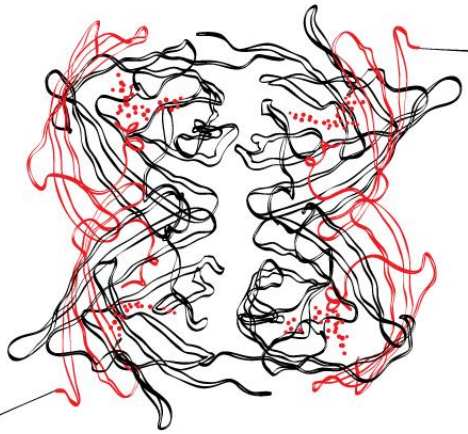
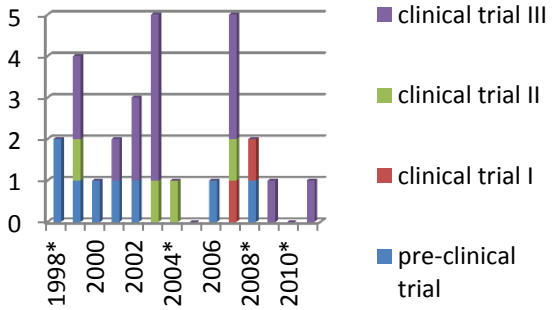
EVIDENCE DEVELOPMENT AND REGULATORY APPROVAL OF DRUGS:

A Case Study on Fibrin Sealant





Evidence Development and Regulatory Approval of Drugs

Master Thesis Health Sciences

University of Twente

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April 2013

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Abstract

Introduction
The process of developing and approving drugs has changed in the past decades. Companies have to pass more hurdles, and present more scientific evidence regarding safety, clinical effectiveness and cost-effectiveness. But there are also new opportunities in emerging markets such as China. Because of these changes, we are interested in finding the relation between scientific evidence development and regulatory approval of drugs in existing markets (US, EU), as well as in China.

Relevance
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. 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. Over time, new indications have been approved, and there are several off-label indications that might be approved by FDA in the near future. Finally fibrin sealant is also approved in China.

Method
A systematic review method based on the Cochrane handbook was used to find the evidence development regarding fibrin sealant. The research is limited to the on-label indications of fibrin sealant. No off-label indications were examined, because these cannot be commercially used in the market and our goal is to examine the relation between evidence development of on-label indications and regulatory approval. 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 in the US, EU, and China, we searched the government website of their regulatory agencies FDA, EMA, and SFDA. We analyzed the relation between evidence development of fibrin sealant and regulatory approval by looking at the relation between publications and approved indications and applications over time.

Results
It was shown that on-label indications for fibrin sealant (hemostat, colon sealing, adhesive, and face-lift) of fibrin sealant were efficacious and effective. We only found a few studies which showed any negative results of using fibrin sealant. Fibrin sealant for obtaining hemostasis was efficacious to control bleeding for all kinds of surgeries, patients needed less blood transfusion. Fibrin sealant used for colon sealing improved the strength of anastomosis and the survival rate. Adhesive used for burns skin grafting increased the survival rate of grafting skin. Fibrin sealant used for face-lift reduced hematoma rate, and shortened the recovery time.

Concerning the drug approval process, this is managed by FDA in US, EMA in EU, and SFDA in China. Generally, the process includes two phases: Clinical Trials (CT) and New Drug Application (NDA) approval process. The processes in US and China are centralized processes. However, in EU there are both centralized and decentralized (national) authorization procedures. Pharmaceutical companies can choose the centralized approval procedures, which is applied to all European countries. Regarding the national approval procedures, the drug can be approved in one or more countries.

From 1998 to 2011, there were four indications of fibrin sealant approved by the FDA. Hemostat and colon sealing were the first approved indications by FDA in 1998. Next, adhesive was approved for burn skin grafts in 2008, and then in 2011 face-lift was approved for using in facial rhytidectomy surgery. In EU, hemostasis was approved by EMA for using in cardiovascular surgery in 2004, and in China it was approved for using in general surgery in 2010. Concerning new market opportunities such as China, it is clear that pharmaceutical companies still focus on the US and EU market. Also, most of the studies included in this study came from there.

If we look at 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 2011. 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. The conclusion is that 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 very good drug, the regulatory approval takes time to catch up.

Foreword and Acknowledgements

Many years ago, I graduated from Medical College in China. Afterwards I worked for seven years at different pharmaceutical companies. At that time, I was still very young, and wanted to see what the world was like. I did not expect any difficulties when I came to the Netherlands. Like one Chinese idiom says ‘chu sheng niu du bu pa hu’, it can say in English ‘newborn calves do not fear tigers’. However, my study was not easy. To be honest, I had to work very hard at it. Finally, I will now graduate from the University of Twente, I have realized the expectations from my parents. But I could not do it alone.

Firstly, I would like to thank my two supervisors Dr. Lotte Steuten and Prof. Dr. Maarten IJzerman. Especially, thanks to my supervisor Lotte Steuten. Thanks for your patience, and thanks for giving me more chance to finish this thesis. Particularly, I would like to thank my study advisor, Mr. Martin Evertzen, thank you very much for helping me resolve many difficulties during my study.

Secondly, I would like to thank to my parents, my two brothers, and my two sister-in-laws in China, thanks for your support. Especially thanks to my husband André van Cleeff, thanks for your support, thanks that you have never given up on me, particularly thanks for your selfless love. Thanks also for the support from my parents in the Netherland.

Haiyan Wang

Nieuwegein, April 2013

Acronyms

BLA	Biologic License Application
CBER	Center for Biologics Evaluation and Research
CDE	Center for Drug Evaluation
CHMP	Committee for Human Medicinal Products
CMSs	Concerned Member States
CT	Clinical Trials
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FS	Fibrin Sealant
IND	Investigational New Drug
MeSH	Medical Subject Headings
MRP	Mutual Recognition Procedure
NDA	New Drug Application
PDAAs	Provincial Drug Administration Authorities
RMS	Reference Member State
SFDA	State Food and Drug Administration

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1. Introduction

1.1 Trends in Drug Development and Approval

The process of developing and approving drugs has changed in the past decades, as it becomes more difficult to get drugs approved. First there are new hurdles for drugs development and approval. Second, pharmaceutical companies invest more on R&D, but only fewer drugs 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 drug approval. Traditionally, safety, efficacy, and quality of manufacture are the first three hurdles. When the drug had passed these three hurdles it would be approved for market access (John E. Paul, 2001). However, the regulatory approval requirements have changed. New guidelines for conducting clinical trials have been published, the regulatory requirements of future drug development have increased, achievement for regulatory marketing approval becomes longer and more resources are needed (Roger M. Echols, 2011). For example in the US, the FDA (Food and Drug Administration) has made the regulatory approval stricter with the FDA Amendments Act of 2007 and introduced mandatory risk evaluation and mitigation strategies (REMS) (Pharmaceuticals & Biotech Industry Global Report., 2011). One reason why the FDA became stricter is because of incidents such as the antibiotic telithromycin incident (Roger M. Echols, 2011). In this incident, two of three recently FDA-approved treatment indications of the antibiotic telithromycin were withdrawn because of serious and fatal adverse events.

Second, to meet the high standard of approval requirements, pharmaceutical companies have to do more research. The current situation is that pharmaceutical companies invested a lot of money in R&D, but fewer drugs were approved by FDA. Figure 1 indicates the cost of international industry on R&D increased from 30 billion USD to 54 billion USD per year from 1994 to 2004; however, the approved new drugs were decreasing from 40 per year to 26 per year (Cockburn, 2007). Thus there is a problem with cost effectiveness of R&D of pharmaceutical companies; more cost must be earned back by fewer drugs.

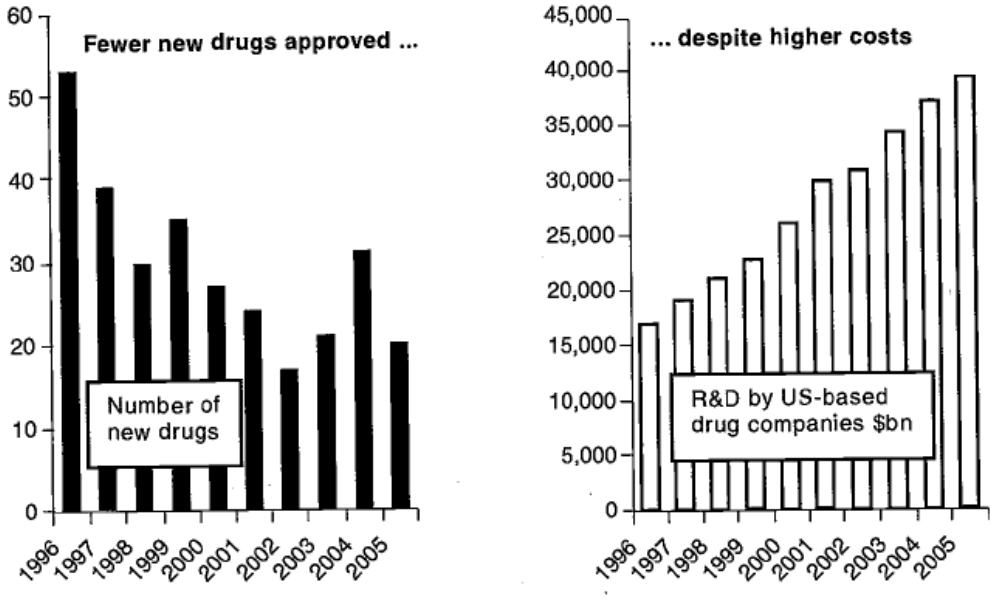

Figure 1-Number of new approved drugs by FDA and cost on R&D of drug companies in US from 1996 to 2005 (Cockburn, 2007)

Third, because of the rising costs, drugs 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 (John E. Paul, 2001). 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 drugs. For example in France, the government has introduced a new reimbursement strategy, the reimbursement rates of 110 drugs of low therapeutic value were cut from 35% to 10-20% (Pharmaceuticals & Biotech Industry Global Report., 2011). In Germany, reimbursement decisions are affected by a cost-effectiveness analysis, and the reimbursement becomes more difficult (Datamonitor Report, 2011).

Fourth, emerging markets present new opportunities for the pharmaceutical industry. (Pharmaceuticals & Biotech Industry Global Report., 2011) Pharmaceutical manufacturers nowadays can turn their business into developing countries, such as China, Brazil, Russia, and India. The business of the pharmaceutical industry in emerging markets has increased two-fold (PAREXEL White Paper, 2010). China is considered to be leading the emerging markets (IMS Health, 2010). There is a rising demand for drugs to treat chronic diseases, the Chinese government spending on healthcare, pharmaceutical market increased 20% in 2009. The size of China's pharmaceutical market will double to 40 billion USD by 2013.

1.2 Impact on Drug and Evidence Development

Given these trends, pharmaceutical 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 pharmaceutical industries. So maybe they will approve more drugs in emerging markets, not only in the US, EU, but also in countries such as in China. Different countries have different drug approval process and requirements. In practice, there are three major drug approval agencies: FDA, EMA (European Medicines Agency), and SFDA (State Food and Drug Administration), the FDA decides about the US, EMA about EU and SFDA about China. Approval procedures and requirements are different in these countries. Most pharmaceutical 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 China. However, the regulatory agencies in the EU and China might work faster or be less strict. The market in China is increasing and thus companies might have different market strategies.

Second, companies can focus on getting existing drugs approved for new purposes. The US (and also the EU) is still a large market. Forty percent of the global pharmaceutical market is still in the US (PAREXEL White Paper, 2010). There are on-label and off-label indications of drugs. On-label indications of drugs are FDA-approved indications. These drugs are widely used in the US. Off-label indications of drugs are non FDA-approved indications. However, off-label indications are also popularly used in clinical trials. Once a drug 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 drug are generally legal, however, promotion of off-label indications by drug manufacturers are illegal, because they have not been approved for market access (Adriane Fugh-Berman, 2008). Off-label indications markets are limited, as promote sales by pharmaceutical companies are illegal, otherwise pharmaceutical companies would be fined seriously (Cinquegrana J, 2008). However, off-label promotion still happens, maybe pharmaceutical companies can invest more on off-label indications of drugs, which can be approved by FDA in the future.

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

1) **Strategy S1**: companies focus on emerging markets
   As emerging markets are essential growing elements for pharmaceutical companies, they have to follow rules in these markets and will publish only studies that help sell in these markets.
2) **Strategy S2**: companies focus on the US and EU
   Forty percent of the global pharmaceutical market is still in the US. Pharmaceutical companies can continue to publish papers for the US market to meet the high standard requirements for drug approval. Pharmaceutical companies can publish more off-label studies of existing drugs.

1.3 Research Objective and Questions

Our research objective is to investigate the evidence development and the regulatory approval of drugs 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 China. Thus, the main research question is:

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

The sub research questions are:

RQ1: *How has the evidence developed about fibrin sealants from pre-clinical trials to clinical trials from 1998 until 2011?*

- ***RQ1.1:*** *What is the quality of the evidence?*
- ***RQ1.2:*** *How efficacious and effective is fibrin sealant?*

RQ2: *How do regulatory hurdles affect the approval of fibrin sealant?*

- ***RQ2.1:*** *What regulatory hurdles exist for fibrin sealants in the US, EU and China?*
- ***RQ2.2:*** *When was fibrin sealant approved in these countries and for what indication?*

RQ3: *What is the relation between the scientific evidence on fibrin sealants and regulatory approval?*

RQ4*: Which of these two strategies S1 and S2 is favored by companies based on the results of RQ1, RQ2 and RQ3?*

1.4 Contributions

There are several contributions of the study:
1) We show the evidence development of fibrin sealant since 1998.
2) We give information about drug approval process and requirements in US, EU and China.
3) We relate 1) and 2), to understand the trends in the pharmaceutical market sector.

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 drugs are. Because costs in hospitals are increasing significantly, doctors and hospitals have to think of cost-effectiveness, cost-savings of using new drugs. Second, governments also take more consideration of cost-savings of using new drugs. The pharmaceutical 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 pharmaceutical market sector can help governments to improve regulation and reduce costs.

