FDA Executive Summary

Prepared for the October 26 & 27, 2022 Meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

Classification of Ultrasonic Surgical Devices

Product Codes:

LFL –Ultrasonic Surgical Instruments
NLQ– Single-Use Reprocessed Ultrasonic Surgical Instruments,
and
LBK – Neurosurgical Ultrasonic Instruments

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of ultrasonic surgical devices, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of three types of ultrasonic surgical devices: ultrasonic surgical instruments (LFL), single-use reprocessed ultrasonic surgical instruments (NLQ), and neurosurgical ultrasonic instruments (LBK) (collectively referred to in this document as ultrasonic surgical devices). The device names and associated product codes are developed by the Center for Devices and Radiological Health (CDRH) to identify the generic category of a device for FDA. While most product codes are associated with a device classification regulation, some product codes, including "LFL," "NLQ," and "LBK," remain unclassified.

FDA is holding this Panel meeting to obtain input on the risks to health and benefits of the ultrasonic surgical instruments under product code "LFL," single-use reprocessed ultrasonic surgical instruments under product code "NLQ," and neurosurgical ultrasonic instruments under product code "LBK." The Panel will discuss whether the ultrasonic surgical devices under product codes "LFL," "NLQ," and "LBK," should be classified into Class II (subject to general and special controls). If the Panel believes that classification into Class II is appropriate for these devices, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1. Current Regulatory Pathways

Ultrasonic surgical instruments, single-use reprocessed ultrasonic surgical instruments, and neurosurgical ultrasonic instruments are each a pre-amendments, unclassified device type. This means that these device types were marketed prior to the Medical Device Amendments of 1976, but were not classified by the original classification panels. Currently these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are "substantially equivalent" to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product codes.

1.2. Device Description

Ultrasonic surgical instruments under product code "LFL" are devices used in surgical procedures for fragmentation, emulsification and aspiration of soft tissue and hard tissue and are indicated for a variety of surgical procedures. Some devices may be indicated for ligation of vessels up to 7 mm in diameter. These devices generally employ a metal tip oscillating at a frequency of at least 20 kHz. Oscillatory mechanical motion of the tip at high velocities and accelerations

causes localized tissue heating, fragmentation, and emulsification. The oscillating tip is enclosed in a handpiece manipulated by the surgeon. Some devices include irrigation and aspiration components to remove the fragmented tissue. The power to generate the oscillation is supplied from a console, which may be operated by a foot pedal or activated on the handpiece. Single use reprocessed ultrasonic surgical devices under product code "NLQ" are single-use reprocessed versions of the devices under product code "LFL." If the indications for use include neurosurgical uses, the devices are regulated as neurosurgical ultrasonic surgical instruments under product code "LBK."

2. Regulatory History

2.1. "LFL" – Ultrasonic surgical instruments

The Cavitron Ultrasonic Surgical Aspirator CUSA was the first device cleared under product code LFL on November 18, 1980. The FDA found the Cavitron Ultrasonic Surgical Aspirator CUSA substantially equivalent to the manufacturer's Ultrasonic Surgical Aspirator Model NS-100, which was marketed prior to 1976.

2.2. "NLQ" – Single-use reprocessed ultrasonic surgical instruments

On October 26, 2002, Medical Device User Fee Modernization Act (MDUFMA) (Public Law 107–250), amended the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 510(o) (21 U.S.C. 360(o)), which provided new regulatory requirements for reprocessed single use devices (SUDs.) According to this new provision, in order to ensure that reprocessed SUDs are substantially equivalent to predicate devices, 510(k)s for certain reprocessed SUDs identified by FDA must include validation data. The required validation data included cleaning and sterilization data, and functional performance data demonstrating that each SUD will remain substantially equivalent to its predicate device after the maximum number of times the device is reprocessed as intended by the person submitting the premarket notification. Under section 302(b) of MDUFMA, a reprocessed SUD is defined as an "original device that has previously been used on a patient and has been subjected to additional processing and manufacturing for the purpose of an additional single use on a patient. The subsequent processing and manufacture of a reprocessed single-use device shall result in a device that is reprocessed within the meaning of this definition."

The product code NLQ was developed to identify ultrasonic surgical instruments that would typically fall under product code LFL, but are reprocessed SUDs. Devices within NLQ were identified as critical SUDs in the Federal Register notice dated April 30, 2003 (68 FR 23139). The Reprocessed Harmonic Scalpel was the first device cleared under product code NLQ, on November 1, 2004. The device was originally cleared under product code LFL on November 7, 2001, but received a second clearance following the submission of supplemental validation

data, as required by MDUFMA, and was therefore the first clearance with the product code NLQ.

2.3. "LBK" – Neurosurgical ultrasonic instruments

The Cooper Laser Sonics CUSA Model 200 was the first device cleared under product code LBK, on October 16, 1985. The FDA found the Cooper Laser Sonics CUSA Model 200 substantially equivalent to the same manufacturer's CUSA Model 100, which was marketed prior to the Medical Device Amendments of 1976.

3. Indications for Use

The Indications for Use (IFU) statement identifies the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

Representative indications for use for ultrasonic surgical instruments under product codes "LFL," "NLQ," and "LBK" are as follows:

[Device name] is indicated for use in surgical procedures where fragmentation, emulsification, and aspiration of soft tissue and hard tissue is desirable, including neurosurgery, gastrointestinal and affiliated organ surgery, urological surgery, plastic and reconstructive surgery, general surgery, orthopedic surgery, gynecological surgery, thoracic surgery, laparoscopic surgery, and thoracoscopic surgery. Contraindication: This ultrasonic surgical aspirator device is not indicated for and should not be used for the fragmentation, emulsification, and aspiration of uterine fibroids.

[Device name] is indicated for use in surgical procedures where fragmentation, emulsification, and aspiration of soft tissue and hard tissue (e.g., bone) is desired, including neurosurgery, gastrointestinal and affiliated organ surgery, urological surgery, plastic and reconstructive surgery, general surgery, orthopedic surgery, gynecological surgery, thoracic surgery, laparoscopic surgery, and thoracoscopic surgery.

All devices currently cleared under "LFL," "NLQ," and "LBK" are for prescription use only. Most devices are indicated for use in the fragmentation, emulsification, and aspiration of both soft and hard tissue. Some devices include additional specification related to bleeding control or ligation of vessels.

Some IFU statements reference these additional surgery types:

- neurosurgery
- gastrointestinal and affiliated organ surgery
- gastroenterology
- general surgery
- gynecological surgery
- laparoscopic surgery

- orthopedic surgery
- plastic and reconstructive surgery
- thoracic surgery
- thoracoscopic surgery
- urological surgery
- wound care

4. Clinical Background

4.1. General Characteristics (LFL/NLQ/LBK)

LFL/NLQ/LBK surgical devices are hand-held tools indicated for use in a wide variety of both open and minimally invasive surgical specialties and their representative operations. The devices are a type of surgical instrument that utilize rapid vibrations in the ultrasonic frequency range, which in turn develops heat at the active site. This heat is used in surgery to divide tissues and provide hemostasis by tissue coagulation. In combination with irrigation and aspiration, the device fragments, emulsifies and removes unwanted soft and hard tissues. Devices with neurosurgical indications are commonly used to treat a variety of intracranial and intraspinal tumors. The use of LBK devices to remove cysts and abscesses in the brain and spinal cord have also been reported.

4.2. Surgical Outcomes

LFL/NLQ devices provide patient benefit as surgical tools employed to treat various conditions within each surgical subspecialty. With any invasive procedure, there are risks both inherent with each specific procedure and with the anesthetic employed to complete the operation. In contrast to a successfully completed surgical operation, surgical misadventures can occur due to numerous circumstances including surgeon factors (insufficient training, error in judgement, error in technique) patient factors (poor physiology, concomitant illness, complex disease processes, anatomic variations, among others) and instrument factors (device failures, design flaws, other factors).

In the peri-operative period, actual patient harm appears when an undesired operative outcome (that may occur during any portion or step of the operation) is not recognized and mitigated by the surgical team in a timely fashion. Surgical errors from any source (surgeon, patient, and instrument) may not necessarily lead to patient harm if the errors are promptly identified and corrected. When these surgical errors cause patient harm, they are adverse events related to the surgical procedure. The challenge, as it relates to surgical device regulation, is separating which adverse events are caused by device-specific reasons as opposed to surgeon and/or patient factors. Additionally, there may be device-specific causes of surgical error that may not cause patient harm, because the errors are promptly found and corrected prior to actual patient injury. In the cases where a device failure leads to a surgical error but does not harm the patient due to diligence of the surgical team, adverse events may not be identified and/or reported.

