review. If the medical devices are from outside of China (imported medical devices), the applications should be applied to FDA directly. Concerning the applications in EU, there are two paths to bring medical devices onto the market-centralized or nationalized approval procedures. Centralized authorization is done by EMA, and nationalized procedures are managed by each country.

We also searched the approved applications on these websites. There were four indications of fibrin sealant approved by FDA from 1998 to 2019. Hemostat was the first approved indication by FDA in 1998, at the same time, the indication tissue sealing was approved, next adhesive was approved for burn skin grafts in 2008, and then in 2019 face-lift was approved for using in facial rhytidectomy surgery. In EU, hemostasis was approved by EMA in 2004 and further indications followed like FDA, and in China it was approved in 2010.

Q3: What is the Relation between the Scientific Evidence on Fibrin Sealants and Regulatory Approval?

In section 4.2 about the scientific evidence accumulation of fibrin sealant, it was shown that each indication of fibrin sealant was very efficacious and effective from pre-clinical trials to phase I, II, and III clinical trials. If fibrin sealant could be sold in the market, it had to meet the regulatory approval requirements for marketing authorization. From the approval letters of fibrin sealant, it could be seen that the scientific evidence development of fibrin sealant met the regulatory approval requirements.

If we look at the cumulative publications of fibrin sealant, we see that they increased almost in a straight line from 1998 to 2019. Concerning the cumulative applications of fibrin sealant, we found that in the first four years after 1998, no new applications were approved, the next four years, two applications were

approved, in the four years after that, there were four new applications. The conclusion is that in the first years, the amount of new approved applications is very low, compared to the amount of publications, but afterwards it goes much faster.

RQ4: Which of These Two Strategies S1 and S2 is Favoured by Companies Based on the Results of RQ1, RQ2 and RQ3?

At the introduction part of this thesis, it was mentioned that there are two strategies S1 (companies focus on emerging markets) and S2 (companies focus on the US and EU) to develop potential markets for companies in the future. It was shown based on the results of these research questions that approved indications of fibrin sealant was growing faster in US and EU, compared to approved indications in China from 1998 to 2019. Also it was indicated from the included studies that most of studies were from US and EU. Now medical device companies still focus on their markets in US and EU.

In total 32485 articles were found that were published between 1998 and 2019, using the method described in section 3. These articles included on-label and off-label indications of fibrin sealant.

The data exclusion process mentioned in section 3.2. Finally, 58 articles were included in this study. There are 30 studies about hemostasis, 15 studies related to tissue sealing, 6 studies for adhesive, and 7 concerning face-lift. For the indications of hemostasis and face-lift, we found more studies of phase III clinical trials; and for tissue sealing more pre-clinical studies were found. We observed efficacy and effectiveness of fibrin sealant for each indication. Most publications of fibrin sealant are from the US and EU. There were no studies from China and India

9. Evaluation of Research Methods

A systematic review method based on the Cochrane handbook was used to find the evidence development regarding fibrin sealant. It was shown that on-label indications are efficacious and effective. However, some articles showed negative results. Even though these articles are the exceptions, we are not sure if there were not more articles about the negative results of using fibrin sealant as tissue sealing, adhesive, and face-lift, because these data are missing. We also looked at the evidence development from letters regarding approval for each indication, some missing evidence could be found in these letters, researchers should check these for missing data. Also 30 articles regarding on-label indications only showed abstracts, detailed information is not available. If we have all these data, the evidence development in all clinical trials could have been a bit different.

To find the procedures and requirements of the approval for fibrin sealant in the US, EU, we searched the government website of FDA, EMA. However, the information about approval procedures there was in 2019, maybe approval process was different before 2019. For the approved fibrin sealant, we did not find the rejected applications for the approval. It could be that the relation between the evidence development and regulatory approval process is more complicated.

It can be seen from the publications of included studies that most of studies were from US and EU, there were no studies from India and China. The Indian and Chinese publications are available in other databases than PubMed. Future research on evidence development should include these databases also

10. Conclusion

In the first years, the amount of new approved applications is very low, compared to the amount of new publications, but afterwards it goes much faster. Even though fibrin sealant seems to be a Medical Device, the regulatory approval takes time to catch up. For the future research, it would be interesting to also include sales data of fibrin sealant to analyse how sales data influences the medical device companies' strategies for publication and market approval.