1.5 Outline

The first chapter of this thesis is the introduction. It is discusses trends of drugs development and approval, how these trends affect drugs development and approval, research objectives and questions, and the contributions of this thesis. The second chapter presents the background of the study. It shows the life cycle of drugs development, and the theoretical framework of evidence-based medicine, Cochrane handbook for systematic reviews, and background of fibrin sealant. The third chapter is methods. It explains search strategies and data inclusion and exclusion of systematic review related to fibrin sealant, and also search strategies for drug approval procedures and approved fibrin sealant. Concerning the research questions, Table 1 shows in which section which research question is answered.

Table 1-Outline of this thesis

Research Question	Answered in Section
RQ1: How has the evidence developed about fibrin sealants from lab to clinical trials from 1998 until 2010?	4.2
RQ1.1: What is the quality of the evidence?	4.3
RQ1.2: How efficacious and effective is fibrin sealant?	4.2
RQ2: How can regulatory hurdles affect the approval of fibrin sealant?	4.4
RQ2.1: What regulatory hurdles exist for fibrin sealants in the US, EU and China?	4.4.1, 4.4.2, 4.4.3
RQ2.2: When was fibrin sealant approved in these countries and for which indication?	4.4.5
RQ3: What is the relation between the scientific evidence on fibrin sealants and regulatory approval?	4.5
RQ4: Which of these two strategies is favored by companies based on the results of RQ1, RQ2 and RQ3?	4.6

2. Background

This chapter explains important literature and concepts. First, it explains Phases in Drug Development. This is used to understand evidence development, because it indicates the drug development from lab and animal studies to different clinical trials. Second, in section 2.2 (Evidence-based Medicine), we use theoretical framework of evidence-based medicine to find the best available evidence and to help make decisions in clinical practice. Third, in section 2.3 we examine how to perform a systematic review. We use this information later to investigate the efficacy and effectiveness of fibrin sealant. Fourth, section 2.4 (Fibrin Sealant) has background information on fibrin sealant.

2.1 Phases in Drug Development

The development of a drug can be distinguished by different stages, Figure 2 shows the drug development life cycle. Phases in drug development can be divided into pre-clinical trials, clinical trials, drug approval process, and market access. Pre-clinical trials means the drug is used in the lab and on animals. If enough safety and efficacy evidence has been shown about the drug, it can be used on patients and clinical trials I, II, III, and IV will start after each other. After finishing these three clinical trials, if the drug shows enough evidence about safety and efficacy in human beings, the company can apply for the approval by drug agencies (FDA, EMA, or SFDA). After the drug is approved by drug agencies, it legally can be sold in the market.
The picture also shows the uncertainty in the process. The earlier the phase, the more uncertainty there is about safety, effectiveness, and cost-effectiveness.

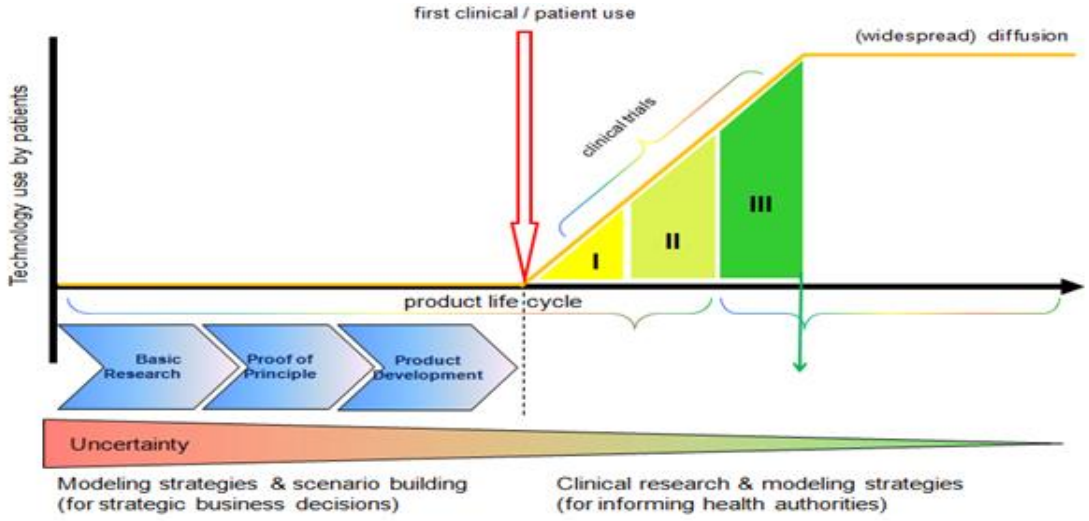

Figure 2-Phases in drug development (Steuten, 2011)

2.2 Evidence-Based Medicine

Practicing evidence-based medicine means using the best available evidence for helping to make decisions for the care of patients (Sackett DL, 1996). This requires combining clinical expertise with the best available external clinical evidence by using systematic research (Sackett DL, 1996) (Muir Gray JA., 2004).

There are five steps (Figure 3) to model evidence-based medicine in practice. They are: formulating a research question, conducting a literature search of to find the best evidence, critically appraising the evidence for its validity, applying the evidence of this appraisal in practice, evaluating the performance, reporting results and recommendations (Tanjong-Ghogomu E, 2009).

Figure 3-Model of evidence-based medicine in practice

2.3 Systematic Reviews

A systematic review collects all the best available evidence from literature regarding a specific research question by using definite, systematic methods (Elliott M. Antman, 1992) (Andrew D. Oxman, 1993). We will discuss two methods, one is Cochrane Handbook for Systematic Reviews, and the other is Standards for Systematic Review.

2.3.1 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 (Green S, 2011).

The *Cochrane Handbook for Systematic Reviews of Interventions* presents advances of systematic review methodology with the latest information (Higgins JPT G. S., 2011).

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

1. Defining the review question and developing criteria for including studies
2. Searching for studies
3. Selecting studies and collecting data
4. Assessing risk of bias in included studies
5. Analyzing data and undertaking meta-analyses
6. Addressing reporting biases
7. Presenting results and 'Summary of findings' tables
8. 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 (O'Connor D, 2008). 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 (O'Connor D, 2008).

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 (Lefebvre C, 2008), 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 OR for searching (Lefebvre C, 2008). 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 (Lefebvre C, 2008) are not included.

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

selecting data, information used for the review has to be extracted from these data (Higgins JPT D. J., 2008).

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 (Higgins JPT A. D., 2008).

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 (Deeks JJ, 2008).

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 (Sterne JAC, 2008).

The seventh step is to present results and summary of findings tables. Tables and figures are good ways to perform selected studies and findings. Many figures and tables are used to present information. For example (Schunemann HJ, 2008):

- Figures: a selection of forest plots, funnel plots, risk of bias plots and other figures.
- Characteristics of included studies tables: including risk of bias tables.
- Data and analyses: the full set of data tables and forest plots.
- Summary of findings tables.
- Additional tables.

The eighth 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 (Schünemann HJ, 2008).

2.3.2 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 2011 (Board on Health Care Services, 2011). It gives several standards for systematic reviews:

- 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.
- 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.
- 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).
- Standards for Reporting Systematic Reviews

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

2.4 Fibrin Sealant

We now explain more about the drug that we will research in this thesis. Figure 4 shows an example of a fibrin sealant syringe. It has two plungers, one for each component.

Figure 4-Fibrin sealant syringe (source TISSEEL)

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 (Radosevich M, 1997).

Hemostat, sealant, and tissue adhesive were FDA approved indications of fibrin sealant (Spotnitz, 2010). Face-lift as the new indication was approved by FDA in 2011 (FDA, 2011). Hemostat is capable of clotting blood; sealant provides a sealing block in the presence or absence of blood; adhesives bond tissues together (Spotnitz, 2004), face-lift adhere tissue flaps in facial rhytidectomy surgery.

2.4.1 Development History

Fibrin sealant was first used to promote wound healing in 1909 (Bergel, 1909). A few years later, Grey's (Grey, 1915) and Harvey's (Harvey, 1918) used fibrin tampons and thin fibrin plaques to bleeding surfaces. When purified thrombin was available, Cronkite et al. (Cronkite EP, 1944) 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 (Matras, 1985). 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 (Radosevich M, 1997). The first commercial fibrin sealant made from human fibrinogen and human thrombin was available in 1972 in Europe, and then in Canada and Japan (Hile, 1978). 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 colon anastomosis, and skin graft adhesive for burning wound. In 2011, face-lift as a new indication was approved by FDA. Fibrin sealant has been used to adhere tissue flaps during facial rhytidectomy surgery (FDA, 2012).

2.4.2 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 (Hile, 1978).

Because more and more clinical researches reported that fibrin sealant were 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 (Scheule AM, 1998). An antifibrinolytic agent and bovine aprotinin were also approved. However the last fibrin sealant had no bovine materials because of side effects to bovine aprotinin (Scheule AM, 1998).

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 (Horowitz B, 1998) and sensitive virus detection techniques were developed (Murthy KK, 1999). Thus, more products derived from human plasma were possible and the risk of diseases transmission became lower (Butler SP, 1997).

2.4.3 On-label and Off-label Indications

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 drug delivery and tissue engineering (William D. Spotnitz, 2010) (FDA, 2011). Table 2 it shows on-label and off-label indications for different applications. Because we are interested in the relation between evidence development of fibrin sealant and regulatory approval, we only focus on on-label indications in this thesis.

Table 2-Clinical usage of on-label and off-label indications

	On-label indications	Off-label indications
Clinical usage	***Hemostats:*** all surgery	
	Sealants: colonic sealing	***Sealants:*** adhesion prevention, anastomosis construction, drain removal, endothelialization, fistula closure, seroma reduction
	Adhesives: skin graft attachment	***Adhesives:*** cartilage, nerve, pleura, dermis, stem cells, mesh
	Face-lifts	***Drug delivery:*** antibiotics, immunization, chemotherapeutic agents, growth factors, local anesthetics
		Tissue engineering: cell culture, graft viability, gene transfer, organ growth

3. Methods

This chapter describes the methods we will use to answer the research questions. The main framework to answer these is evidence-based medicine (see chapter 2). Here, clinical decisions to develop and adopt biomedical innovations should be determined by the best available evidence about safety, effectiveness and cost-effectiveness. For this case study, there are five steps (Figure 5) to model evidence-based medicine regarding fibrin sealant. In the first four steps, the actual research is done, and in the last step, there is an evaluation of these steps and results and recommendations are reported.

Figure 5-Model of Evidence-based Medicine regarding fibrin sealant

Table 3 shows the research questions and the methods to answer them. Below we explain these in more detail.

Table 3-Research questions and main method

Research Question	Main Method
RQ1: How has the evidence developed about fibrin sealants from lab to clinical trials from 1998 until 2010?	Systematic review
RQ1.1: What is the quality of the evidence?	Risk of bias assessment
RQ1.2: How safe, efficacy, and effective is fibrin sealant?	Systematic review
RQ2: How can regulatory hurdles affect the approval of fibrin sealant?	We use results from RQ2.1 and RQ2.2
RQ2.1: What regulatory hurdles exist for fibrin sealants in the US, EU and China?	Searching through the FDA, EMA, and SFDA official website to study the regulations
RQ2.2: When was fibrin sealant approved in these countries and for which indication?	Searching through the FDA, EMA, and SFDA official website
RQ3: What is the relation between the scientific evidence on fibrin sealants and regulatory approval?	Systematic review and timeline for each on-label indication
RQ4: Which of these two strategies is favored by companies based on the results of RQ1, RQ2 and RQ3?	Combine the results of RQ1, RQ2, RQ3

3.1 Systematic Review for Fibrin Sealant

To answer the first research question, a systematic review was used to find the evidence development regarding fibrin sealant. Evidence development focused on the safety, efficacy, and effectiveness of fibrin sealant from lab, animal studies, to different clinical trials.

We used the Cochrane Handbook for Systematic Reviews as a basis for this. There are eight steps for systematic reviews in this handbook; seven steps were used in this thesis. Meta-analyses of analyzing data and addressing reporting biases were excluded. Meta-analysis is to use the statistical technique to integrate the results from different studies, which is not suitable for this study. We used an excel sheet to combine the results from studies instead of meta-analysis. Because the research is a case study, addressing reporting bias was also excluded. Below we list the seven steps we used in this research:

1. Defining the review question and developing criteria for including studies
2. Searching for studies
3. Selecting studies and collecting data
4. Assessing risk of bias in included studies
5. Analyzing data
6. Presenting results and 'Summary of findings' tables
7. Interpreting results and drawing conclusions

We explain several of the steps below.

3.1.1 Searching for Studies

Relevant studies to investigate the scientific evidence development for fibrin sealant were identified using the computerized database PubMed. The MeSH major search terms and specific terms for fibrin sealant were used. The MeSH major search term was *"fibrin tissue adhesive"*. The specific terms included: fibrin sealant, fibrin glue, fibrin adhesive, and tissue glue. We combined the MeSH search term *"fibrin tissue adhesive"* with the publication year for search. For example, for the publication year 1998, the combined search is *"(("Fibrin Tissue Adhesive"[MeSH Major Topic]) AND ("1998"[Publication Date]))".*
The search terms were identified in the title, abstract of articles. We included articles from 1998 to 2011.

To determine to which clinical trial step an article belongs to we can use the guidelines from the US National Institutes of Health. Clinical trials are typically done in three phases, phase I, II, III (see Table 4). In phase I clinical trials, the drug focuses on safety and pharmacokinetics in a small number of people, around 20-80. In phase II studies, the main objective is to evaluate dosage, broad efficacy and additional safety in 100 to 300 people. Phase III clinical trials are concerned more about safety and effectiveness of drug from data of different populations, dosages, also in combination with other drugs and involve thousands of individuals (1000-3000) (US National Institutes of Health, 2011).

Table 4-Phases in clinical trials

Clinical trials	Category
Pre-clinical trials	In vitro (test tube or cell culture), in vivo (animal), preliminary efficacy, toxicity and pharmacokinetics
Phase I trials	Safety (pharmacovigilance), tolerability, pharmacokinetics, pharmacodynamics, safe dosage range, side effects
Phase II trials	Effectiveness: dosing requirements (how much drug should be given), and study efficacy (how well the drug works at the prescribed dose), safety
Phase III trials	Effectiveness, side effects, safety, comparison to commonly used treatments
Phase IV trials	Post marketing or post-approval studies, drugs risks, benefits, and optimal use

In this search, we classified data mostly on phases mentioned in articles.