Surgical outcomes following the use of LBK devices are based on a combination of parameters including neurological evaluations, functional improvement (e.g., modified Rankin Scale (mRS)), imaging outcomes (e.g., tumor burden), overall survival, progression free survival, and complication rate, including subsequent surgical interventions and neurologic complications.

LBK devices are commonly used in intracranial and intraspinal tumor resection. Each procedure can be assessed using different measures for the success of the treatment. Potential intra-surgical and post-surgical adverse events for intracranial and intraspinal tumor resection using LBK devices include infection, neurological deficits (motor and sensory deficit, hemiparesis, and speech disturbance), seizure, hydrocephalus, thermal injury, and leptomeningeal seeding (LMS). The effectiveness of intracranial and intraspinal tumor resection using LBK devices is measured by post-surgery tumor recurrence or progression (PSTRP), overall and progression free survival, gross tumor resection, length of surgery and hospital stay, and post-surgical improvement.

4.3. Currently Available Treatment

There are many cleared surgical tools that assist surgeons in completing operations for a wide variety of disease process and surgical indications that are similar in function to LFL/NLQ/LBK devices. Hand-held, hand-powered sharp instruments are commonly employed by surgeons to divide tissues. These instruments divide tissue but do not control hemostasis, which usually requires additional operative steps with a separate set of instruments. The draw of LFL/NLQ/LBK devices is that the single device can perform both tissue division and hemostasis, thus preserving and promoting economy of motion and can shorten operative times. LBK devices are considered part of clinical usual care in the United States (US) when fragmentation and aspiration of neurological tissues is desired.

Surgical hemostasis can be achieved by other electrosurgical devices capable of tissue coagulation, as well as suture ligation methods. Electrosurgical coagulation devices, when employed correctly, can achieve hemostasis faster than suture ligation, at the expense of heat generation which could cause inadvertent tissue damage by thermal spread. Suture ligation requires additional instruments to correctly deploy the suture material at the bleeding site and generally requires more dexterity and skill to use properly. Additionally, the successful deployment of sutures to stop bleeding is generally slower compared to coagulation methods, without the risk of inadvertent tissue damage due to thermal spread. Lastly, staplers can be employed for the control and division of larger blood vessels and/or vascular pedicles. Staplers are not effective for smaller, more extensive tissue bleeding. Staplers control bleeding by mechanical compression of the vessel walls between the closed staple-line. No heat is generated with staplers, thus eliminating tissue damage by thermal spread. However, staplers are much more bulky than other hemostatic instruments and are not designed for precision

hemostatic control. Inadvertent tissue injury can occur due to errors in deployment, and the correct staple height must be utilized based on the tissue thickness for the device to function as intended.

Generally, surgeons choose to use one or more methods of tissue division and hemostasis for a specific operation and may vary use on a case-by-case basis depending on patient and other factors. In summary, LFL/NLQ/LBK devices comprise one of the many tools available to a surgeon to complete the necessary steps of an operation. All available devices have their strengths and weaknesses, and surgeons commonly develop preferences to one or more methods.

4.4. Risks

FDA has identified the following risks to health associated with ultrasonic surgical devices under product codes "LFL," "NQL," and "LBK":

Table 1: Risks to Health and Descriptions/Examples for Ultrasonic Surgical Devices

Identified Risk	**Description/Examples**
Infection	This can result from the use of devices that are not adequately sterilized or reusable device components that are not adequately cleaned and sterilized.
Adverse Tissue Reaction	This can result from the use of device materials that are not biocompatible and may also result from non-resorbable material fragments from the device left in the body due to device mechanical failure.
Bleeding/Hemorrhaging/Blood Loss	This can result from unintended damage to surrounding blood vessels or device malfunction/failure leading to a failure to seal or cauterize.
Tissue Injury (Thermal, Mechanical, Electrical)	Tissue injury can result due to excessive energy or heat applied to tissues causing burns or thermal injury, or mechanical injury due to the power of the device from fragmentation, emulsification, and aspiration. Tissue injury can occur from electric shock resulting from malfunction or failure of the electrical components of the device. Tissue injury can also result in: • Neurological Deterioration (neurological indications) • Prolonged surgical procedure

	• Death
Interference with other Devices	Device electromagnetic (EM) emissions may affect other nearby surgical equipment. Device may be susceptible to EM interference from emissions from other nearby surgical equipment.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by ultrasonic surgical devices under product codes "LFL," "NLQ," and "LBK" and whether any other risks should be included in the overall risk assessment of these device types.

5. Literature Review

Three systematic literature reviews were conducted in an effort to gather any published information regarding the safety and effectiveness of ultrasonic surgical devices generally under produce codes "LFL" and "NLQ," as well as those with neurological indications specifically under product code "LBK."

5.1. Methods

For ultrasonic surgical devices under product codes LFL and NLQ, two electronic databases (Embase and PubMed/MEDLINE) were searched for studies published from January 1, 2007, through January 1, 2022, using the search terms Ultrasonic Surgical Instruments (LFL), Ultrasonic Surgical Aspirators (LFL), and Reprocessed Ultrasonic Surgical Instruments (NLQ). The full search terms and review inclusion criteria are shown in Appendix A.

In total, 632 unique records were identified from the database searches and screened at the title/abstract level. The article retrieval and selection process are presented in Appendix A. After excluding 583 records that were not relevant to the review at the title/abstract level, there were 49 full-text records to assess for eligibility. Forty-six records were retrieved and screened full-text. Three records were not available for full-text screening. Of the 46 records, after a comprehensive literature review, 18 articles were identified that addressed incidence of adverse events with the use of ultrasonic instruments.

For LBK, a search was conducted that was limited to relevant references in the English language that were published from January 1, 2010, to September 1, 2020, with a follow-up review conducted for additional literature published between September 1, 2020, to May 13, 2022. Both searches included two electronic databases (PubMed and Embase) using search terms limited to ultrasonic or ultrasound devices in the neurological field or neurosurgery with a focus on all central nervous system tumors (including brain and spinal tumors), brain hemorrhage and brain trauma. The full search terms and review inclusion criteria are shown in Appendix A.

A total of 534 references were identified after the initial search. The references included original research articles (including case report/case series) and review articles. The article retrieval and selection process are presented in Appendix A. There were 514 references remaining after removing duplicates. Following a review of titles and abstracts, 366 articles were excluded. The remaining 148 articles were reviewed in greater detail for eligibility. An additional 110 articles were further excluded after the review of the full-text articles, resulting in 16 articles on devices under the LBK product code for full text abstraction and qualitative synthesis. There were also 22 articles identified on devices that appear to be ultrasonic surgical instruments used for neurological indications, but that do not appear to have been cleared under product code LBK.

Following the supplemental search (September 1, 2020, to May 13, 2022), two additional publications were considered. This information was assessed, as it can also be informative in the identification of risks for this device type.

5.2. Results

For product codes LFL and NLQ, of the 18 articles assessed for safety and effectiveness information, the publications consisted of 13 randomized controlled trials (RCTs), 2 prospective studies, 2 retrospective studies, and 1 meta-analysis. One retrospective study was conducted in the US and 17 studies were conducted outside of the US. The overall combined sample size of the 18 studies was 2,505 patients, with a sample size range of 15 to 336 ultrasonic surgical device patients. The ages of patients ranged from 5 to 81 years. The devices used in the studies included the following: ultrasonic scalpel, ultrasonic dissector, ultrasonic cutting device, ultrasonic coagulation shear device, and Harmonic scalpel.

For product code LBK, the selected articles consisted of 3 retrospective cohort studies, 2 review articles, 1 single-blinded RCT, 2 single-arm clinical trials, and 30 case reports or case series (median sample size of 9 patients, range 1-67). There were 16 LBK studies identified, and among the studies not specifically identified as devices cleared under LBK, there were 6 total studies. Most of the studies were conducted outside of the US, and only 11 (29%) were US studies. Among the conditions or diseases assessed, 21 articles studied brain tumors, 5 studied spinal tumors, 1 studied both brain and spinal tumors, and 1 each studied brain abscess and Onyx removal for non-Cavitron Ultrasonic Surgical Aspirator (CUSA) devices. The sample size ranged from 1 to 354.