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References

1. John E. Paul, PT. 'Fourth hurdle reviews', NICE, and database applications. Pharmaco epidemiology and Medical Device Safety. 2001; 10:429-438.
2. Roger M. Echols. Understanding the regulatory hurdles for antibacterial medical device development in the post-Ketek world. Annals of the New York Academy of Sciences. 2019.p. 153-161.
3. Class 2 Device Recall Viva ICD. [Internet]. US FDA; 2016 Aug 25 [cited 2020 Dec 06]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=148794
4. Cockburn IM. Is the Medical Device Industry in a Productivity Crisis? Innovation Policy and the Economy. MIT Press. 7: (pp. 1 - 32).
5. Data monitor Report. (2019). Germany Medical Device Market Overview – New pricing rules set to negatively impact medical device sales both domestically and internationally. Research Store, Code: HC00002-001; 2007.
6. IMS Health. Pharmerging Shake-up; 2010.
7. PAREXEL White Paper. Medical device innovation, approval, market access, and the "new normal": Emerging FDA review outcome trends for new medical devices; 2010.
8. Adriane Fugh-Berman D M. Off-Label Promotion, On-Target Sales. PLoS Medicine. 2008; 5: 1432-1435.
9. Cinquegrana J, L. D. Legal: Shifting perspective on off-label promotion. Medical device Executive. [Internet]. pharmexec; 2008 [cited 2020 Dec 05]. Available from: http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=282490.
10. Elliott M. Antman, e. a. A Comparison of Results of Meta-analyses of Randomized Control Trials and Recommendations of Clinical Experts. Treatments for Myocardial Infarction. 1992; 268(2).

11. Andrew D. Oxman G H. The Science of Reviewing Research. Annals of the New York Academy of Sciences. 1993;703: 125–133.
12. Green S, H. J. Chapter 1: Introduction. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. [Internet]. 2019 Mar [cited 2020 Nov 21]. Available from: www.cochrane-handbok.org
13. Higgins JPT, G. S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration [Internet]. 2019 Mar [cited 2020 Nov 21]. Available from: www.cochrane-handbok.org
14. O'Connor D, G. S. Chapter 5: Defining the review question and developing criteria for including studies. Cochrane Handbook of Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons; 2008.
15. Lefebvre C, M. Chapter 6: Searching for studies. Cochrane Handbook for Systematic Reviews of Interventions. Wiley; 2008.
16. Higgins JPT, A. D. Chapter 8: Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008
17. Deeks JJ, H. J. Chapter 9: Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons; 2008.
18. Sterne JAC, E. M. Chapter 10: Addressing reporting biases. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons; 2008.
19. Schunemann HJ, O. A. Chapter 11: Presenting results and 'Summary of findings' tables. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons;2008.
20. Schumann HJ, Chapter 12: Interpreting results and drawing conclusions. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons; 2008.
21. Board on Health Care Services. Finding What Works in Health Care: Standards for Systematic Reviews. Institute of Medicine of the National Academies; 2019.
22. Radosevich M, G. H. Fibrin sealant: scientific rationale, production methods, properties and current clinical use. Vox Sang. 1997; 72:133-143.
23. TachoSil, human fibrinogen / human thrombin [Internet]. EMEA; 2016 May 25 [cited 2020 Nov 21]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tachosil
24. Spotnitz WD, Burks S. Hemostats, sealants, and adhesives: components of the surgical toolbox. Transfusion. 2008;48(7):1502-1516.
25. Bergel, S. Uber Wirkungen des Fibrins. Dtsch Med Wochenschr. 1909; 35:633.
26. Grey, E. Fibrin as a hemostatic in cerebral surgery. Surg Gyn Obstet., 21:452-454, 1915
27. Harvey, S, Fibrin paper as a hemostatic agent. Ann Surg. 1918; 68:66-70.
28. Cronkite EP, L. E, Use of thrombin and fibrinogen in skin grafting. JAMA. 1944;124: 976-978.
29. Matras, H. Fibrin seal: the state of the art. Journal of Oral and Maxillofacial Surgery. 1985; 43(8):605-11.
30. Radosevich M, G.H. Fibrin sealant: scientific rationale, production methods, properties, and current clinical use. Vox Sang. 1997; 72:133-143.
31. Hile, J. Fibrinogen (human): revocation of licenses. Fed Regist. 1978; 43:1131-1132.
32. FDA. Opgehaald van. [Internet]. US FDA; 2012 [cited 2020 Dec 03]. Available from: http://www.fda.gov/
33. Scheule AM, B. W. Repeated anaphylactic reactions to aprotinin in fibrin sealant. Gastrointest Endo. 1998; 48:83-85.
34. Murthy KK, H. D. Redefining the HIV infectious window period in the chimpanzee model: evidence to suggest that viral nucleic acid testing can prevent blood-borne transmission. Transfusion. 1999; 39:688-693.
35. Butler SP, Current progress in the production of recombinant human fibrinogen in the milk of transgenic animals. Thromb Haemost. 1997;78:537-542.
36. William D. Spotnitz. Fibrin Sealant: Past, Present, and Future: A Brief Review. World J Surg. 2010; 34:632-634.