3.1.2 Criteria for Data Inclusion and Exclusion

There are three criteria that are used for data inclusion and exclusion for this thesis:

1. We distinguished data from on-label and off-label indications by using Table 2. All off-label indications were excluded, as off-label indications cannot be commercially used in the market and we focus on the relation between evidence development of on-label indications and regulatory approval in this thesis. All non-human fibrinogen and human thrombin derived fibrin sealant were also excluded because all approved indications were human fibrinogen and human thrombin derived fibrin sealant.
2. We classified studies by language. Only articles published in English were included.
3. We included data from 1998 to 2011, because the first on-label indication was approved by FDA in 1998, and new indications have been approved since 1998 untill now.

3.1.3 Addressing Risk of Bias in Included Studies

Type of Bias

Biases include selection bias, performance bias, attrition bias, detection bias, and reporting bias. Each of these biases has one or more causes. Each type of cause is called a domain in the Cochrane handbook (Higgins JPT A. D., 2008) and Table 5 indicates the definitions of different biases and related domains.

Table 5-Classification of bias

Bias	Definition	Related Domains
Selection bias	A systematic error that is caused by sample selection of intervention in clinical trials.	• Sequence generation • Allocation concealment
Performance bias	A systematic difference in care provided other than the interventions are being assessed.	• Blinding of participants, personnel • Other potential threats to validity
Attrition bias	A systematic difference about participants'	• Incomplete outcome data

Bias	Definition	Related Domains
	withdrawals from the interventions.	• Blinding of participants, personnel
Detection bias	A systematic difference in the ways of how outcomes are made.	• Blinding of participants, personnel • Other potential threats to validity
Reporting bias	A systematic difference in reported and unreported findings in studies.	• Selective outcome reporting

Risk of Bias Tool

The 'risk of bias' tool from Cochrane Handbook for systematic reviews is used to measure the risk of bias assessment for studies. There are two parts in this tool. The first part is talking about domain of risk of bias. The second part is to allocate a judgment for each domain of risk of bias (Higgins JPT A. D., 2008). Table 6 represents the risk of bias tool.

Table 6-Method for assessing risk of bias

Domain	Description	Judgment Criterion
Sequence generation	Check which ways were used for preventing bias in providing interventions to participants.	Was the allocation sequence completely addressed?
Allocation concealment	Check measurements used for hiding the allocation sequence and to decide if intervention allocations would be prevented in advance.	Was allocation fully hidden?
Blinding of participants, personnel and outcome assessors	Check how it was prevented that participants and personnel know which interventions of participants' received.	Was knowledge of the allocated interventions completely avoided in the article?
Incomplete outcome data	Check the completeness of outcome data.	Were incomplete outcome data fully reported?
Selective outcome reporting	Check whether the selective outcome reporting was evaluated.	Was the selective outcome reporting evaluated?
Other sources of bias	Some other biases that are not discussed before.	Were some other biases found or reported?

One of objectives of the thesis is to find scientific evidence development of fibrin sealant. Related to fibrin sealant for the method of assessing risk of bias for included studies, one of the domains 'selective outcome reporting', which doesn't influence that much on this thesis, we excluded this part for assessment and will focus on sequence generation, allocation concealment, blinding of participants, personnel, and incomplete outcome data.

Criteria for Deciding Risk of Bias

There are specific criteria for deciding risk of bias from Cochrane Handbook for Systematic Reviews. We will use these criteria to judge risk of bias in included studies. The answer of a judgment of 'Yes' shows low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias (Higgins JPT A. D., 2008). The answer 'Yes, No or Unclear' will be given based on criteria for judging risk of bias from Cochrane Handbook for systematic reviews.

Table 7-Criteria for deciding risk of bias

Domain: Sequence Generation **The Judgment: Complete sequence generation?**	
Criteria for 'yes'	To use a random way in the procedure of sequence generation, for example: Using a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice.
Criteria for 'no'	The investigators used a non-random way in the procedure of sequence generation, for example: Using date of birth; Using some rule dependent on date of admission; Determine by some rule based on hospital or clinical record number.
Criteria for 'unclear'	There is no enough information to give a clear 'Yes or No' answer.
Domain: Allocation Concealment **The Judgment: Allocation concealment?**	
Criteria for 'yes'	Participants could not see assignments of the study in advance because allocation concealed methods were used. Such as: Central allocation, which includes telephone, web-based and pharmacy-controlled randomization; Drug containers with the same appearance were numbered sequentially; Sealed envelopes were number sequentially
Criteria for 'no'	Participants could possibly see assignments of the study in advance, because: An open random allocation progress was used; Using unsealed envelops; Alternation or rotation; Date of birth; Case record number.
Criteria for 'unclear'	There is no enough information to give a clear answer 'Yes or No'.
Domain: Blinding of Participants, Personnel **The Judgment: Blinding?**	

Criteria for 'yes'	Any one of these situations below: No blinding, as the reviewers think that this situation will not affect the outcomes; Blinding to participants and key personnel, and impossibly this situation will be broken; Both participants and personnel were not blinded, but outcome distribution was blinded, bias would not be introduced.
Criteria for 'no'	Any one of these situations below: No blinding or part of blinding, this situation will affect the outcome; Both participants and key personnel were blinded, possibly the situation will be broken; Neither participants nor key personnel were blinded, bias could be introduced.
Criteria for 'unclear'	There is no enough information to give a clear answer 'Yes or No'; This outcome didn't show in the study.
Domain: Incomplete Outcome Data The Judgment: Incomplete outcome data reported?	
Criteria for 'yes'	Any one of these situations below: Outcome data complete; The missing outcome data would not affect true outcome, bias will not be presented; Numbers in intervention groups were balanced by missing outcome data; The percentage of missing outcomes is not enough to affect bias.
Criteria for 'no'	Any one of these situations below: True outcome is affected by the missing outcome data; The percentage of missing outcomes could cause bias.
Criteria for 'unclear'	There is no enough information to give a clear answer 'Yes or No'; This outcome didn't show in the study.

Example of Addressed Risk of Bias

First we now give an example of how sequence generation was addressed in several studies in Figure 8.

Table 8-Examples of descriptions for sequence generation

Study	Descriptions of Sequence Generation	Risk of Bias
Chen RJ, 1998	Sequence information is not mentioned in the study.	Unknown risk of bias
Levy O, 1999	Quote: fifty-eight patients were divided into two groups randomly.	Low risk of bias
Schenk WG, 2003	Quote: adult patients were randomized to the treatment group using fibrin sealant.	Low risk of bias
Paolo Del Rio, 2005	We performed the treatment of anastomotic leaks of the upper and lower gastro-intestinal tract with fibrin glue in 13 selected patients.	Unknown risk of bias
Jorge AG, 2010	Quote: patients were divided into study and control groups.	High risk of bias

Second, we use one article as an example to show how 'risk of bias' table for all types of domains. The title of published article is "Prospective randomized multicenter trial of fibrin sealant versus thrombin-soaked gelatin sponge for suture- or needle-hole bleeding from

polytetrafluoroethylene femoral artery grafts" (Lloyd M. Taylor, 2003). Table 9 shows the estimation of risk of bias.

Table 9-Example of how 'risk of bias' table addressed in one article

Judgment Criteria	Answer	Reason	Risk of Bias
Complete sequence generation?	Yes	Two hundred and one patients were randomized into two groups.	Low risk of bias
Allocation concealment?	Unclear	There is no information mentioned about this situation in this study.	Unknown risk of bias
Blinding?	Yes	The study was single-blinded to patients. Key personnel could not be blinded to the experimental compared with control treatment.	Low risk of bias
Incomplete outcome data reported?	Yes	It was reported in this study, one of 201 patients was excluded because surgery was not finished before completion of the vascular graft.	Low risk of bias

3.1.4 Analyzing Data

From the articles, we extracted the following types of information: title, published year, application, type of fibrin sealant, phase in clinical trials, and outcome in an excel sheet. Table 10 indicates the types of information in excel sheet.

Table 10-Categories in Excel Sheet

Data	Explanation
Title	
Published year	
Application	Studies were classified into hemostat, sealant, adhesive, or face-lift respectively.
Type of fibrin sealant	The data was selected by type of fibrin sealant that is derived from bovine, human, or autologous plasma.
Phase in clinical trial	The selected data was classified into different clinical trials by using the criteria from Table 4.
Outcome	We labeled the positive or negative outcomes of using fibrin sealant in clinical trials. For example, the positive outcomes: hospital stay and operation time can be reduced with using fibrin sealant; the negative outcomes: the blood loss during operation or after operation have not been reduced by using fibrin sealant.
Risk of bias assessment	The included articles were assessed risk of bias by using 'Risk of bias' table from the Cochrane Handbook for systematic reviews.

3.2 Data Collection for Approval Procedures and Approved Fibrin Sealant

3.2.1 Search Strategy for Approval Procedures

To find the procedures and requirements of the approval for fibrin sealant in the US, EU, and China, relevant data was searched from the government website of FDA, EMA and SFDA. "Drug approval", "new drug approval process", or "approval process" were used as key words for search. In this section, we answered the research question 2.1. Table 11 indicates the specific website of drug approval procedures from the government website of FDA, EMA and SFDA.

Table 11-Specific website of drug approval procedures

Authorization	Drug Approval Procedures Website
FDA	(Approval Requirements, 2011) (New Drug Application, 2011)
EMA	(Central Authorization Procedures, 2011) (National Health Authority, 2011)
SFDA	(Application and Approval Procedures for Clinical Trials, 2011) (Application and Approval Procedures for Imported Drugs, 2011)

3.2.2 Search Strategy for Approved Fibrin Sealant

To find the approved fibrin sealant by FDA, EMA and SFDA, and answer research question 2.2, the search terms: *"approved fibrin sealant"*, or *"fibrin sealant"* were used as the key words. The Chinese characters for fibrin sealant "纤维蛋白胶" (Pinyin: xian wei dan bai jiao) were used for searching approved fibrin sealant by SFDA. To answer the regulatory procedures and regulatory hurdles affect the fibrin sealant we searched the official websites of FDA, EMA, and SFDA. Table 12 indicates the process of finding approved fibrin sealant on the government websites, and the specific website of fibrin sealant.

Table 12-Process of finding approved fibrin sealant on the government website of FDA, EMA, and SFDA

Authorization	Website of Approved Fibrin Sealant
FDA	Home page of FDA website—vaccines, blood & biologics--blood and blood products—approved products—licensed products (BLAs)—fractionated plasma products—fibrin sealant (FDA website (1)) The products can be found by alphabetical order here (FDA website (2))
EMA	Approved Fibrin Sealant in EU (EMA website (1))
SFDA	Home page of SFDA (in Chinese)—search "纤维蛋白胶" in the category "国产药品" (medicine produced in China)—fibrin sealant (SFDA website (1))

4. Results

This chapter presents the results of our research. First, in section 4.1, it shows all publications and data inclusion and exclusion process. Second, in section 4.2, we can see the evidence accumulation for the application of hemostat, colon sealing, adhesive, and face-lift. Next we discuss the quality of included studies by using risk of bias assessment in section 4.3. Afterwards, the drug approval process and requirements about the US, EU, and China are presented in section 4.4. Next, we try to find the relation between evidence development and regulatory approval, and then we show pharmaceutical companies' preferred strategy based on the approved indications of fibrin sealant in section 4.5 and 4.6.

4.1 Data Inclusion and Exclusion of Fibrin Sealant

4.1.1 Published Data Related to Fibrin Sealant

In total 1556 articles were found that were published between 1998 and 2011, using the method described in chapter 3. These articles included on-label and off-label indications of fibrin sealant. Figure 6 shows the number of all published articles between 1998 and 2011.

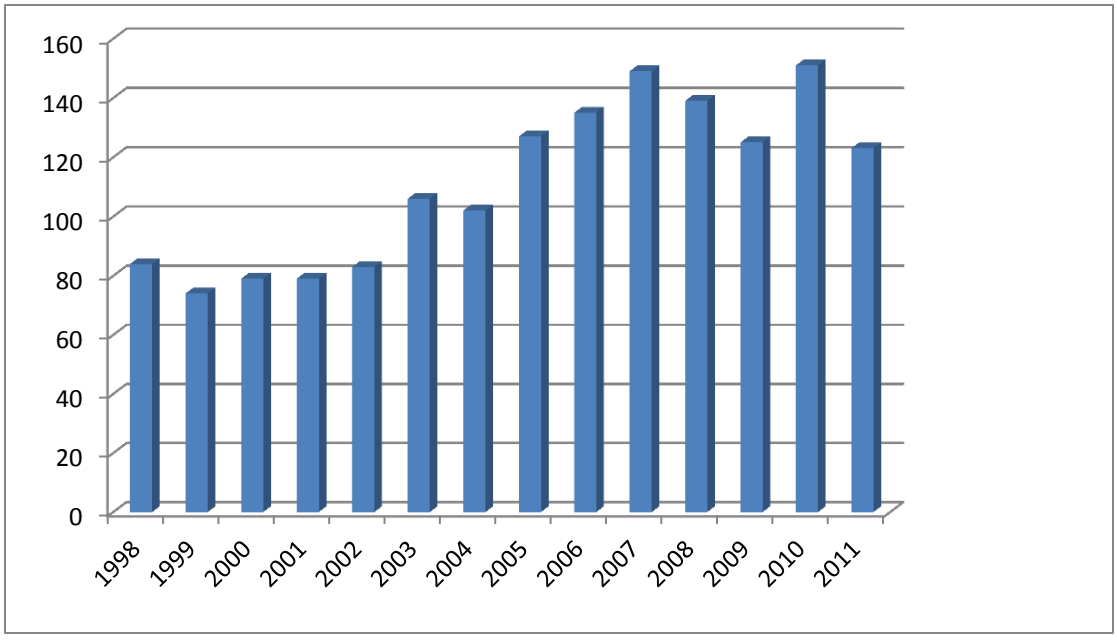

Figure 6-Number of published articles between 1998 and 2011

4.1.2 Data Exclusion Process

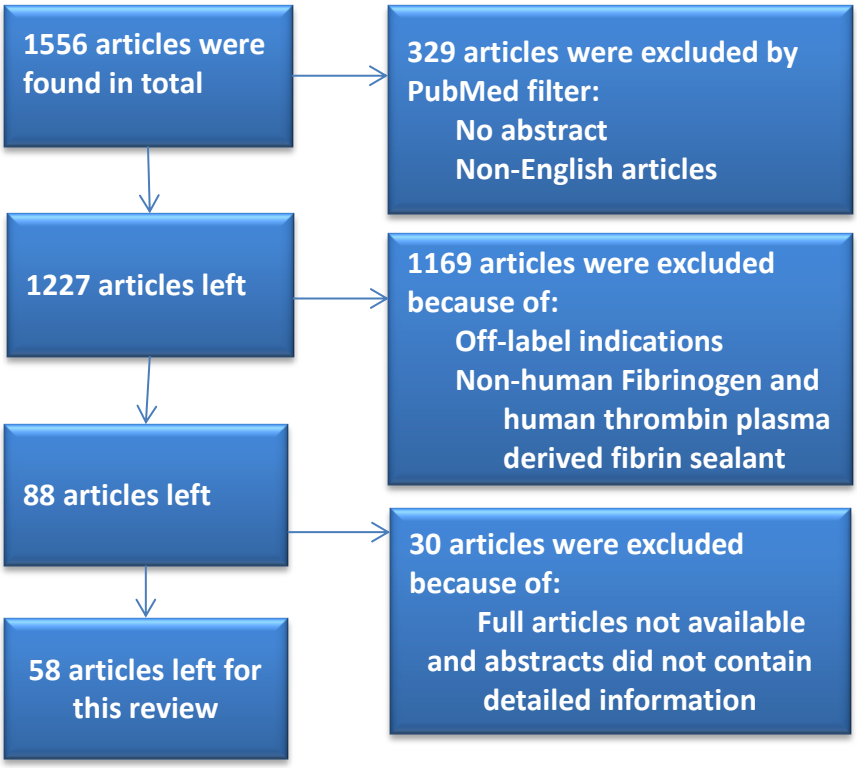

Figure 7-Data exclusion process

We now explain the data exclusion process that is shown in Figure 7. Firstly, 329 articles with no abstracts or those publications that are not in English were filtered out by using PubMed filter. Secondly, off-label indications of fibrin sealant were excluded by the criteria of on-label and off-label indications in Table 2 because we only focus on on-label indications in this thesis. Because all approved indications contain human fibrinogen and human thrombin, non-human fibrinogen and human thrombin plasma derived fibrin sealant were excluded. Thirdly, thirty non-full articles were excluded as we could not get detailed enough information from abstracts. Finally, 58 articles were included in this study.