5.3. Adverse Events Associated with Ultrasonic Surgical Devices

Within the literature assessed associated with LFL and NLQ devices, pain, reported in 14/18 of the studies, was the most reported safety outcome, followed by infection rates which were reported in 9/18 studies. Mortality was reported in one study with an incidence of 1/237 (0.004%). Pain was measured inconsistently

among the 14 studies, and the results were mixed with some studies reporting statistically significant pain difference when comparing ultrasonic surgical devices to other cutting methods and others reporting no statistically significant differences. Infection incidence with the use of ultrasonic surgical devices ranged from 0.7% to 6.5% among the 9 studies and difference in infection rates compared to other cutting devices was not statistically significant in any of the 9 studies. Tissue injury was reported in three studies. In one study, hematoma was reported in two of the 40 ultrasonic scalpel patients compared to one of the 40 conventional treatments (5% vs. 2.5%; p=0.62). There were no reports of device malfunction or device-related injuries to the user or patients.

For the LBK related search, there was a great variation of device-related adverse events across studies. The adverse events included mortality, morbidity and complications (e.g., any in-hospital surgical complication, post-surgery recurrence or progression, second surgery and intro/post-surgery complications, and long-term complications), LMS and thermal injury. Generally, aside from complications specific to neurological surgery, the potentially device-related adverse events appear to be consistent with those identified under the more general search of products associated with product codes LFL and NLQ. The detailed findings of this literature survey are provided as Appendix B.

5.4. Effectiveness Associated with Ultrasonic Surgical Devices

Given the specificity of the LBK product code to neurological surgical uses in contrast to LFL and NLQ, which encompass a wide variety of surgical procedures, the literature associated with LBK was also assessed for effectiveness outcomes, while LFL and NLQ were not. Given that these devices are generally surgical tools, the outcomes related to specific surgeries are not particularly influential in the classification decision making for these products. Nonetheless, the outcomes identified in the literature are detailed in Appendix B. The evidence suggests that overall, these devices are reported to be effective for the removal of soft or hard tissue in the brain and spine. Additional, well-designed studies are needed to address how these devices may perform compared to alternative neurosurgical approaches.

6. Risks to Health Identified through Medical Device Reports (MDRs)

6.1. Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2. MDR Data

On May 23, 2022, a query was conducted of the Medical Device Reporting System (MDR) for product code LFL over a 20 year period with date limiters of January 01, 2002, to December 31, 2021. A total of 46,673 reports were identified. Additionally, on July 12, 2022, a search was conducted for product code LBK to identify any additional adverse events related to the use of ultrasonic surgical instruments specifically for neurological surgeries. That search was not time frame restricted and included all MDRs entered into the MDR database by July 12, 2022, that were reported under product code LBK. A specific query for NLQ was not conducted. Because adverse events are most commonly entered under the product code of the original single use device, a query for the reprocessed versions of single use devices could be duplicative and result in skewing the data inappropriately..

In total, the LFL search identified 44,354 malfunctions, 2,263 serious injuries, and 56 deaths for a total of 46,673 reports. Table 2 identifies the most common health effect clinical codes.

Table 2: Common Health Effect Clinical Codes in LFL literature search

Health Effect Clinical Code	Count
No Consequences or Impact to Patient	30066
No Known Impact or Consequence to Patient	5647
No Clinical Signs, Symptoms or Conditions	3563
Foreign body, removal of	2140
Not Applicable	1413
No Code Available	1264
No Patient Involvement	1003
No Information	961

Unknown (for use when the patient's condition is not known)	727
Blood Loss	350
Hemorrhage/Bleeding	270
Burn(s)	198
Nonresorbable materials, unretrieved in body	187
Bleeding	174
Surgery, prolonged	173
Therapy/non-surgical treatment, additional	147
Surgical procedure, additional	146
Surgical procedure	121
Burn, Thermal	121
Device Embedded in Tissue or Plaque	115
Tissue Damage	97
Injury	96
Insufficient Information	96
Foreign Body in Patient	89
Pain	74
Laparotomy	66
Other (for use when an appropriate patient code cannot be identified)	65
Hematoma	63
Failure to Anastomose	57
Unspecified Infection	53

As shown in the table, the vast majority of events had no clinical consequence or impact on the patient. To the extent possible, the remaining adverse events were informative as to possible patient risks associated with use of the device.

The search under product code LBK identified 57 MDRs, including one death report, 17 injury reports and 39 malfunction reports. In order to identify possible patient risks related to the use of ultrasonic surgical devices for neurosurgical use from the MDR data, the patient and device problems reported in the 17 injury reports were further reviewed. Reported patient problems included delayed, prolonged or additional procedures, device fragments left in the patient, tissue damage (e.g., dural tears, burns, swelling), CSF leaks, wound healing issues, and pseudomeningocele. Generally, these patient problems are consistent with the reports for product code LFL.

Additionally, reported deaths were assessed separately in order to further examine the possible risks associated with use of these devices.

The reports labeled as “Death” (N=56) for the LFL search were reviewed in their entirety. Of the 56 deaths reported, 34 did not implicate the device in the death of the patient, 9 were initiated from literature review, and 13 were identified as

potentially related to the use of the device. Data was extracted from the 13 event reports that implicated the device in the death of the patient. In one case, during a liver dissection, uncontrolled bleeding occurred after using the harmonic scalpel to dissect tissue and the patient died intra-operatively. The remaining 12 event narratives detailed that at the time of surgery the device appeared to seal and cut the tissues and vessels without incidence. The patients were closed and transferred to the Intensive Care Unit or Post Anesthesia Care Unit. Post operative vital signs began showing signs of distress and potential internal bleeding. The patients were taken back to the operating room for exploration and found to have bleeding from the site of dissection where the harmonic scalpel was utilized. In one case an unidentified vessel of the neck that had been sealed and cut with the harmonic scalpel had re-opened causing massive bleeding that led to patient death. The event narratives from 2 reports detailed bleeding from mesenteric vessels where the harmonic scalpel was used to seal and dissect tissue. The remaining nine event narratives all detailed dissection of gastric vessels that appeared to be sealed and dry during surgery but opened after the patients were transferred out of the operating room. Of the nine gastric vessels identified, five were definitively identified as short gastric arteries, one was identified as the gastroduodenal artery, and three were identified as unspecified gastric vessels.

The narrative for the single MDR reported as “death” for product code LBK narrative indicated that the device was not in contact with the patient and that the death was not device related.

7. Recall History

7.1. Overview of Recall Database

The Medical Device Recall database contains Medical Device Recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date (“create date”) identified on the database indicates the date FDA classified the recall, it does not necessarily mean that the recall is new.

7.2. Recall Results

The FDA conducted queries of the Medical Device Recall database to identify recalls related to ultrasonic surgical devices under product codes LFL, NLQ, and LBK. The search identified a reported 32 recalls: 27 for LFL, 4 for NLQ, and 1

for LBK, all of which were identified as class II or class III recalls.[1] Due to the number of events, the recalls for LFL are organized in Table 3, below, while the recalls for NLQ and LBK are summarized in more detail.

Table 3: Recall Report Results (LFL)

Recall Class	Root Cause	Recalling Firm	Recall Product Trade Name
Class II	Labeling False and Misleading	MISONIX, INC	LYSONIX 2000 ULTRASONIC SURGICAL SYSTEMS
Class III	Packaging Process Control	INTEGRA LIFESCIENCES CORP.	SELECTOR ULTRASONIC INTEGRA ULTRASONIC ASPIRATOR SYSTEM 24KHZ NEURO SHORT STERILE TIP SET.
Class III	Labeling Mixups/Errors	INTEGRA LIFESCIENCES CORP.	SELECTOR ULTRASONIC INTEGRA ULTRASONIC ASPIRATOR SYSTEM, SELECTOR 24KHZ MICROSURGICAL STERILE TIP SET.
Class II	Device Design	SOUND SURGICAL TECHNOLOGIES, LLC	WIRELESS FOOTSWITCH.
Class II	Component Design/Selection	INTEGRA LIFESCIENCES CORP.	CUSA NXT Ultra Surgical Aspirator System
Class II	Device Design	STRYKER INSTRUMENTS DIV. OF STRYKER CORPORATION	Sonopet Ultrasonic Surgical System
Class II	Device Design	INTEGRA LIFESCIENCES SALES LLC	Integra
Class II	Release of Material/Component Prior to Receiving Test results	INTEGRA LIFESCIENCES CORP	Integra
Class II	Nonconforming Material/Component	ETHICON ENDO-SURGERY INC	HARMONIC Blue Hand Piece & HARMONIC Hand Piece
Class II	Process Control	AMERICAN OPTISURGICAL INC	TX1 Tissue Removal System Console

[1] Recalls are classified into a numerical designation (I, II, or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled. A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

Class II	Nonconforming Material/Component	AROBELLA MEDICAL, LLC	AR1000 Qoustic Qurette"
Class II	Device Design	AMERICAN OPTISURGICAL INC	TX1 Tissue Removal System
Class II	No Marketing Application	AMERICAN OPTISURGICAL INC	TX1 Tissue Removal System
Class II	Component Change Control	STRYKER INSTRUMENTS DIV. OF STRYKER CORPORATION	Sonopet Ultrasonic Aspirator Console
Class II	Material/Component Contamination	INTEGRA LIFESCIENCES CORP.	Integra LifeSciences Corporation
Class II	Error In Labeling	INTEGRA LIFESCIENCES CORP.	Integra® CUSA® Excel+ Sterile Torque Wrench (23 kHz)
Class II	Packaging	TENEX HEALTH INC	TX1"Tissue Removal System
Class II	Device Design	STRYKER INSTRUMENTS DIV. OF STRYKER CORPORATION	Sonopet Ultrasonic Aspirator Console
Class II	Device Design	INTEGRA LIFESCIENCES CORP.	Integra
Class II	Device Design	ETHICON ENDO-SURGERY INC	HARMONIC ACE+ 7 Laparoscopic Shears
Class II	Mix-up of Material/Components	STRYKER INSTRUMENTS DIV. OF STRYKER CORPORATION	The Spetzler Claw"
Class II	Process Control	INTEGRA LIFESCIENCES CORP.	Footswitch accessory
Class II	Other	ETHICON ENDO-SURGERY INC	HARMONIC ACE Shears + Adaptive Tissue Technology
Class II	Device Design	INTEGRA LIFESCIENCES CORP.	C7000 CUSA® Clarity Console
Class II	Under Investigation by the Firm	COVIDIEN LLC	Covidien
Class II	Process Control	ETHICON ENDO-SURGERY INC	Ethicon
Class II	Under Investigation by the Firm	COVIDIEN LLC	Covidien Sonicision Battery Charger

27 total recalls are listed above. The recalls summarized above are related to device design, component integrity, and packaging and sterile barrier integrity. These recalls do not suggest that there are general safety concerns related to the class of ultrasonic surgical instruments because the risks can be properly mitigated through the proposed special controls.

A total of 5 recalls have been reported to date for devices with the product code "NLQ" and "LBK", and are described below:

- Z-1327-2021: This recall was initiated due to the Harmonic ACE +7, Shears with Advanced Hemostasis 5mm Diameter x 36cm being distributed without regulatory clearance.
- Z-2484-2018: This recall was initiated due to an increase in reports indicating that the affected Reprocessed HARMONIC Ace +7, 5mm Diameter Shears with Advanced Hemostasis (HARH) devices displaying an error code, "No Instrument Uses Remaining", upon initial connection to the generator. When this error code is present, the device is not able to be used.
- Z-1644-2013: This recall was initiated due to compromised packaging of the medical device. The seal which maintains a sterile barrier for reprocessed medical devices became compromised to the point where product could fall out of the pouch.
- Z-0559-2009: This recall was initiated due to compromised packaging of the medical device. The seal which maintains a sterile barrier may not be properly sealed on one end. A breach in packaging seal or a failure in packaging integrity has the possibility of risk to the patient in terms of transmitting organisms capable of harm.
- Z-0920-2013: This recall was initiated due to complaints that when the CUSA CEM ("CUSA Electrosurgery Module") Nosecone is used under certain circumstances, there is a potential for erosion of the CUSA Excel Tip used with the CUSA CEM Nosecone. This erosion could potentially lead to tip breakage. The CUSA CEM Nosecone is an accessory used when the surgeon desires the CUSA Excel Ultrasonic Surgical Aspirator System to also provide electrical coagulation capability.

The first four recalls were associated with product code NLQ. Two of these recalls are related to packaging of the devices, one was related to the lack of a regulatory clearance, and the fourth seems to be a technical issue. The final recall was associated with product code LBK, and is related to an accessory of the CUSA Excel Ultrasonic Surgical Aspirator System that is used for electrocautery with or without ultrasonics. These recalls do not suggest that there are general safety concerns related to the class of ultrasonic surgical devices, but instead, except for the lack of regulatory clearance, are risks that can be mitigated through the proposed special controls.

8. Summary

In light of the information available, the Panel will be asked to comment on whether all ultrasonic surgical devices currently assigned to product codes "LFL", "NLQ" and "LBK" meet the statutory definition of a Class III device in accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act):

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and
- the device is purported or represented to be for use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or
- if the device presents a potential unreasonable risk of illness or injury

or would be more appropriately regulated as Class II, in which:

- general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness

or as Class I, in which:

- the device is subject only to general controls, which include registration and listing, good manufacturing practices (GMPs), prohibition against adulteration and misbranding, and labeling devices according to FDA regulations.

For the purposes of classification, FDA also considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

The Panel will be asked whether they believe ultrasonic surgical devices would be appropriately regulated as Class II. If the Panel does not agree with FDA's proposed classification, the Panel will be asked to provide their rationale for recommending a different classification.

8.1. Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified, and provide a reasonable assurance of the safety and effectiveness of ultrasonic surgical devices. The

following is a risk/mitigation table, which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks:

Table 4: Summary of Risks to Health and Recommended Mitigation Measures for Ultrasonic Surgical Devices

Identified Risk	Recommended Mitigation Measure
Infection	Sterilization Validation Reprocessing Validation Pyrogenicity Evaluation (neurosurgical devices only) Shelf-life Testing Packaging Validation Labeling
Adverse Tissue Reaction	Biocompatibility Evaluation Shelf-life testing
Bleeding, Hemorrhaging, Blood Loss	Non-clinical Performance Testing Bench Testing Animal Performance Testing
Tissue injury resulting from: Thermal effects, burns Mechanical failure, device breakage Electrical hazards, shock Software malfunction Use error	Labeling Non-clinical Performance Testing Bench Testing Device Reliability Testing Electrical Safety Testing Electromagnetic compatibility (EMC) testing Software Verification, Validation, and Hazard Analysis Animal Testing Shelf-Life Testing Use-Life Testing
Interference with other Devices	Electromagnetic Compatibility (EMC) Testing Labeling

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for ultrasonic surgical devices under product codes "LFL," "NLQ," and "LBK":

1. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including the following:
    a. Characterization of the ultrasonic and power parameters (e.g., sonication frequency and displacement, irrigation rate, suction (negative) pressure).

b. Bench testing of material strength to demonstrate the device will withstand forces encountered during use and maintain device integrity over the labeled shelf-life and use-life, including repeated cleaning/use cycles if reprocessed.

2. Software used to operate the device hardware must be described in detail in the software requirements specification (SRS) and software design specification (SDS). Software verification, validation, and hazard analysis must be performed.

3. Electrical safety, thermal safety, mechanical safety, and electromagnetic compatibility (EMC) testing must be performed.

4. Performance data must demonstrate the sterility of the tissue-contacting components of the device and must evaluate pyrogenicity (if intended for neurosurgical use).

5. Performance data must support the shelf-life and use-life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf-life and use-life.

6. The tissue-contacting components of the device must be demonstrated to be biocompatible.

7. Animal performance data must demonstrate that the device performs as intended and will not result in unintended tissue injury, including mechanical and thermal damage to surrounding tissue structures.

8. The labeling must include:
   a. Qualifications needed for the safe use of the device.
   b. A detailed summary of the device technical parameters.
   c. A detailed summary of the device- and procedure-related complications pertinent to use of the device.
   d. Information on how the device operates.
   e. A shelf-life for sterile components.
   f. The use-life of the device for reusable components.
   g. Validated methods and instructions for reprocessing of any reusable components.
   h. Information on the electrical safety and electromagnetic compatibility of the device.
   i. Prominent labeling adjacent to original equipment manufacturer (OEM) identifying the reprocessor for single-use reprocessed ultrasonic surgical instruments.