4.2 Scientific Evidence Accumulation of Fibrin Sealant for On-label Indications

We now present the evidence accumulation for different indications, hemostats, colon 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 2011. The evidence development of on-label indications will be shown from pre-clinical trials to clinical trials.

Table 13-General information about included studies

Indication	Phase	Observations	Country
Hemostasis (30)	Pre-clinical trial: 8 Clinical trial I: 2 Clinical trial II: 4 Clinical trial III: 16	27 efficacious and effective results 3 negative results	US: 10 EU: 12 Turkey: 2 Israel: 2 Brazil: 1 Japan: 1 Taiwan: 1 Thailand: 1
Colon sealing (15)	Pre-clinical trial: 13 Clinical trial I: 1 Clinical trial III: 1	15 efficacious and effective results	US: 2 EU: 11 Turkey: 1 Korea: 1
Adhesive (6)	Pre-clinical: 3 Clinical trial II: 1 Clinical trial III: 2	6 efficacious and effective results	US: 5 EU: 1
Face-lift (7)	Clinical trial III: 6 Review: 1	7 efficacious and effective results	US: 4 EU: 2 Singapore: 1

Table 13 shows general information about the included studies. There are 30 studies about hemostasis, 15 studies related to colon 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 colon 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. Next we explain the results for each indication separately.

4.2.1 Hemostat

Bleeding control is one of the most important things during and after operations. Bleeding has to be controlled as fast as possible, because the mortality rate can be decreased dramatically by less blood loss. Hemostasis can be used for all kinds of surgeries (William D. Spotnitz, 2010). We investigate the efficacy of fibrin sealant as a hemostat to compare the blood loss with or without using fibrin sealant during surgeries on animal and human studies in clinical trials. We also indicated the effectiveness of fibrin sealant on hemostasis time by using or without using fibrin sealant.

Table 14 indicates the comparison of blood loss with or without using fibrin sealant during and after operations on animals and human beings. This table indicated that fibrin sealant used for hemostasis were very effective to control bleeding during and after operations. For example, if we look at fibrin sealant used for suture hole bleeding on pigs and human beings, they both showed that the amount of blood loss was much less with using fibrin sealant compared

without using fibrin sealant (9.2 +/- 10.6 mL and 178.8 +/- 125.5 respectively). The amount of blood loss not using fibrin sealant was more than 19 times more than with using fibrin sealant. The intraoperative blood loss was 4.0 mL and 15.6 mL with and without using fibrin sealant respectively on human beings (Dickneite G, 2000) (Lloyd M. Taylor, 2003). Other articles indicated the same result. The amount of blood loss was significantly less with using fibrin sealant in total knee arthroplasty. Table 14 reported that the range of more blood loss were 223.8 mL to 535.5 mL without using fibrin sealant in total knee arthroplasty from pre-clinical to clinical trials (William A. Curtin, 1999) (Levy O, 1999) (Wang GJ, 2001). Fibrin sealant used for hemostasis were also effective in others surgeries compared with standard surgical techniques, are like sutures. For instance, in liver injuries, aortic anastomosis, total hip arthroplasty, tonsillectomy, calvarial remodeling, and some surgeries else. The blood loss was controlled significantly with using fibrin sealant in those surgeries (Stephen M. Cohn, 1998) (Kheirabadi BS, 2002) (McConnell JS, 2011) (Vaiman M, 2003) (White N, 2009). Table 14 reports the blood loss difference, and the column in green represents the blood loss of using fibrin sealant. However, the evidence development of hemostasis of controlling blood loss during and after surgeries in phase I and II clinical trials is missing, because a lot of articles were published before 1998, and we only included studies from 1998.

There were also negative results. In a study Figueras et al presented negative results by using fibrin sealant in liver resection. The total intraoperative blood loss was higher with 883.9 +/-614 mL in the fibrin sealant group, compared with the group without using fibrin sealant with 820.3 +/- 522 mL blood loss. The results also showed in Table 14. It can be seen that 13% patients received intraoperative transfusion in fibrin sealant group, compared with the non-fibrin sealant treated group with 12%. In this study it also indicated that hospital mortality rate were 4% and 1% in group with or without using fibrin sealant respectively. The postoperative hospital stays were 13.3 +/- 13 days and 12.6 +/- 9 days in group with or without using fibrin sealant (Figueras J, 2007).

Table 14-Comparison of blood loss with or without using fibrin sealant

Phase in Clinical Trials	Blood Loss with Using FS (mL)	Blood Loss without Using FS (mL)	Duration of Blood Loss	Type of Surgery	Study
Pre	299	875	Intra- and postoperative blood loss	Liver injury	(Stephen M. Cohn, 1998)
Pre	0	107.6	Intraoperative blood loss	Aortic anastomosis	(Kheirabadi BS, 2002)
Pre	9.2	178.8	Intraoperative blood loss	Suture hole bleeding (Vascular surgery)	(Dickneite G, 2000)
III	4.0	15.6	Intraoperative blood loss	Suture hole bleeding (femoral	(Lloyd M. Taylor, 2003)

Phase in Clinical Trials	Blood Loss with Using FS (mL)	Blood Loss without Using FS (mL)	Duration of Blood Loss	Type of Surgery	Study
				artery grafts)	
Pre	469.8	1005.3	Intra- and postoperative blood loss	Total knee arthroplasty	(William A. Curtin, 1999)
III	360	878	Postoperative blood loss	Total knee arthroplasty	(Levy O, 1999)
III	184.5	408.3	Postoperative blood loss	Total knee arthroplasty	(Wang GJ, 2001)
III	820	1200	Intraoperative blood loss	Total hip arthroplasty	(McConnell JS, 2011)
III	15	29	Intraoperative blood loss	Tonsillectomy	(Vaiman M, 2003)
III	301	441	Postoperative blood loss	Calvarial remodelling	(White N, 2009)
III	883.9	820.3	Intraoperative blood loss	Liver resection	(Figueras J, 2007)

.

Fibrin sealant achieved effective hemostasis. For instance, fibrin sealant was used for the treatment of liver injuries. Liver injuries can be caused by blunt abdominal trauma and those injuries bring about a quarter of mortality rate by uncontrolled bleedings (Moore EE, 1991). To reduce the mortality rate by liver injuries, to achieve hemostasis in a short time plays an important rule. It was mentioned in the article of Tovar MC, et al. 1998 that fibrin sealant controlled hemostasis within 58 seconds in hepatic injuries in rats compared with horizontal mattress sutures achieved hemostasis with 346 seconds. Fibrin sealant controlled bleeding was more than 5 times faster compared without using fibrin sealant (Tovar MC, 1998). In other articles, it was also mentioned that fibrin sealants were much faster to achieve hemostasis compared with sutures in livery injuries. The hemostasis time was around 80 seconds with using fibrin sealant, and hemostasis time was about 180 seconds with using sutures. Fibrin sealant was much faster to control bleeding used for animals (Taha MO, 2006) (Arif Hakan Demirel, 2008). It was also very effective to control bleeding on human beings. The bleeding was controlled around 57 seconds with using fibrin sealant in peripheral vascular surgeries, however, the hemostasis time was about 1270 seconds with pressure in the same surgeries (Schenk WG, 2003). Fibrin sealant was much faster to achieve hemostasis time during a variety of surgeries. Table 15 indicated the comparison of hemostasis time with or without using fibrin sealant.

Table 15-Hemostasis time with or without using fibrin sealant

Phase in Clinical Trials	Hemostasis Time with Using FS (seconds)	Hemostasis Time without Using FS (seconds)	Method to Achieve Hemostasis without Using FS	Type of Surgery	Study
Pre	58	346	Suture	Liver injury	(Maria C. Tovar, 1998)
Pre	80	181.5	Suture	Liver injury	(Taha MO, 2006)
Pre	59	113	Suture	Liver injury	(Arif Hakan Demirel, 2008)
III	193	393		Skin grafting	(Nervi C, 2001)
III	56.3	1,269.6	Pressure	Peripheral vascular surgery	(Schenk WG, 2003)

There are other benefits of using fibrin sealant as hemostat:

- **Less liver abscesses**: the percentages of postoperative liver abscesses were much lower in fibrin sealant treated group, compared with the suture group. Maria et al showed that the percentages of liver abscesses were 7% and 3% in the suture and fibrin sealant treated group respectively (Maria C. Tovar, 1998). It was explained that the technique of fibrin sealant used in liver surgeries does not cause closed dead spaces or produce hematomas or because the fibrin clots produced by fibrin sealant. They are a poor medium for the growth of bacteria compared to normal blood clots (Bosch P, 1982). Taha et al showed that there were fewer occurrences of abscesses were significantly less with one case in fibrin sealant intervention group compared with five cases in suture group (Taha MO, 2006).
- **Less operation time**: The use of fibrin sealant also reduced the number of sutures required for an arterial anastomosis, therefore, simplified and shortened the vascular operation time in a safe and effective manner (Kheirabadi BS, 2002). Taha et al indicated that the operation time in the fibrin sealant treated group was 8.75 minutes lower compared with the suture group (Taha MO, 2006).
- **Less hospital stay**: the length of patients hospital stay was much less in the fibrin sealant group compared the group without using fibrin sealant (Avanogmacrlu A, 1999) (Mikhail AA, 2003) (Olmi S, 2007). Mikhail et al reported that patients hospital stay was 1.14 days with fibrin sealant, 1.85 days without using fibrin sealant, Olmi et al also indicated the length of hospital stay in the fibrin sealant group was 50% less compared the group without using fibrin group (Mikhail AA, 2003) (Olmi S, 2007).

In other cases fibrin sealant did not perform better. We now give some examples of these. For example, fibrin sealant was used to control bleeding on the epicardial surface in aortocoronary bypass operations. The results showed that the bypass time was much higher in fibrin sealant treated group with 115 minutes, compared with non-fibrin sealant used group with 93 minutes. It also indicated that mortality rate in fibrin sealant group was more than twice as high with

7.8%. The mortality rate in non-fibrin sealant treated group was 2.8% (Lamm P, 2007). Goerler et al 2007 also reported similar results, the bypass time was longer in fibrin sealant treated group, and the mortality rate was much lower in non-fibrin sealant treated group (Goerler H, 2007). Table 16 shows the comparison of these results.

Table 16-Comparison of bypass time and mortality rate with or without using fibrin sealant in cardiovascular surgery

Phase in Clinical Trials	Bypass Time with Using FS (min)	Bypass Time without Using FS (min)	Mortality Rate with Using FS in Cardiovascular Surgery (%)	Mortality Rate without Using FS in Cardiovascular Surgery (%)	Study
III	115	93	7.8	2.8	(Lamm P, 2007)
III	110	91	8.5	3.5	(Goerler H, 2007)

4.2.2 Colonic Sealing

Currently, there are two methods used for colonic anastomosis, sutures and staples anastomotic techniques. However, leakage is the major complication regarding to colonic anastomosis (G. Martel, 2007). The leakage rate of colonic anastomosis is approximately 4%-8% (Clemmensen T, 1983). Anastomosis could be ruptured because of infection and increased collagen defect (Hawley PR., 1973). Fibrin sealant can be used to seal the colon, when blood is present or absent (William D. Spotnitz, 2010). Fibrin sealant as a new anastomosis technique decreased leakage rate. It is easy to perform without foreign body reaction and it also decreased the wound healing time for the colonic anastomosis (Galletti G, 1986) (Detweiler MB e. a., 1995).

Bursting pressure is one of the measurements to show the strength of anastomosis. The higher bursting pressure showed the stronger strength of anastomosis. It was reported that the bursting pressure was zero when anastomotic rupture happened (Kanellos D, 2007) (Kanellos I., 2006). Table 17 shows a comparison of bursting pressure with or without using fibrin sealant after colonic anastomosis, and the column in green represents the bursting pressure with using fibrin sealant. It can be seen that bursting pressure was significantly higher with using fibrin sealant, compared with sutures in each study. Those results indicate that fibrin sealant was effective for colonic anastomosis in pre-clinical studies.