If the Panel believes that Class II is appropriate for ultrasonic surgical devices under product codes LFL, NLQ, and LBK, the Panel will be asked whether the

identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

8.2. Overview of Proposed Classification/FDA Recommendation

Based on the safety and effectiveness information gathered by the FDA, the identified risks to health and recommended mitigation measures, we recommend that ultrasonic surgical devices under product codes "LFL," "NLQ" and "LBK" indicated for use as identified in section 3 be regulated as Class II devices.

21 CFR 878.4XXX Ultrasonic Surgical Device.

(a) *Identification.*
An ultrasonic surgical device is a prescription device intended to heat, fragment, emulsify, or remove tissue by use of ultrasonic frequency displacement and vacuum suction. This type of device may include ultrasonic scalpels, ultrasonic vessel sealers, ultrasonic surgical aspirators, and accessories such as assembly tools (wrenches), footswitches, and end effector tips.

(b) *Classification.*
Class II (special controls) for ultrasonic surgical devices. The special controls for these devices are:

1. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including the following:
    a. Characterization of the ultrasonic and power parameters (e.g., sonication frequency and displacement, irrigation rate, suction (negative) pressure).
    b. Bench testing of material strength to demonstrate the device will withstand forces encountered during use and maintain device integrity over the labeled shelf-life and use-life, including repeated cleaning/use cycles if reprocessed.

2. Software used to operate the device hardware must be described in detail in the software requirements specification (SRS) and software design specification (SDS). Software verification, validation, and hazard analysis must be performed.

3. Electrical safety, thermal safety, mechanical safety, and electromagnetic compatibility (EMC) testing must be performed.

4. Performance data must demonstrate the sterility of the tissue-contacting components of the device and must evaluate pyrogenicity (if intended for neurosurgical use).

5. Performance data must support the shelf-life and use-life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf-life and use-life.

6. The tissue-contacting components of the device must be demonstrated to be biocompatible.

7. Animal performance data must demonstrate that the device performs as intended and will not result in unintended tissue injury, including mechanical and thermal damage to surrounding tissue structures.

8. The labeling must include:
    a. Qualifications needed for the safe use of the device.
    b. A detailed summary of the device technical parameters.
    c. A detailed summary of the device- and procedure-related complications pertinent to use of the device.
    d. Information on how the device operates.
    e. A shelf-life for sterile components.
    f. The use-life of the device for reusable components.
    g. Validated methods and instructions for reprocessing of any reusable components.
    h. Information on the electrical safety and electromagnetic compatibility of the device.
    i. Prominent labeling adjacent to original equipment manufacturer (OEM) identifying the reprocessor for single-use reprocessed ultrasonic surgical instruments.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of the ultrasonic surgical devices currently identified by product codes "LFL," "NLQ," and "LBK."

Appendix A: Literature Search Methods

Literature Search Methods for LFL/NLQ

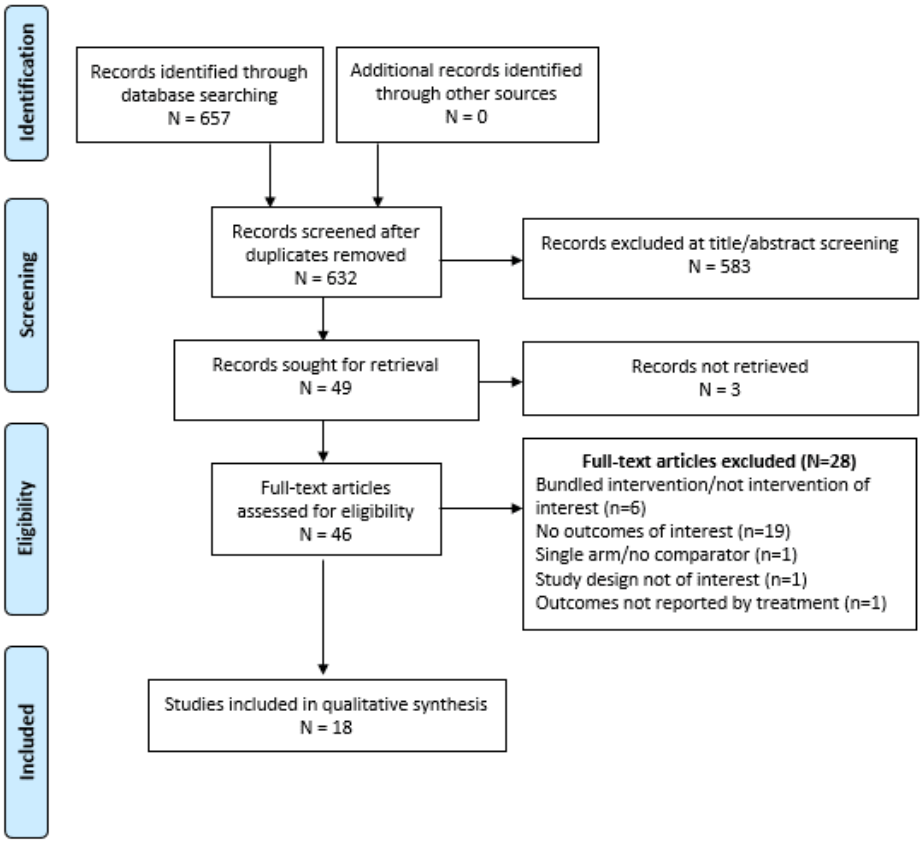
Table 5: PubMed Search Strategy

No.	Query	Results
Filters: Humans, English, from 2007-2022		
#5	#3 NOT #4	276
#4	comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] OR annual[tiab] OR book[tiab] OR comment[tiab] OR chapter[tiab] OR note[tiab] OR review[tiab] OR symposium[tiab] OR poster[tiab] OR abstract[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab] OR animal[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR goat[tiab] OR goats[tiab] OR pig[tiab] OR pigs[tiab] OR cadaver[tiab] OR dog[tiab] OR dogs[tiab] OR monkey[tiab] OR monkeys[tiab] OR ape[tiab] OR apes[tiab] Filters: Humans, English, from 2007/1/1 - 2022/1/1	2,592,740
#3	#1 OR #2	347
#2	(reprocessed[tiab] OR reprocessing[tiab] OR reusing[tiab] OR decontaminating[tiab]) AND (surgical[tiab] OR medical[tiab]) AND (instrument[tiab] OR instruments[tiab]) Filters: Humans, English, from 2007/1/1 - 2022/1/1	79
#1	("Surgical Instruments"[Mesh] AND "Ultrasonics"[Mesh]) OR "ultrasonic scalpel"[tiab] OR "ultrasonic scalpels"[tiab] OR "ultrasonic aspirator"[tiab] OR "ultrasonic aspirators"[tiab] Filters: Humans, English, from 2007/1/1 - 2022/1/1	268

Table 6: Embase Search Strategy

No.	Query	Results
Filters: Humans, English, from 2007-2022		
#5	#3 NOT #4	518
#4	('editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR 'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti OR animal:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR goat:ab,ti OR goats:ab,ti OR pig:ab,ti OR pigs:ab,ti OR cadaver:ab,ti OR dog:ab,ti OR dogs:ab,ti OR monkey:ab,ti OR monkeys:ab,ti OR ape:ab,ti OR apes:ab,ti) AND [english]/lim AND [humans]/lim AND [2007-2022]/py	6,762,816
#3	#1 OR #2	817
#2	(reprocess*:ab,ti OR reusing:ab,ti OR decontaminat*:ab,ti) AND (surg*:ab,ti OR medical:ab,ti) AND (ultrasonic:ab,ti OR ultrasound:ab,ti) AND [english]/lim AND [humans]/lim AND [2007-2022]/py	48
#1	('ultrasonic surgical equipment'/de OR 'ultrasonic scalpel'/de OR 'ultrasonic aspirator'/de OR 'ultrasonic scalpel*':ab,ti OR 'ultrasonic aspirator*':ab,ti) AND [english]/lim AND [humans]/lim AND [2007-2022]/py	769

Article Retrieval and Selection Process for LFL/NLQ



Literature Search Methods for LBK

***PubMed Search Syntax*:**

1. (ultrasonic OR ultrasound) AND (neurosurgery OR (neuro AND surgery)) AND (aspiration OR fragmentation) AND (brain tumor OR hemorrhage OR trauma OR spinal tumor OR central nervous system tumor) AND "2010/01/01"[PDat] : "2020/09/01"[PDat] AND English[lang] AND "humans"[MeSH Terms] AND hasabstract[text]
2. **(**Cusa OR Dissectron OR Amerimed OR Bovie OR Cooper OR Olympus) AND (ultrasonic OR ultrasound) AND (neurosurgery OR (neuro AND surgery)) AND (aspiration OR fragmentation) AND (brain tumor OR hemorrhage OR trauma OR spinal tumor OR central nervous system tumor) AND "2010/01/01"[PDat] : "2020/09/01"[PDat] AND English[lang] AND "humans"[MeSH Terms] AND hasabstract[text]

***Embase Search Syntax*:**

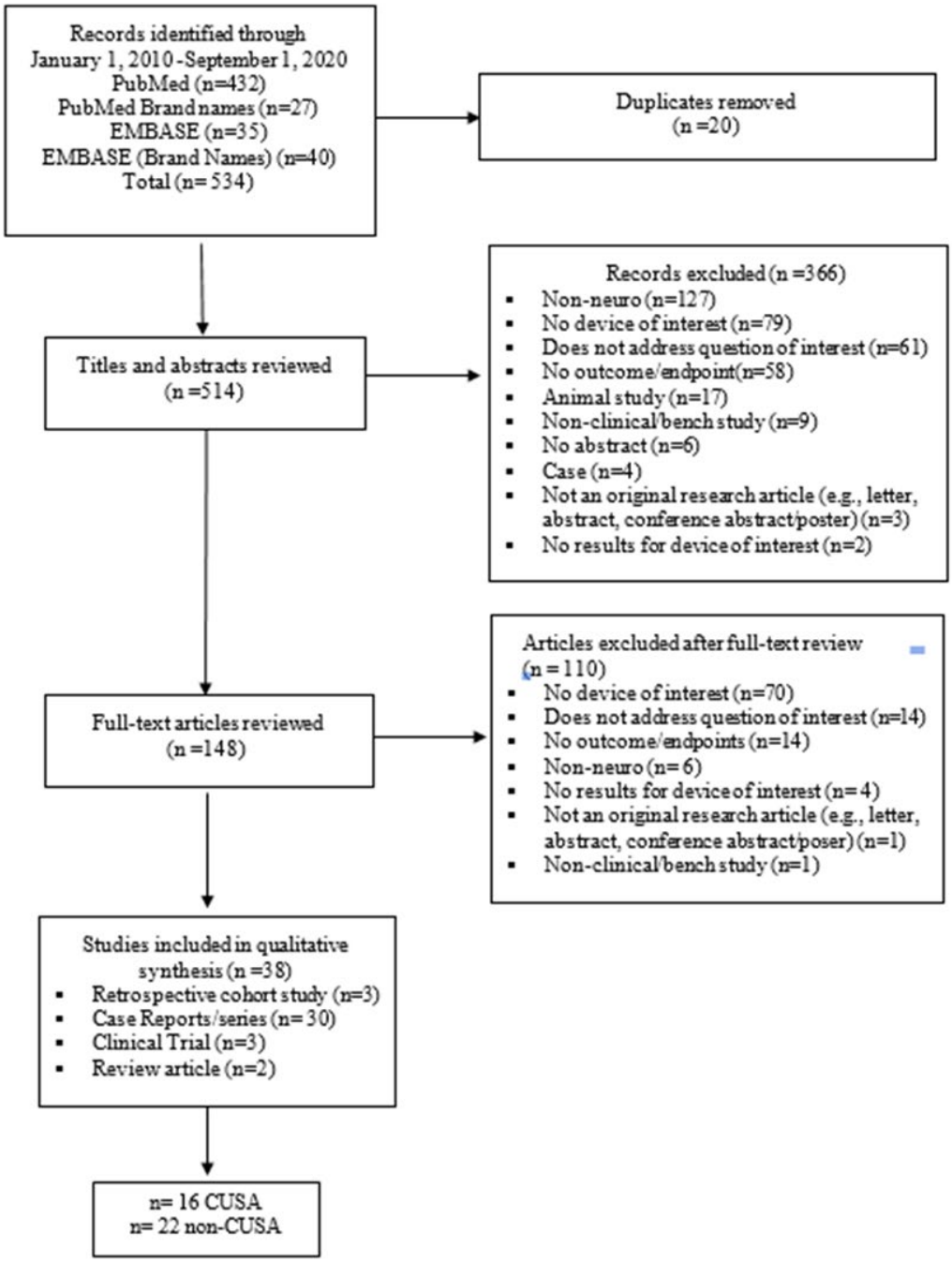
1. ('ultrasound surgery'/exp OR 'ultrasonic surgical procedures' OR 'ultrasound surgery' OR ultrasound OR ultrasonic OR 'ultrasonic scalpel'/exp OR 'cavitron ultrasonic aspirator' OR 'scalpel, ultrasonic' OR 'ultrasonic scalpel' OR 'ultrasonic surgical aspiration system' OR 'ultrasound aspirator') AND ('neurosurgery'/exp OR 'neurologic surgery' OR 'neurological surgery' OR 'neurosurgery' OR 'neurosurgical emergency' OR 'neurosurgical

operation' OR 'neurosurgical patient' OR 'neurosurgical procedures' OR (('neurology'/exp OR 'clinical neurology' OR 'neurology') AND surgery)) AND ('aspiration, puncture and suction'/exp OR 'aspiration, puncture and suction' OR 'fragmentation'/exp) AND ('brain tumor'/exp OR 'brain neoplasm' OR 'brain neoplasms' OR 'brain supratentorial tumor' OR 'brain supratentorial tumour' OR 'brain tumor' OR 'brain tumor diagnosis' OR 'brain tumour' OR 'brain tumour diagnosis' OR 'cerebral tumor' OR 'cerebral tumour' OR 'cerebroma' OR 'cerebrum tumor' OR 'cerebrum tumour' OR 'encephalophyma' OR 'intracerebral tumor' OR 'intracerebral tumour' OR 'intracranial neoplasm' OR 'midline tumor' OR 'midline tumour' OR 'multiple brain tumor' OR 'multiple brain tumour' OR 'subtentorial tumor' OR 'subtentorial tumour' OR 'supratentorial brain tumor' OR 'supratentorial brain tumour' OR 'supratentorial neoplasms' OR 'supratentorial tumor' OR 'supratentorial tumour' OR 'tumor cerebri' OR 'tumor, brain' OR 'tumour cerebri' OR 'tumour, brain' OR 'brain hemorrhage'/exp OR 'bleeding, corpus callosum' OR 'brain bleeding' OR 'brain haemorrhage' OR 'brain haemorrhage, traumatic' OR 'brain hemorrhage' OR 'brain hemorrhage, traumatic' OR 'brain microhaemorrhage' OR 'brain microhemorrhage' OR 'brain stem haemorrhage, traumatic' OR 'brain stem hemorrhage, traumatic' OR 'cerebral haemorrhage' OR 'cerebral haemorrhage, traumatic' OR 'cerebral hemorrhage' OR 'cerebral hemorrhage, traumatic' OR 'cerebral microbleed' OR 'corpus callosum bleeding' OR 'corpus callosum haemorrhage' OR 'corpus callosum hemorrhage' OR 'encephalorrhagia' OR 'haemorrhage, brain' OR 'haemorrhage, intracranial' OR 'haemorrhagic apoplexy' OR 'haemorrhagic stroke' OR 'haemorrhagic stroke intracerebral bleeding' OR 'hematencephalon' OR 'hemorrhage, brain' OR 'hemorrhage, intracranial' OR 'hemorrhagic apoplexy' OR 'hemorrhagic stroke' OR 'hemorrhagic stroke intracerebral bleeding' OR 'hypertensive intracranial haemorrhage' OR 'hypertensive intracranial hemorrhage' OR 'intracerebral bleeding' OR 'intracerebral haemorrhage' OR 'intracerebral hemorrhage' OR 'intracortical haemorrhage' OR 'intracortical hemorrhage' OR 'intracranial bleeding' OR 'intracranial haemorrhage' OR 'intracranial haemorrhage, hypertensive' OR 'intracranial haemorrhage, traumatic' OR 'intracranial haemorrhages' OR 'intracranial hemorrhage' OR 'intracranial hemorrhage, hypertensive' OR 'intracranial hemorrhage, traumatic' OR 'intracranial hemorrhages' OR 'intraventricular haemorrhage' OR 'intraventricular hemorrhage' OR 'periventricular haemorrhage' OR 'periventricular hemorrhage' OR 'posterior fossa haemorrhage' OR 'posterior fossa hemorrhage' OR 'traumatic intracranial haemorrhage' OR 'traumatic intracranial hemorrhage' OR 'cerebrovascular accident'/exp OR 'cva' OR 'accident, cerebrovascular' OR 'acute cerebrovascular lesion' OR 'acute focal cerebral vasculopathy' OR 'acute stroke' OR 'apoplectic stroke' OR 'apoplexia' OR 'apoplexy' OR 'blood flow disturbance, brain' OR 'brain accident' OR 'brain attack' OR 'brain blood flow disturbance' OR 'brain insult' OR 'brain insultus' OR 'brain ischaemic attack' OR 'brain ischemic attack' OR 'brain vascular accident' OR 'cerebral apoplexia' OR 'cerebral insult' OR 'cerebral stroke' OR 'cerebral vascular accident' OR 'cerebral vascular insufficiency' OR 'cerebro vascular accident' OR 'cerebrovascular accident' OR 'cerebrovascular arrest' OR 'cerebrovascular failure' OR 'cerebrovascular injury' OR 'cerebrovascular insufficiency' OR 'cerebrovascular insult' OR 'cerebrum vascular accident' OR 'cryptogenic stroke' OR 'ischaemic cerebral attack' OR 'ischaemic seizure' OR 'ischemic cerebral attack' OR 'ischemic seizure' OR 'stroke' OR (('bleeding'/exp OR 'abnormal bleeding' OR 'bleeding' OR 'bleeding complication' OR 'blood effusion' OR 'blood loss' OR 'capillary bleeding' OR 'haemorrhage' OR