Table 17-Comparison of bursting pressure with or without using fibrin sealant in colonic anastomosis

Phase in Clinical Trials	Bursting Pressure with Using FS (mmHg)	Bursting Pressure without Using FS (mmHg)	Method for Anastomosis without Using FS	Study
Pre	192.0	180.0	Suture	(Kanellos I M. I., 2002)

Phase in Clinical Trials	Bursting Pressure with Using FS (mmHg)	Bursting Pressure without Using FS (mmHg)	Method for Anastomosis without Using FS	Study
Pre	244.13	151.60	Suture	(Kanellos I e. a., 2003)
Pre	240	152	Suture	(Kanellos I M. I., 2004)
Pre	240	180	Suture	(Kanellos I., 2006)
Pre	123.2	68.0	Suture	(Akgün A, 2006)
Pre	252	180	Suture	(Kanellos D, 2007)
Pre	145	115	Suture	(Subhas G, 2011)

There are other benefits of using fibrin sealant as colonic anastomosis:

- **Less inflammatory reaction**: Zilling et al 1999 reported that the group treated with fibrin sealant showed little or no inflammatory reaction, compared with the stapled anastomoses, which showed the mild inflammatory reaction (Zilling TL, 1999), less inflammatory in fibrin sealant group was also shown in Detweiler 1999 (Detweiler MB K. J., 1999).
- **Less leakage**: the leakage rate was much lower in the fibrin sealant intervention group compared with the control group, the leakage rate were 0%-5.8% and 6.25%-10.9 % respectively (Kanellos I., 2006) (Kanellos I M. I., 2004) (Huh JW, 2010). It showed the similar result in the other pre-clinical study, the leakage rate was lower in fibrin sealant treated group (Kanellos I e. a., 2003). The evidence indicated a lower leakage rate with fibrin sealant treated group in clinical trials. The leakage rate was 5.8% and 10.9% in non-fibrin sealant group and the fibrin sealant treated group respectively (Jung Wook Huh, 2010).

We did not find any articles that showed that fibrin sealant was worse than other methods. However, the data about bursting pressure of fibrin sealant used for colonic anastomosis was missing in later clinical trials (stage I to III).

4.2.3 Adhesive

Severe acute burn wounds need a skin graft to replace the burned or missed skin to prevent the fluid loss, hypothermia, and infection of the body. Auto graft has become the standard treatment for extensive full thickness wounds (Herndon DN, 1986) (Muller MJ, 2001). Sutures and staples were the current standard treatment for graft fixation, however, which brought a lot of complications (Kulber DA, 1997). Full contact of graft with the wound surface could not be achieved by sutures or staples. Especially, severely burned patients with large grafted wound surface would loss skin grafts (Branski LK, 2011). Fibrin sealant as adhesives is to link tissues together, especially used for burns skin grafting attachment (William D. Spotnitz, 2010). Fibrin sealant has been an alternative fixation method to reduce those complications (Currie LJ, 2001). We explain how fibrin sealant as adhesives worked for skin grafting in different clinical trials.

There are two tables below, which show a comparison of skin graft survival rate with or without using fibrin sealant and a comparison of skin graft survival rate with using thin or thick fibrin sealant.

Table 18 shows that the skin graft survival rate with using fibrin sealant was similar compared to the standard methods staple and suture in different clinical studies (O'Grady KM, 2000) (Mittermayr R, 2006). The column in green represents the skin graft survival rate with using fibrin sealant. But the skin graft survival rate in fibrin sealant treated group was still higher compared with suture and suture intervention group. In two other studies, fibrin sealant used for skin graft was compared with staple in phase II and III clinical trials. The results showed that fibrin sealant was safe and effective for skin grafts fixation, and was better than staple fixations (Gibran N, 2007) (Foster K, 2008). In general, fibrin sealant is better than sutures and staples for skin graft fixation.

Table 18-Comparison of skin graft survival rate with or without using fibrin sealant

Phase in Clinical Trials	Skin Graft Survival Rate with Using FS (%)	Skin Graft Survival Rate without Using FS (%)	Method for Adhesive without Using FS	Study
Pre	97.8	92	Staple	(O'Grady KM, 2000)
Pre	99.73	95.86	Suture	(Mittermayr R, 2006)
II	79.5	59	Staple	(Gibran N, 2007)
III	70.3	65.8	Staple	(Foster K, 2008)

Table 19 indicates that the skin graft survival rate with thin layer application of fibrin sealant compared with thick layer fibrin sealant used for skin grafting. Thin layer was 0.015 mL fibrin sealant used for per square centimeter skin, the thick layer was 0.05 mL fibrin sealant used for per square centimeter skin. The skin graft survival rate was significantly higher with thin layer fibrin sealant compared with thick layer fibrin sealant in O'Grady 2000, the survival rate were 97.8 and 63.1 percent respectively. The other study reported that the survival rate was a little bit higher (O'Grady KM, 2000) (Mittermayr R, 2006). Overall, thin layer fibrin sealant used for skin graft has higher survival rate.

Table 19-Comparison of skin graft survival rate with using thin or thick fibrin sealant

Phase in Clinical Trials	Skin Graft Survival Rate with Using Thin Layer FS (%)	Skin Graft Survival Rate with Using Thick Layer FS (%)	Study
Pre	97.8	63.1	(O'Grady KM, 2000)
Pre	99.73	96.86	(Mittermayr R, 2006)

There are other benefits of using fibrin sealant as skin graft:

- **More comfortable**: patients felt more comfortable with sprayed fibrin sealant compared with sutures and staples. Patients had less anxiety regarding staple removal and pain (Mittermayr R, 2006) (Foster K, 2008).
- **Less hematoma and seroma formation**: hematoma and seroma formation was significantly less in the fibrin sealant treatment group than the staples group on the first day after surgery. The median percent area was 0% and 1.2-2.1% respectively (Gibran N, 2007) (Foster K, 2008).
- **Less time for wound closure**: wound closure was faster with fibrin sealant treated group. In the studies Foster 2008 on the day 28 after surgery, the wound closure rate was 70.3% and 65.8% with or without using fibrin sealant respectively. Rapid wound closure influenced skin graft survival rate, especially for severely burned patients (Foster K, 2008) (Branski LK, 2011).

Also in the case of adhesives, we did not find any articles that showed negative results.

4.2.4 Face-lift

We now explain the efficacy of fibrin sealant used for face-lift surgeries. There are two criteria to measure success of operations, hematoma and drainage. Hematoma is a major complication after face-lifting. It has been reported that the rate of incidence is 1.86-9% (Jones BM, 2004). Hematoma formation brought risks because of a large raw surface under the skin flap. It would cause skin necrosis if the drainage of hematoma is not appropriate. Hematoma may lead to a long-term healing process, and secondary surgical treatment (Yong-Chen Por, 2009). Prevention of acute hematoma after face-lift influenced the success of surgeries (G. M. Beer, 2010). A reduction of postoperative wound drainage can reduce complications and speed up recovery (Yong-Chen Por, 2009). Face-lift is to adhere tissue flaps during facial rhytidectomy surgery. Fibrin sealant was used to reduce hematoma and drainage in facial rhytidectomy surgery.

There are two tables below, which show the comparison of hematoma rate and drainage in face-lift surgeries by with or without using fibrin sealant in clinical trials.

Table 20 shows that hematoma rate with using fibrin sealant was less dramatically compared the hematoma rate without using fibrin sealant in face-lift surgeries, and the column in green shows the hematoma rate with using fibrin sealant. The hematoma rate with the intervention of fibrin sealant was 0-1%. However, the hematoma rate without the treatment of fibrin sealant was 3-22% in phase III clinical trials. Hematoma rate was 22 times more without using fibrin sealant, compared with the intervention with using fibrin sealant (Fezza JP, 2002) (Kamer FM, 2007) (Zoumalan R, 2008) (Lee S, 2009). Hematoma rate was decreased significantly by using fibrin sealant in face-lift surgeries. Therefore we concluded that fibrin sealant is very effective to control hematoma for face-lift surgeries.

Table 20-Comparison of hematoma rate with or without using fibrin sealant in face-lift surgeries

Phase in Clinical Trials	Hematoma Rate with Using FS (%)	Hematoma Rate without Using FS (%)	Study
III	0	8.3	(Fezza JP, 2002)
III	1	3	(Kamer FM, 2007)
III	0.4	3.4	(Zoumalan R, 2008)
III	0	22	(Lee S, 2009)

Table 21 compares the results of 24 hours postoperative drainage with or without using fibrin sealant. In the study Oliver DW 2001, the 24 hours postoperative drainage with the treatment of fibrin sealant was 3 times lower compared with the sides without using fibrin sealant in face-lift surgeries. The median drainage in fibrin sealant side was 10 mL, the other side without fibrin sealant was 30mL (Oliver DW, 2001). Less postoperative drainage in 24 hours after surgery also mentioned in the study Marchac D. 2005. The mean amount of drainage with using fibrin sealant was 26 mL, compared with 33.5 mL without using fibrin sealant (Marchac D, 2005). Thus, fibrin sealant is efficacious to reduce the postoperative drainage in clinical trials.

Table 21-Comparison of 24 hours postoperative drainage with or without using fibrin sealant in face-lift surgeries

Phase in Clinical Trials	24 Hours Postoperative Drainage with Using FS (mL)	24 Hours Postoperative Drainage without Using FS (mL)	Study
III	10	30	(Oliver DW, 2001)
III	26	33.5	(Marchac D, 2005)

There are other benefits of using fibrin sealant as face-lift:

- **Less ecchymosis**: several studies mention that ecchymosis was reduced, even in some studies it was decreased significantly (Fezza JP, 2002) (Marchac D, 2005) (Kamer FM, 2007) (Lee S, 2009).
- **Less pain**: patients had less pain on the fibrin sealant treatment sides. Oliver DW 2001 reported that 30 percent patients had less pain compared with the side without using fibrin sealant (Oliver DW, 2001). It was mentioned in Kamer et al as well that patients in the fibrin sealant group had less pain (Kamer FM, 2007).
- **Less operation time**: the results in the study Fezza JP showed that the average operating times were 13.3 minutes less in the fibrin sealant group, compared with non-fibrin sealant group. It was also indicated that patients had repaid recovery time and returned to their normal life quickly (Fezza JP, 2002).

Again, no negative results were found for using fibrin sealant for face-lifts.

4.3 Risk of Bias Assessment

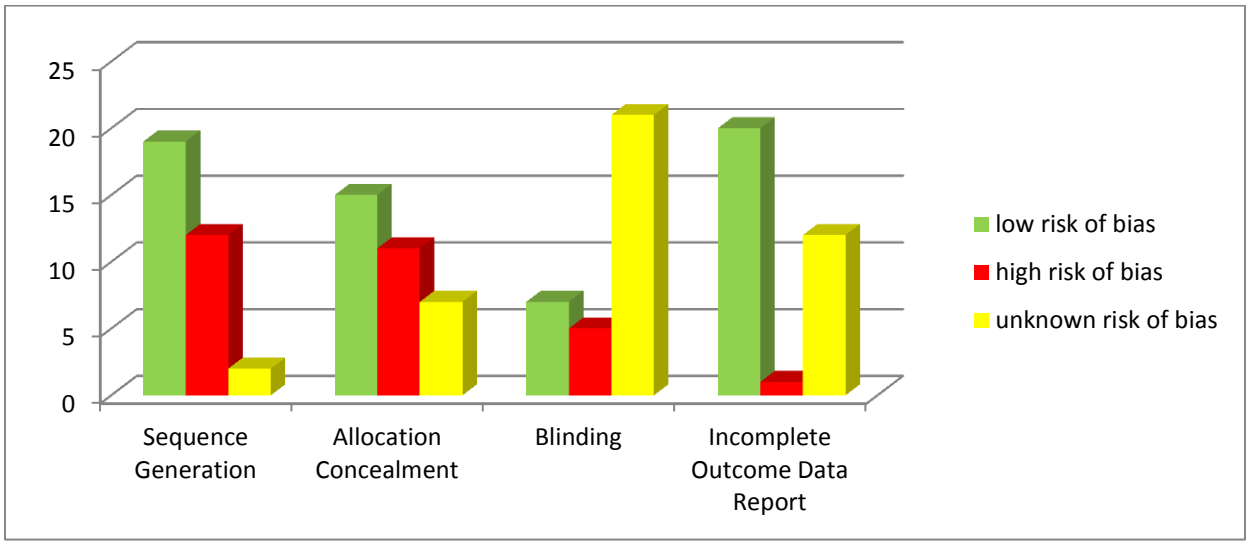

Figure 8-Analysis of risk bias assessment

According to the Cochrane handbook, the risk of bias for a literature review has to be addressed, the chance that the results published in the studies might be systematically wrong. We investigated four possible sources of bias (domains): sequence generation, allocation concealment, blinding and incomplete outcome data report. The criteria for addressing low risk of bias, high risk of bias, and unknown risk of bias were mentioned in the section 3.1.4 (Addressing Risk of Bias in Included Studies) of the method part. Figure 8 indicates the number of risk of bias in included studies based on Cochrane Handbook for Systematic Reviews. We excluded the studies in pre-clinical trials because some type of biases is no applicable. For instance, animals cannot be informed of what treatment they received. The risk of bias for these pre-clinical studies was unclear.

It can be seen that the number of 'low risk of bias' was higher compared to 'high risk of bias or unknown risk of bias'. For example, for sequence generation, the number of low risk of bias was higher than the number of high risk of bias and unknown risk of bias. This represents that most of studies were randomly controlled studies. These studies had low risk of bias. In the part of blinding, the number of unknown risk of bias was much higher than other two risk of bias, the risk bias for blinding of studies was unknown. Most studies discuss incomplete outcome data, leading to a low risk of this domain.

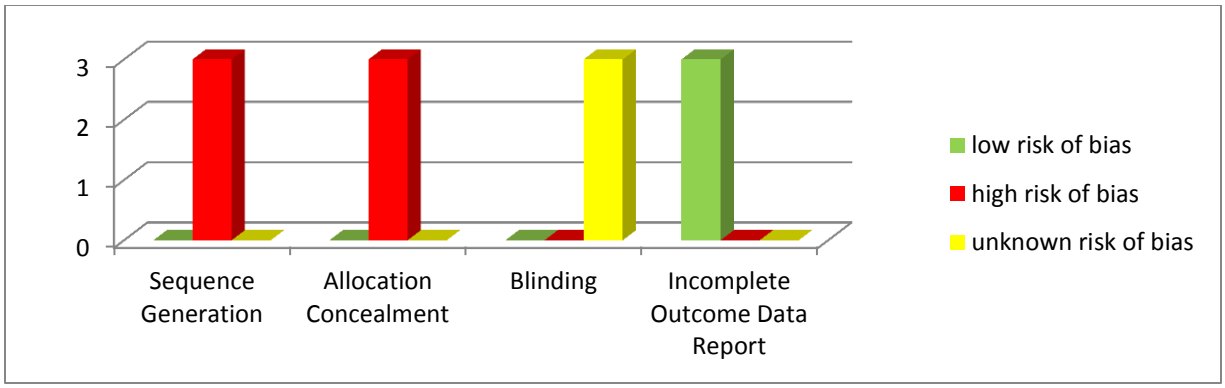

Figure 9-Analysis of risk bias in phase I clinical trials

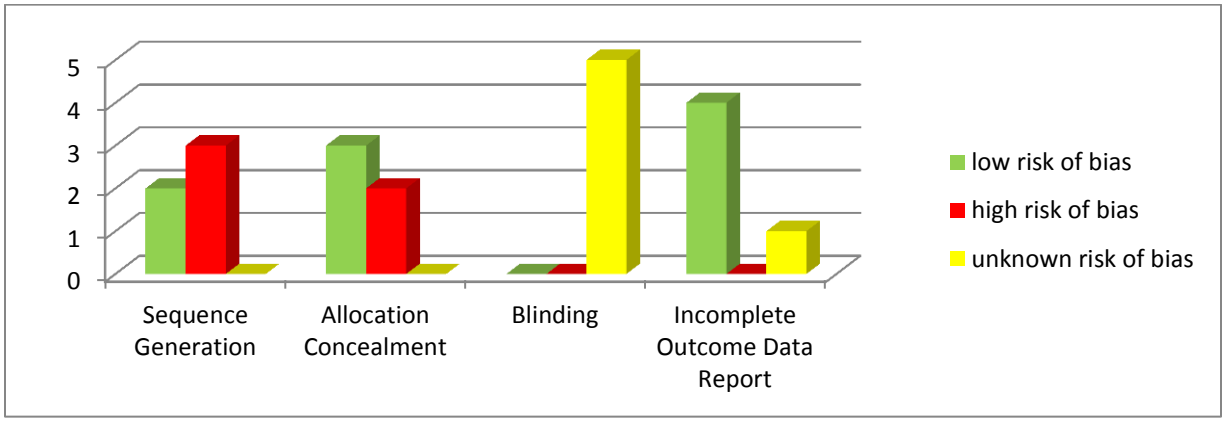

Figure 10-Analysis of risk bias in phase II clinical trials

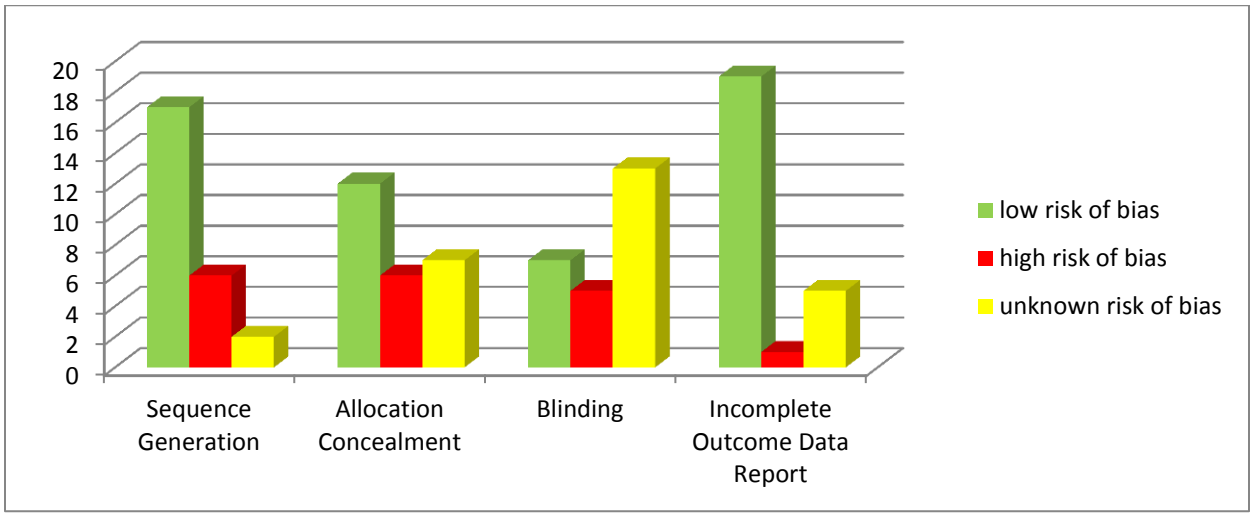

Figure 11-Analysis of risk bias in phase III clinical trials

Figure 9, Figure 10, and Figure 11 shows the risk of bias of included studies in phase I, II, and III clinical trials respectively. There were 3 studies in phase I clinical trials, 5 in phase II clinical trials, and 25 in phase III clinical trials.

When comparing these three figures, it becomes clear that the risk bias of sequence generation, allocation concealment, and blinding was reduced from phase I to phase III clinical trials. All studies in phase I clinical trials had high risk bias of sequence generation and allocation concealment, and the risk bias of blinding was unclear. The risk bias of sequence generation and allocation concealment in phase II clinical trials was decreased compared to the risk bias in phase I clinical trials. Still the risk bias of blinding was unclear for some studies. The risk of bias in phase III clinical trials was further reduced. For example, most of these included studies had low risk bias of sequence generation and allocation concealment, and some studies had low risk bias of blinding. We also compared the risk bias of incomplete outcome data report in phase I, II, and III clinical trials. Even though all studies in phase I clinical trials had low risk bias of incomplete outcome data, most included studies in phase II and III had low risk of bias of incomplete outcome data report. The number of studies in phase III was much higher than the studies in phase I and II.

Thus, in general 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. The risk bias of blinding for these studies was unknown.

4.4 Drug Approval Process and Requirements in US, EU and China

In the past section we looked at the evidence development. Now we look at the approval process of drugs. First we describe the drug approval process in US, EU, and China, and then we show how approval requirements (regulatory hurdles) affect the drug approval in these countries. Because fibrin sealant is a biomedical drug, this general information about drug approval process and requirements is applicable to the fibrin sealant approval process and requirements.

The new drug approval process includes clinical trials and marketing authorization of these two phases. Non-clinical studies can be pre-clinical trials that are laboratory and animal studies to ensure efficacy and safety of the new drug, and then application for starting to use the new drug on patients, that means application of clinical trials must be submitted to the competent authority in the concerned country. Afterwards, the new drug can be used in a large group of patients gradually from clinical trials I, II, III, until IV the post market clinical trial. When enough evidence about safety, efficacy, and optimizing the dose of drug on patients in clinical trials were showed, or this drug does better than harm, then the approval of drug for marketing is submitted to the competent authority (Ng R., 2004). In different countries such as the US, EU, and China, the regulatory requirements for approval of a new drug is different. The single regulatory approach for marketing authorization application (MAA) of a new drug product

applicable to various countries is very difficult. Therefore, the specific and detailed regulatory requirements for MAA in different countries should be known to establish good regulatory strategies (Hörner A., 2005).

4.4.1 Drug Approval Process in US

New drug approval process is managed by the Food and Drug Administration (FDA) in the US. The process includes two phases: Clinical Trials (CT) and New Drug Application (NDA) approval process (Martinez L.J., 2002). New biologic drugs are approved by Biologic License Application (BLA) instead of NDA.

The new drug approval process starts with the submission of an Investigational New Drug (IND) to the FDA. The IND application should provide high quality data about safety and efficacy of the new drug in laboratory, animal studies and in humans. The first process is clinical trials. The second step is the new drug application (NDA). In the case of fibrin sealant, a Biologics License Application (BLA) is needed instead of NDA. If the new drug succeeds in all the three phases of clinical trials, then a BLA can be submitted. In the US, the Center for Biologics Evaluation and Research (CBER) is in charge of the biological products approval process. One of the missions of this center is to evaluate safety, efficacy, and effectiveness of the new drug before it can be sold in the market. The CBER evaluates the scientific and clinical evidence of new drugs. For the case of fibrin sealant, they evaluated the scientific evidence development of fibrin sealant in different clinical trials. Afterwards, the CBER decides if the new products meet their standards for approval (FDA, 2012).

4.4.2 Drug Approval Process in EU

In the European Union (EU), medicines can be authorized by the centralized authorization procedure or by national authorization procedures. Similarly, in EU the drug approval process is also accomplished in two phases: clinical trial and marketing authorization. The clinical trials are started when the application is approved by European Medicines Agency (EMA). If three phases in clinical trials are successful, market authorization application is submitted with laboratory, animal, and human data to ensure the safety and efficacy of the new drug (Commission Directive 2005/28/EC, 2005).

Centralized Authorization Procedure

The EMA evaluates new drug applications for European marketing authorizations in EU. Applications of the new drug approval should be sent to EMA directly. The Committee for Human Medicinal Products (CHMP) has to evaluate the applications. When the assessment is finished, the information is sent to the European Commission within 210 days. After that, it is decided if it should be marketed or not. When it is approved by the European Commission, a centralized marketing authorization is valid in all European Union countries (European Medicines Agency, 2011). The simplified procedure is showed in Figure 12.

National Authorization Procedures

National Procedure

Because each EU member state has its own procedures for the new drug approval, with their own domain, many available medicines are not approved by EMA. In each member state, marketing authorization is granted by the competent authorities (Davis H., 2003). The marketing authorization is only valid in the granted country. Specific information about approval process in each member state can be found on the website in the concerned country (European Medicines Agency, 2011).

Decentralized Procedure

The decentralized procedure is that pharmaceutical companies can apply for the same drug in different European countries.

To get marketing authorizations of the same new drug in many European countries, the decentralized procedure is used, and the centralized procedure is not mandatory. First, the application has to be sent to the competent authority in each member state. Then the data of the drug safety, efficacy, and quality should be submitted. Second, a list about all Concerned Member States (CMSs) and a Reference Member State (RMS) should be sent to the competent authorities. The Concerned Member States (CMSs) and Reference Member State (RMS) check the application.

However, if the new drug could cause serious risk to public health, CMSs will inform to other CMS and RMS. For the points of disagreement, all member states reach to an agreement on the action to be taken. After accomplishing an agreement from the member states, the RMS records the agreement and sends the information to the applicant. However, if the member states could not reach the same agreement, then the Committee for Human Medicinal Products (CHMP) is involved in and take a final decision to write explanations to the applicant (European Commission C. 7., 2004) (European Commission C. 1., 2005). The simplified procedure is shown in Figure 12.

Mutual Recognition Procedure

The mutual recognition procedure (MRP) is different from the decentralized procedure. MRP is applicable to the new drug that has been approved by one member state, but has not been approved by other member states. Companies that have a new drug with marketing authorization in one EU member state can apply for this authorization to be recognized in another EU country. Decentralized procedure is suitable for the new drug that has not received a marketing authorization in any member states in EU. It takes 90 days for the evaluation of application by RMS instead of 120 days in decentralized procedure (European Commission C. 2., 2007).

4.4.3 Drug Approval Process in China

In China, the SFDA (State Food and Drug Administration) is responsible for the new drug approval process. The registration process also includes the clinical study application and the new drug application. The simplified procedure is showed in Figure 12.

In China, the application should be submitted to the Provincial Drug Administration Authorities (PDAAs) first. If the application meets the requirements of PDAAs, then the SFDA takes further review of the materials submitted by PDAAs. However, if the drug comes from outside (the import drug) of China, it has to be applied to SFDA directly. SFDA's Department of Drug Registration checks the applications, and decides which of those qualify. All the documents of qualified applications are sent to the Center for Drug Evaluation (CDE). CDE estimates if the safety and effectiveness information are enough for manufacturing and marketing authorization, and then send the report of review to SFDA. Recommendations and review results from CDE are considered by SFDA to make a decision if the new drug can be approved or not (Zhen L.H., 2003) (Deng R., 2004) (Provisions for Drug Registration (SFDA Order No. 28), 2008) (Drug Administration Law of the People's Republic of China, 2011).

4.4.4 Comparison and Summary of Drug Approval Processes

Generally, the drug approval process includes mainly the two steps, application to conduct clinical trials and application to the regulatory authority for marketing authorization of drug.

The drug approval processes are managed by FDA in US, EMA in EU, and SFDA in China. 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 Drug Administration Authorities, and then the SFDA will take the next review. If the drugs are from outside of China (imported drugs), the applications should be applied to FDA directly. Concerning the applications in EU, there are two paths to bring drugs onto the market—centralized or nationalized approval procedures. Centralized authorization is done by EMA, and nationalized procedures are managed by each country. The EMA does not investigate drugs. Inspections of facilities in the EU are done by regulators in each country, which are initiated independently and from requests by the EMA.

Figure 12 shows a comparison of drug approval processes in US, EU, and China. Some differences are also presented in Table 22, for instance, the duration of the approval of a CTA application, and the time taken in evaluation of marketing authorization application (FDA, 2011) (European Medicines Agency, 2011) (Drug Administration Law of the People's Republic of China, 2011).