'haemorrhage model' OR 'haemorrhagic activity' OR 'hemorrhage' OR 'hemorrhage model' OR 'hemorrhagia' OR 'hemorrhagic activity' OR 'spontaneous haemorrhage' OR 'spontaneous hemorrhage') AND head) OR 'head injury'/exp OR 'cerebrocranial injury' OR 'cerebrocranial trauma' OR 'cranial injury' OR 'cranial trauma' OR 'craniocerebral injury' OR 'craniocerebral lesion' OR 'craniocerebral trauma' OR 'craniocerebral wound' OR 'head injuries' OR 'head injuries, closed' OR 'head injuries, penetrating' OR 'head injury' OR 'head trauma' OR 'head wound' OR 'injury, head' OR 'trauma capitis' OR 'trauma, cranial' OR 'trauma, head') AND [2010-2020]/py AND [english]/lim AND [abstracts]/lim AND [humans]/lim AND ('article'/it OR 'article in press'/it OR 'review'/it) NOT [9-1-2020]/sd

2. ('ultrasound surgery'/exp OR 'ultrasonic surgical procedures' OR 'ultrasound surgery' OR ultrasound OR ultrasonic OR 'ultrasonic scalpel'/exp OR 'cavitron ultrasonic aspirator' OR 'scalpel, ultrasonic' OR 'ultrasonic scalpel' OR 'ultrasonic surgical aspiration system' OR 'ultrasound aspirator') AND ('neurosurgery'/exp OR 'neurologic surgery' OR 'neurological surgery' OR 'neurosurgery' OR 'neurosurgical emergency' OR 'neurosurgical operation' OR 'neurosurgical patient' OR 'neurosurgical procedures' OR (('neurology'/exp OR 'clinical neurology' OR 'neurology') AND surgery)) AND ('Cusa':dn OR 'Cusa'/dn OR 'Cusa':ti OR 'Cusa':ab OR 'ultrasonic cavitation device'/exp OR 'Dissectron':dn OR 'Dissectron'/dn OR 'Dissectron':ti OR 'Dissectron':ab OR 'Amerimed':dn OR 'Amerimed'/dn OR 'Amerimed':ti OR 'Amerimed':ab OR 'Bovie':dn OR 'Bovie'/dn OR 'Bovie':ti OR 'Bovie':ab OR 'Cooper':dn OR 'Cooper'/dn OR 'Cooper':ti OR 'Cooper':ab OR 'Olympus':dn OR 'Olympus'/dn OR 'Olympus':ti OR 'Olympus':ab) AND [2010-2020]/py AND [english]/lim AND [abstracts]/lim AND [humans]/lim AND ('article'/it OR 'article in press'/it OR 'review'/it) NOT [9-1-2020]/sd

Article Retrieval and Selection Process for LBK



Appendix B: Literature Search Detailed Results

Adverse Events

A detailed summary of the most common adverse events identified from the two literature searches associated with LBK are provided below.

Mortality

Henzi et al. conducted a retrospective cohort study comparing the safety profiles of 3 commonly used neurosurgical ultrasonic aspirator models (i.e., CUSA, Sonopet and Soring) for resecting intracranial tumors using data from a patient registry in Switzerland. This is the first study published that evaluated the comparative safety profiles of ultrasonic aspiration devices in neurosurgery. The study found that the safety profiles of these devices appeared mostly similar after controlling for potential confounders. There were only two deaths reported in the Soring group during hospitalization, but 4.5% (16/354), 5.2% (24/461), and 2.3% (5/213) of subjects who underwent surgery using CUSA, Soring, and Sonopet devices respectively were deceased at three months. The mortality rates were similar among the three device groups at three months in multivariate analysis. The authors stated that mortality would likely result from device-specific surgical complications. However, whether deaths can be attributable to the devices is uncertain without a control group with no NFADs used in the surgery. The strengths of this study include a large sample size, detailed prospective data collection and a direct comparison of 3 NFADs. A limitation of this study may include residual confounding despite mostly adequate adjustment in the analyses.

All-cause mortality for the CUSA device was also reported in two case series studies. In Turkey, Baran et al. assessed long-term clinical and seizure outcomes of insular gliomas among patients 26-73 years old, via the transopercular approach. Subpial/endopial resections were done using CUSA. Among the 22 patients, 50% were females, 7 (31.8%) were deceased during the 12-84 months follow-up, 5 (22.7%) of which died of high-grade glioma. Two others died of myocardial infarction 84 months post-surgery and a traffic accident 37 months after surgery, and both were unrelated to the underlying condition.

Wright et al. described a combined approach of laser interstitial thermal therapy followed by minimal-access trans-sulcal resection for the treatment of large and difficult to access brain tumors in patients aged 51-84 years in the US. Lesion volume range was 10.6-77.7 cm. Under microscopic magnification and stereotactic guidance, tumors were removed with a CUSA or Sonopet device. Of 10 patients, 50% were females, four patients (three males and one female) (40%) had died from their primary disease (brain tumors) at the end of the study follow-up (46-501 days). It should be noted that the mortality rate estimates are not robust due to the small sample sizes. In addition, the high mortality rates observed in the case series could in part be associated with the natural history of brain tumors, or the learning curves and experience of physicians who operated the device.

Morbidity and Complications

Henzi et al. reported that the morbidity rate for LBK device use (constructed from the Karnofsky Performance Scale) was 9.6% at discharge and 11.3% at three-month follow-up. There were

33.3% (118/354) of patients who experienced in-hospital complications, and 14.7% (52/354) of patients had complications that were a direct result of surgery trauma.

Post-surgery tumor recurrence or progression (PSTRP) was described in two studies. In a clinical case series study, Baran et al. reported a PSTRP rate of 18.2% (4/22) when using LBK devices for insular gliomas resection. Bakhshi et al. provided their experience of management and outcomes of intramedullary spinal cord tumors in 43 patients aged 33.2 years (median), from a single center in Pakistan. The authors indicated that their use of LBK devices is very limited due to the high cost associated with its disposables. They reported a PSTRP rate of 18.6% (8/43) partly due to limited maximum safe resection and gross total resection was not achieved. Second surgery rate was 27.2% (6/22) noted only in the Baran et al. study.

Intra- and post-surgery complications include neurological deficits (motor and sensory deficit, hemiparesis, and speech disturbance) and seizure. Israel, Roth et al. described a novel technique of continuous subcortical mapping using an electrified CUSA in children 1-18 years with supratentorial lesions in proximity to the corticospinal tract (CST). Among 11 children in the study, five were girls and six were boys. Mild worsening of hemiparesis was observed in 27.3% (3/11) of the children immediately post-surgery, two of which improved at two- to three-week follow-up, and one was back to pre-operative baseline condition. Cheng et al. sought to determine whether intraoperative changes in transcranial motor evoked potentials (TcMEPs) and somatosensory evoked potentials (SSEPs) predicting outcome in children with intramedullary spinal cord tumors. Data from 12 patients 3-72 months-old were analyzed. Intraoperative motor evoked potentials (MEP) changes were noted in 50% (6/12) of patients who experienced reduction in MEP duration by 27-100% and post-operative reduction in MRC (Medical Research Council) motor scale (0–5) by 1-2. Seven (58.3%) patients experienced intraoperative decreases in SSEPs. Two (16.7%) of which were LBK device related. In the Schucht's study carried out in Switzerland, 67 patients (age range 22-77 years) who underwent 5-aminolevulinic-acid–guided surgery for a glioblastoma multiforme (GBM) adjacent to the corticospinal tract (CST; < 10 mm) with continuous dynamic monopolar motor mapping. Post-operative worsening in motor status on the first ^{t} day after surgery was noted in 29.9% (20/67) of patients who underwent GBM surgery. At discharge, 13 patients (19%) had complete motor recovery and seven patients (10%) had persisting deficits. One patient had an intra-operative seizure but disappeared at discharge. In patients who underwent insular glioma removal surgery, Baran reported that 31.8% (7/22) had hemiparesis and 4.5% (1/22) had speech disturbance. In Wright's study, 20% (2/10) of patients suffered mild postoperative neurological deficits, 1 transiently. One patient had hydrocephalus (10%) and the fourth patient had pin site infection unrelated to the surgical wound.

Germany, Payer et al. retrospectively analyzed 22 patients aged 21-86 years with intramedullary spinal cord metastases. Methods used during surgery included the application of intravenous corticosteroids, CO_2 laser, LBK devices, and intraoperative monitoring (IOM). LBK devices were used in only three patients. One patient (33%) worsened in neurological deficit after surgery measured by the McCormick Scale Grade.

Long-term neurological deficit complication rates were 4.5% (3/67) at three months in the Schucht's study on GBM and 13.6% (3/22) in patients with gliomas (two of which had seizures and one had speech disturbance) who were followed up 12-84 months post operation. Cheng reported a 33.3% (4/12) long-term complication rate with an average follow-up of 17 months

(range 3–72 months), two (16.7%) of which were motor related and two were sensory related. One of the two cases with sensory complications was related to the use of a LBK device. Unsgård et al. provided three case examples illustrating the technique of 3-dimensional (3D) ultrasound–guided resection of low-grade gliomas from a university hospital in Norway. The authors used a neuronavigation system with an integrated 3D ultrasound scanner, which enables simultaneous navigation in both magnetic resonance imaging (MRI) and ultrasound volumes (SonoWand Invite). The tumor was resected using the navigated CUSA guided by the 3D ultrasound images. The navigated CUSA enables precise low-grade glioma resection even in deep-seated areas. In one (33.3%) patient, ophthalmological assessment eight weeks after the operation demonstrated a right-sided upper quadrantanopia with no subjective discomfort. A subtle semantic paraphasia was noted.

Ao et al., 2021 used the aspirator to resect spheno-orbital meningiomas in nine procedures in seven patients (two patients experienced tumor recurrence). Visual acuity worsened following one procedure (11% of procedures) and improved or remained stable following the remaining eight procedures (89% of procedures). Color vision worsened following one procedure (11% of procedures) and improved or remained stable following the remaining eight procedures (89% of procedures). There was no worsening of proptosis in any patient (0%). Two patients (29%) developed post-operative ptosis, and two patients (29%) developed frontalis palsy, which was described as transient. Two patients (29%) developed partial third nerve palsy, one of whom developed permanent trigeminal hypoesthesia (14%). Finally, one patient (14%) experienced cerebrospinal fluid (CSF) rhinorrhea, which was treated and resolved. In their discussion, the authors note that both CSF leakage and post-operative cranial nerve palsies are “not uncommon” with resection of sphenoid wing meningiomas and are seen in similar rates in other studies.

Leptomeningeal Seeding (LMS)

Ahn et al. investigated whether the use of the CUSA (LBK device) was associated with LMS in a retrospective cohort study (n=242). They found that when comparing patients who received CUSA with patients where the CUSA was not used, the use of CUSA was associated with a statistically significantly higher rate of LMS in patients who underwent resection for brain metastases during a median follow-up of eight months [unadjusted hazard ratio (HR) 2.64, 95% confidence interval (CI): 1.38-5.04]. However, this association was no longer statistically significant after controlling for potential confounders including age, tumor volume, time from diagnosis to brain metastases, type of primary cancer, proximity to the cerebrospinal fluid (CSF) pathway and mode of resection (HR 0.94, 95% CI: 0.42-2.10). The authors cautioned that piecemeal resection using the CUSA should be limited because of the potential risk of post-surgical LMS, especially when the tumor is in contact with the CSF pathway.

Thermal Injury

Avula et al. proposed a new hypothesis implicating thermal injury resulting from the use of the CUSA (LBK device) as an important mechanism in the pathogenesis of posterior fossa syndrome after reviewing evidence on existing theories in the review article. Specifically, thermal tissue damage produced from the CUSA plays a major role in the injury to the brain parenchyma, in particular the proximal efferent cerebellar pathway, which is an important anatomical substrate in the development of posterior fossa syndrome. The authors stated that implication of CUSA in the causation of posterior fossa syndrome has been reported before and that while pathogenesis

of posterior fossa syndrome is likely to be multifactorial, CUSA should be regarded as a contributor to posterior fossa syndrome pathogenesis because avoidance of CUSA has reduced the rate of posterior fossa syndrome but has not prevented it.

Effectiveness

A detailed summary of any effectiveness outcomes identified in the literature search for LBK are provided below. Effectiveness outcomes reported in the published literature as potentially associated with LBK devices include gross total resection (GTR), length of surgery and hospital stay, and overall post-surgery improvement.

Gross Total Resection (GTR)

There were nine publications that reported on GTR when LBK devices were used. The GTR rates varied greatly across publications mostly due to relatively small sample sizes and various patient and disease characteristics of the clinical case series. Two studies had three subjects, two studies had 10 subjects, and the other five studies had 11, 12, 22, 43, and 67 subjects, respectively. The GTR rates ranged from 25% (3/12) reported in Cheng's study on spinal cord tumors and 100% (10/10) reported in Tang's study where the authors discuss their short experience on the application of the CUSA Excel Ultrasonic Aspiration System in the resection of skull base meningiomas. Another case report on low-grade glioma by Unsgård also achieved a 100% (3/3) GTR. The rest of the six studies reported GTR rates ranging from 45.5% (5/11) in Roth's study on supratentorial lesions to 73% (49/67) in Schucht's study on GBM.

Length of Surgery and Length of Hospital Stay

Henzi et al. systemically compared the performance of three models of ultrasonic aspiration devices (CUSA, Sonopet, and Soring) using data from a registry in Switzerland. The sample sizes for the three devices were 354, 213 and 461, respectively. The average (standard deviation (SD)) length of surgery was 309.1 minutes (133.1) for CUSA, 299.3 minutes (128.6) for Sonopet, and 255.7 minutes (120.2) for Soring. The average (SD) length of hospital stay was 8.7 days (5.1) for CUSA, 8.9 days (5.2) for Sonopet, and 8.1 days (5.0) for Soring. Bakhshi reported that the median (interquartile range (IQR)) of hospital stay was 7 days (4-10 days).

Detchou et al., 2020 used the ultrasonic aspirator to improve precision in a navigated osteotome procedure. No intraoperative or post-operative complications occurred in this case report. The authors report surgical time (Stage I: 422 minutes; Stage II: 256 minutes) and estimated blood loss (Stage I: 1500 mL; Stage II: 100 mL), as well as hospital length of stay (18 days). They indicate that use of navigated ultrasonic osteotomy using Sonopet may reduce potential complications and blood loss but provide no data from related procedures for comparison.

Overall Post-Surgery Improvement

Four studies reported the outcome of LBK devices for post-surgery improvement. Cheng reported that two out of 12 (16.7%) children (aged 2-13 years) were improved in motor grade and two children (16.7%) with sensory deficit (paresthesia) resolved after spinal cord tumor surgery. In Schucht's study, 19% of patients (13/67) had complete motor recovery at discharge. Motor status improved in three out of 11 (27.3%) children (< 18 years of age) with supratentorial

lesions in proximity to the CST. In Payer's study where CUSA was used in surgery for only three patients, all (100%) were improved as measured by the McCormick Scale Grade.

Appendix C: References

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