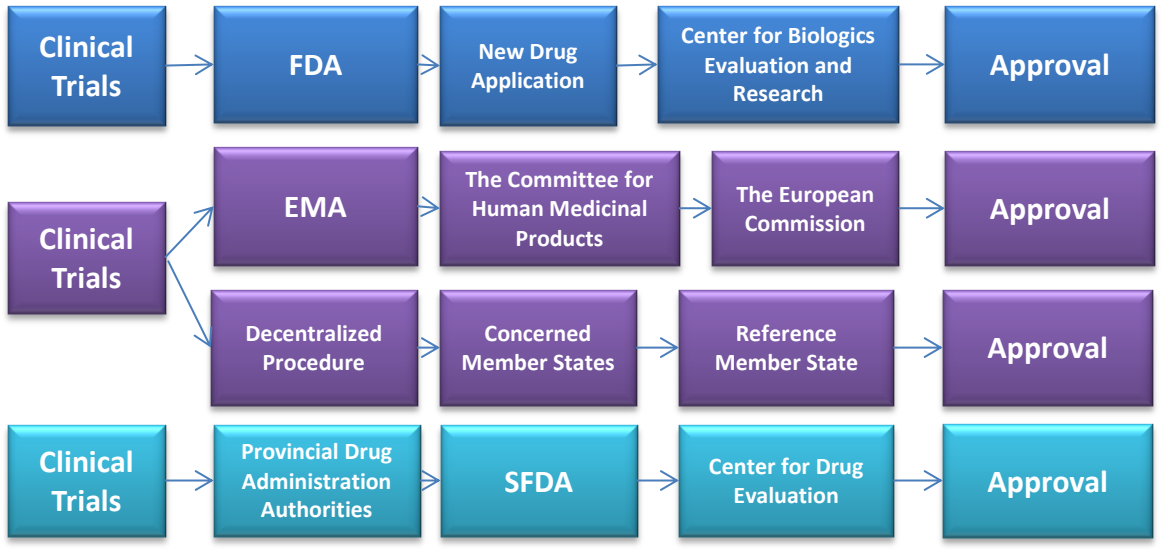

Figure 12-Comparison of approval process in US, EU, and China

Table 22-Comparison of drug approval process in US, EU, and China
MAA: Marketing Authorization Application, CTA: Clinical Trial Authorization

Country	Agency	Time for Regulatory Approval of CTA Application	Time for Evaluation of MAA	Evidence Evaluation Center	Approval Procedure
US	FDA	30 days	180 days	CDER	Centralized authorization procedure
EU	EMA	35 days	210 days	CHMP	Centralized authorization Procedure
China	SFDA	50 days	180 days	CDE	Centralized authorization procedure

Based on the comparison of regulatory approval processes in US, EU and China, we believe that the approval processes are quite similar in US and China, and they should require a similar amount of time and effort. However, the EU is more complicated.

4.4.5 Approval of Fibrin Sealant

TISSEEL was the first FDA-approved fibrin sealant in 1998. Afterwards there were more new indications and applications that were approved because fibrin sealants were more safe, efficacious, and effective.

Table 23 shows the specific approved indications and applications by FDA, EMA, and SFDA. This answers research question 2.2 (RQ 2.2).

Table 23-Currently authorized fibrin sealant in US, EU, and China
HF: Human Fibrinogen, HT: Human Thrombin

Trade Name	Manufacturer	Source	Indication	Application and Date of Authorization	Issued by
TISSEEL	Baxter Healthcare Corp	HF and HT	Hemostasis	05-01-1998: cardiopulmonary bypass	FDA
				01-29-2010: splenic injuries	
EVICEL	OMRIX Biopharmaceuticals Ltd	HF and HT	Hemostasis	03-21-2003: liver surgery	FDA
				05-09-2007: vascular surgery	
				01-02-2008: general surgery	
				04-02-2010: cardiovascular surgery	EMA
TachoSil	Nycomed Danmark ApS	HF and HT	Hemostasis	08-06-2004: cardiovascular surgery	EMA
				10-06-2008: cardiovascular surgery	FDA
Kang Pu Xin (康普欣)	Hualan Biological Engineering, Inc.	HF and HT	Hemostasis	08-17-2010: general surgery	SFDA
TISSEEL	Baxter Healthcare Corp	HF and HT	Sealant	05-01-1998: colonic anastomosis	FDA
ARTISS	Baxter Healthcare Corp	HF and HT	Adhesive	03-21-2008: burn skin grafts	FDA
			Face-lift	08-29-2011: facial rhytidectomy surgery	

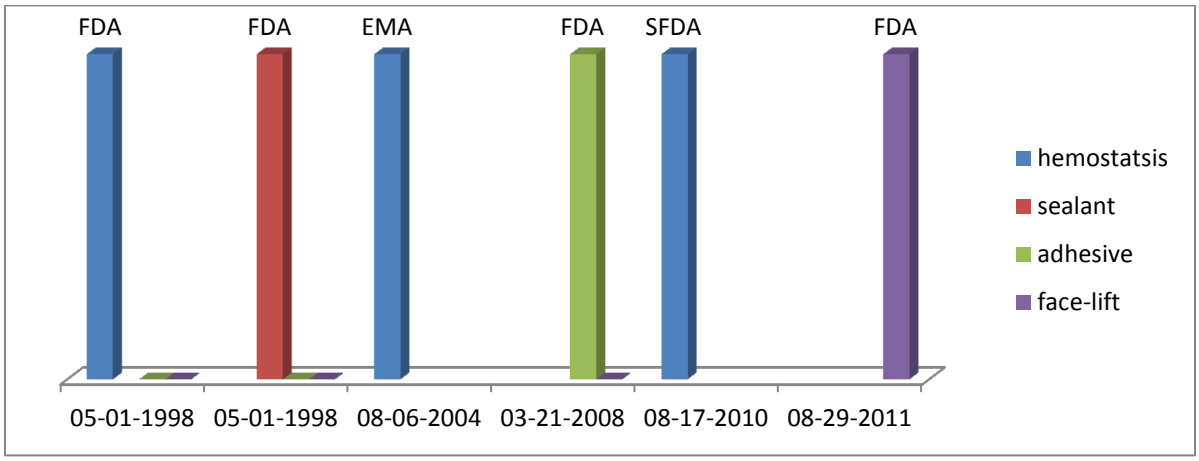

Figure 13-Approved indications of fibrin sealant from 1998 to 2011

Figure 13 indicates approved indications of fibrin sealant from 1998 to 2011. Hemostasis was the first approved indication by FDA in 1998. At the same year the indication of sealant was approved for colonic anastomosis. Then fibrin sealant was approved for indications of adhesive

and face-lift in 2008 and 2011, which can be used in burn skin grafts and facial rhytidectomy surgery respectively. In EU, hemostasis was approved by EMA for using in cardiovascular surgery in 2004, and in China it was approved for using in general surgery in 2010.

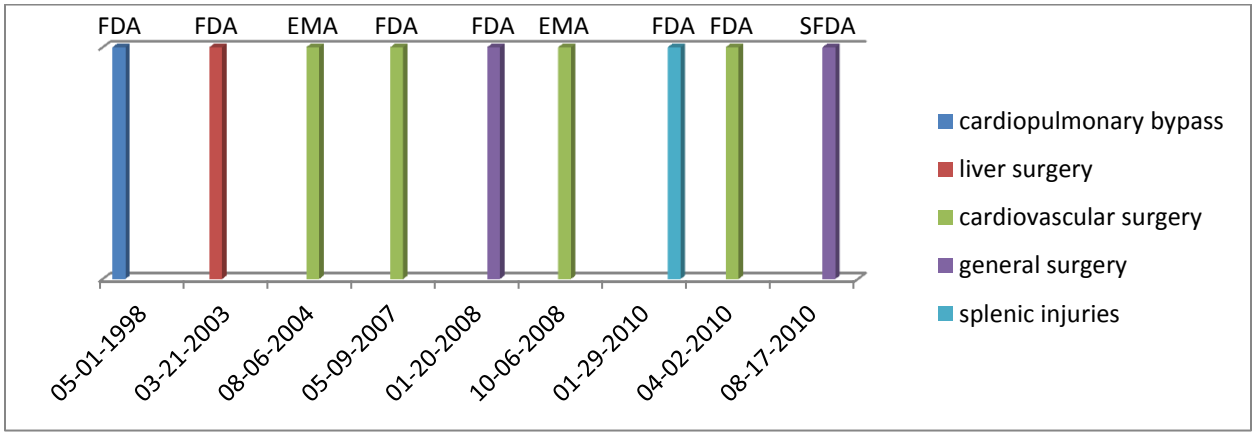

Figure 14-Approved applications of hemostasis from 1998 to 2010

Figure 14 it shows the approved applications of hemostasis by FDA, EMA, and SFDA from 1998 to 2011. Cardiopulmonary bypass was the first approved application of hemostasis by FDA in 1998. Afterwards hemostasis was approved for many applications, such as hemostasis was used in liver surgery, cardiovascular surgery, general surgery, and splenic injuries. It can be seen that the application used for cardiovascular surgery was approved twice by FDA and EMA respectively. This means that the approved products were from different pharmaceutical companies. In 2010 hemostasis was the first approved by SFDA for using in general surgery in China.

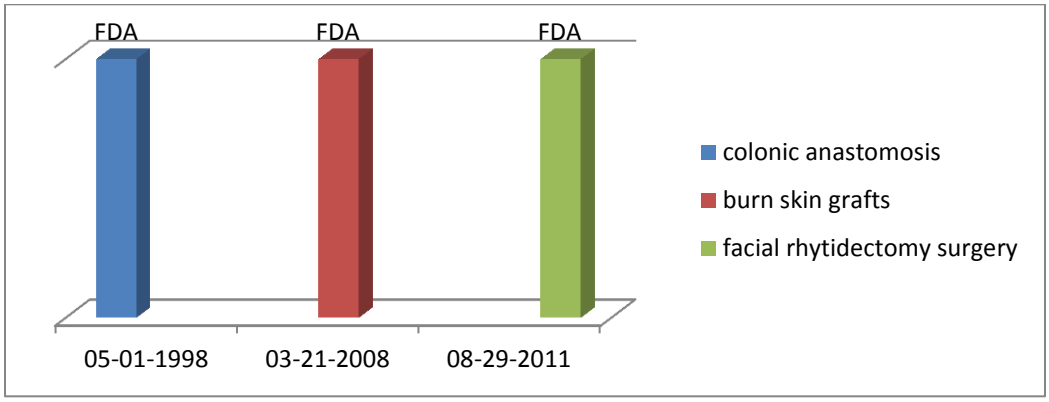

Figure 15-Approved applications of sealant, adhesive, and face-lift

Figure 15 shows the approved applications of sealant, adhesive and face-lift from 1998 to 2011. The indication sealant was approved for using colonic anastomosis, adhesive was approved for

the treatment of burn skin grafts, and face-lift was approved for using in facial rhytidectomy surgery.

4.5 Relation between Evidence Development and Regulatory Approval

In this section we answer the research question three (RQ3) about the relation between evidence development of fibrin sealant and regulatory approval. In theory, there are two phases in the drug approval process. One is clinical trials (CT) and the second is new drug application (NDA). If there is enough evidence to show that the drug was safe, efficacy and effective, or their benefits outweigh its risks, then the drug can be approved. First, we checked the evidence development of fibrin sealant in different clinical trials, and then the regulatory approval. We checked the theory in two ways:

- First, we checked the relation between evidence development of each indication and the approved applications. Figure 16, Figure 17, Figure 18, and Figure 19 show the relation between evidence development of each indication and approved years by FDA, EMA, and SFDA from 1998 to 2011 respectively.
- Second, we checked the relation between all the publications and all applications. Figure 20 indicates the relation between all indications and all publications from 1998 to 2011.

4.5.1 Evidence Development and Approval for Individual Indications

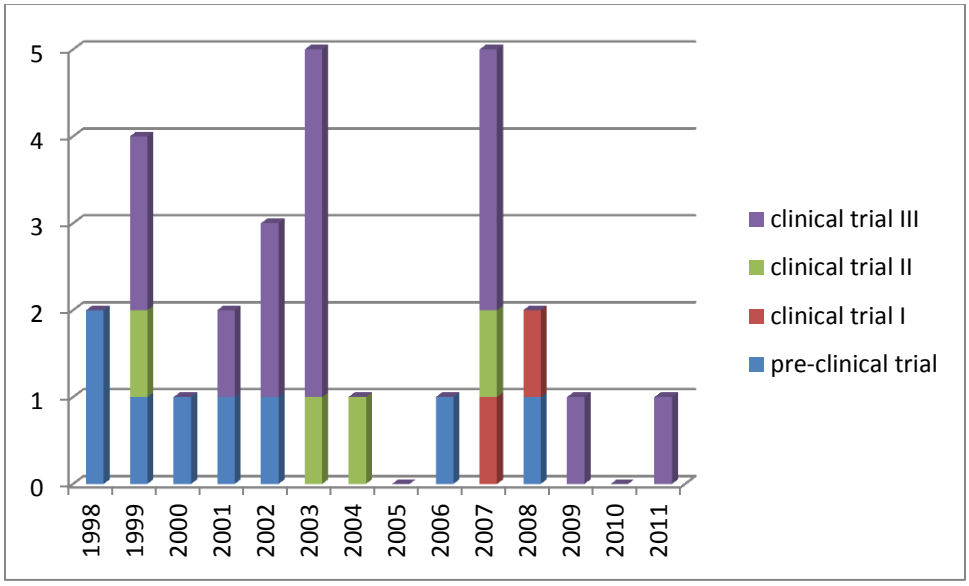

Figure 16-Evidence development of hemostat

Hemostat was the first approved indication by FDA in 1998, and afterwards, it was approved by EMA in EU 2004 and by SFDA in China 2010. It can be seen in Figure 16 that the evidence development of hemostat from pre-clinical trials to phase I, II, and III in clinical trials. It was approved for six applications from 1998 to 2011 that were showed in Figure 14. From this figure

it was showed that some data appears to be missing. For example, data in clinical trials in 2005 and 2010 is missing.

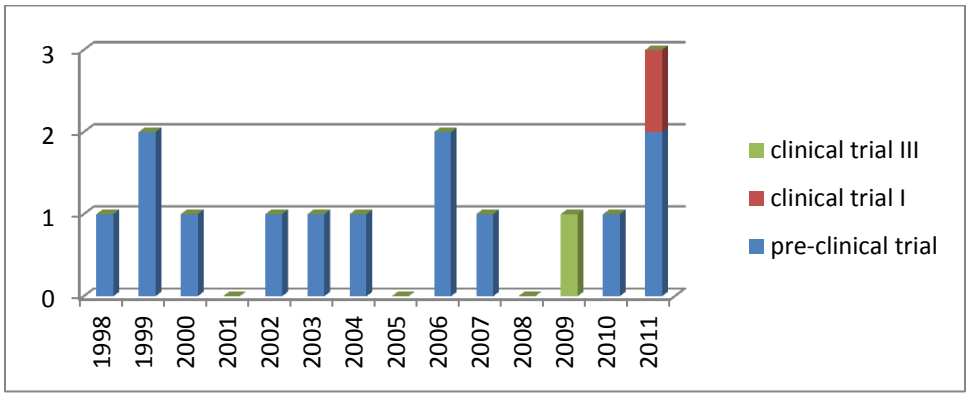

Figure 17-Evidence development of colonic sealing

Colonic sealing was approved by FDA in 1998. Figure 17 shows the evidence development of colonic sealing from pre-clinical trials to phase I and III in clinical trials. However, we do not find the data about phase II in clinical trials and also some data in 2001, 2005, and 2008 are missing as well. Because our research starts from 1998 and colonic sealing was approved in 1998, published data before 1998 in phase II clinical trials is missing. We also have not found that colonic sealing was approved by EMA in EU or by SFDA in China.

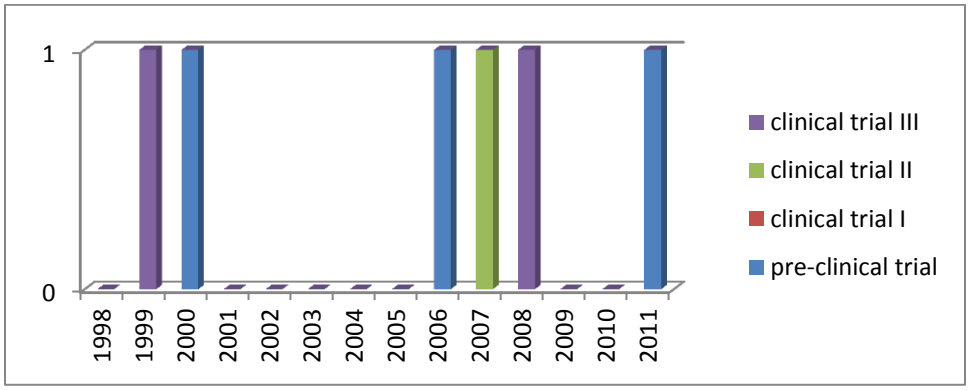

Figure 18-Evidence development of adhesive

Adhesive was approved by FDA in 2008, it was the third indication approved by FDA since 1998. Adhesive was used for burns skin grafting. Figure 18 presents the evidence development of adhesive in different clinical trials. It only shows the evidence in several years. Again, a lot of data appears to be missing.

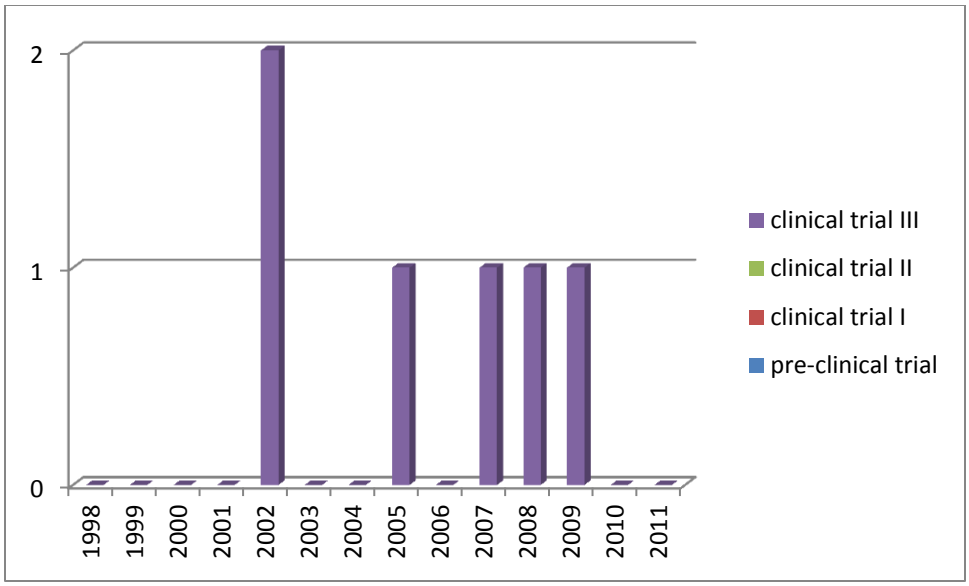

Figure 19-Evidence development of face-lift

Face-lift was an indication approved by FDA in 2011, used for facial rhytidectomy surgery. Figure 19 shows the evidence development of face-lift, but the data was only available in phase III clinical trials. Some data in pre-clinical and clinical trials are missing. For example, we do not have data from phase I to phase II.

Evidence from Letters Used in the Approval Process

From our research it can be seen that our search did not find all the data to show the evidence development of fibrin sealant for each indication. However, new applications of hemostasis and new indications of fibrin sealant were still approved by FDA, EMA, and SFDA. Further analysis showed that some of this evidence is available in the approval letters sent by the manufacturer to the regulatory agency. Below we briefly present some of evidence found in the contents of these letters.

- **Hemostasis (EVICEL, TISSEEL)**
  Concerning the evidence development of hemostasis, we can see in the assessment report for the product EVICEL (EMA, 2008), that the hemostatic efficacy of using fibrin sealant in pre-clinical studies was reported, as well as the primary pharmacodynamics, pharmacokinetics, toxicology, genotoxicity of using fibrin sealant on animals. Second, this report also presents the hemostatic efficacy of EVICEL that was used in two phase III, random controlled studies. Hemostasis time was achieved in 7 minutes with 90.7-90.9% patients during vascular surgeries by using EVICEL, compared to manual pressure with 59.7-76.8% patients. EVICEL reduced the hemostasis time significantly. This evidence of EVICEL met the regulatory approval requirements, and the Committee for Medicinal Products for Human Use (CHMP) recommended that EVICEL be given marketing authorization. The similar results also showed from letter related to approval for the

product TISSEEL (Kimberly Lindsey, Efficacy Supplement of TISSEEL., 2011). This report indicated that the hemostasis time dramatically reduced by using TISSEEL in phase II and III random controlled, double-blinded clinical trials during vascular surgery.

- **Colonic Sealing (TISSEEL)**
  It was reported as well from the letter about fibrin sealant was used for sealing colonic anastomoses. Patients treated with fibrin sealant had significantly less leakage compared to the non-fibrin sealant treated patients (FDA, Summary Basic for Approval: Fibrin Sealant -- TISSEEL., 1998).
- **Adhesive (ARTISS)**
  We also found the evidence development of adhesive used for burn skin grafting from the letter related to approval. It was reported in phase II clinical trials that the burn wounds closure was much more in the fibrin sealant treated group with 61.5%, compared to the stapled group with 46.2% on the fifth day after operation, also patients had less hematoma and seroma formation in the group treated with fibrin sealant. The similar results also showed in the phase III clinical trials (Kimberly Lindsey, Final Review Memo., 2008).
- **Face-lift (ARTISS)**
  Another example is that the product of ARTISS was used for face-lift surgeries. In the letter regarding approval for ARTISS (Mitchell Frost, 2011), it was shown that 24 hours postoperative drainage was significantly less with 7.7-8.0mL in the group treated with ARTISS, compared to the group with the standard of care (staples and/or sutures) with 20.0-20.5mL in phase II and III random controlled studies. Also the number of hematoma was less with ATRISS treated patients. We did not find the evidence development of face-lift in pre-clinical trials by systematic review. The evidence in pre-clinical trials was not shown in the letter regarding approval as well.

The approved products of fibrin sealant from different pharmaceutical companies for the same indication were quite similar, and the evidence development of each product was quite similar as well. For example, products TISSEEL and EVICEL were approved for hemostasis. However, we did not find the evidence development in pre-clinical trials and clinical trials from TISSEEL used for the approval of EVICEL or for the approval of other indications. Thus, even after studying the letters, some information remains missing. Possibly this information is available from other sources in the FDA.

Publications in Chinese

Because we could not find any publication about fibrin sealant from China using our systematic review, we also tried to find Chinese language publications, which could explain why our data is missing. For this we used '纤维蛋白胶 (fibrin sealant in Chinese)' as a key word to search the publications in the Chinese Biomedical Literature Database (CBM, 2011) or Wan Fang Data (WFD, 2011). Indeed, we could find several publications on fibrin sealant from 1996 to 2011. We did not further research this.

4.5.2 Evidence Development and Approval for Fibrin Sealant in General

We now examine the evidence development and approval for all fibrin sealants. Figure 20 shows the 58 included publications of on-label indications cumulatively from 1998 to 2011. The included studies were increased gradually. From 2002 to 2004, and from 2007 to 2009, the publications were increased slightly.

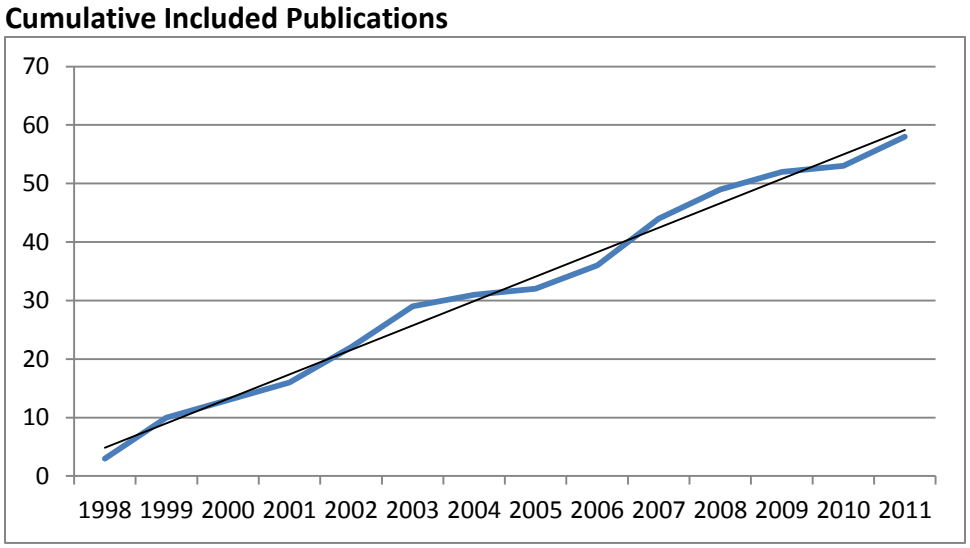

Figure 20-The included publications of on-label indications

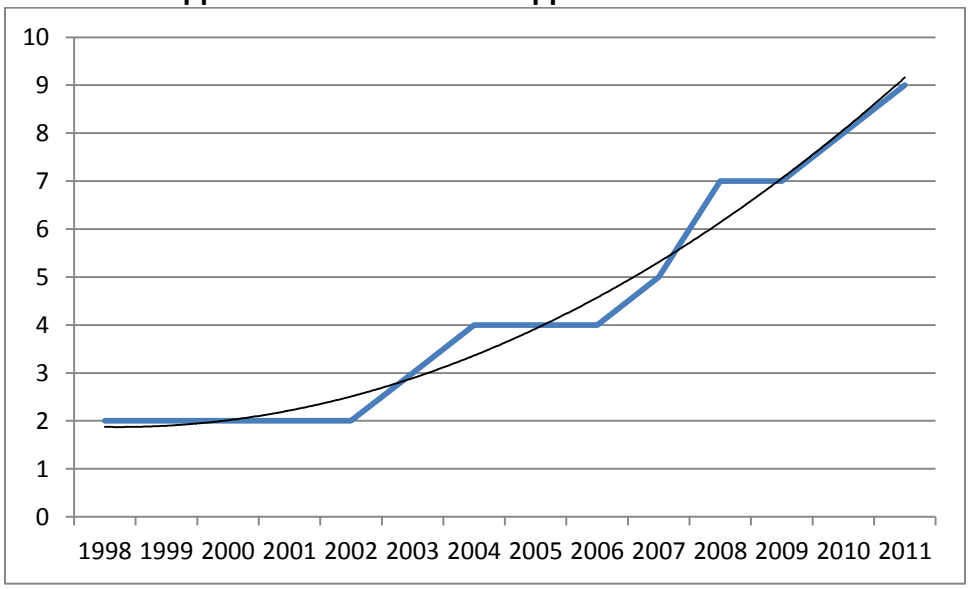

Figure 21-Trend of approved applications from 1998 to 2011

In total, there were 4 indications of fibrin sealant that were approved by FDA. However, hemostasis was approved for many indications, which were already shown in Figure 14. In

Figure 21 we indicated the trend of approved indications and applications from 1998 to 2011. The conclusion is that in the first years, the amount of new approved applications is very low, compared to the increased publications, but afterwards it goes much faster.

4.6 Strategies of Pharmaceutical Companies

At the introduction part of this thesis, it was mentioned that 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. Which one will they prefer based on the results of our research question 1, 2, and 3? In this section, we answer our research question 4.

First in Table 23 it was shown that more indications and applications of fibrin sealant were approved in US and EU since 1998 until now. However, we have not found approved fibrin sealant by SFDA, which was made in US and EU, we only found the approved fibrin sealant by SFDA, which was produced by Chinese manufactures. Second, fifty-eight studies were included in this study, they were classified that most of them were from US and EU. There were no studies from China. This evidence shows that companies still focus on their markets in US and EU. From the results follows that strategy 2 is preferred by the companies.

5. Conclusion

In this final chapter we discuss the results, and summarize the answers to the research questions.

5.1 Summary of Results

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

RQ1: How has the Evidence Developed about Fibrin Sealants from Pre-clinical Trials to Clinical Trials from 1998 until 2011?

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. There were no studies from China. 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. Colon sealing is used to construct a sealing in colonic 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.

RQ2: How do Regulatory Hurdles Affect the Approval of Fibrin Sealant?

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

We searched the data about the regulatory approval processes and requirements in the government websites of FDA, EMA, and SFDA. 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 Drug Administration Authorities, and then the SFDA will take the next review. If the drugs are from outside of China (imported drugs), the applications should be applied to FDA directly. Concerning the applications in EU, there are two paths to bring drugs 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 2011. Hemostat was the first approved indication by FDA in 1998, at the same time, the indication colonic sealing was approved, next adhesive was approved for burn skin grafts in 2008, and then in 2011 face-lift was approved for using in facial rhytidectomy surgery. In EU, hemostasis was approved by EMA in 2004, and in China it was approved in 2010.

RQ3: 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 2011. 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 Favored 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 2011. Also it was indicated from the included studies that most of studies were from US and EU. Now pharmaceutical companies still focus on their markets in US and EU.

5.2 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 colon 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, and China, we searched the government website of FDA, EMA, and SFDA. However, the information about approval procedures there was in 2011, maybe approval process was different before 2011. 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 China. The Chinese publications are available in other databases than PubMed. Future research on evidence development should include these databases, especially the Chinese Biomedical Literature Database (CBM, 2011) or Wan Fang Data (WFD, 2011).

5.3 Recommendation

For the future research, it would be interesting to also include sales data (but that was not available for this study) of fibrin sealant to analyze how sales data influences the pharmaceutical companies strategies for publication and market approval.

6. Appendix

6.1 List of Figures

6.2 List of Tables

7. References

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