

WhitePaper

Advances in Pathology Tissue Management Reduce Formalin Use, Improve Quality and Cut Costs

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DARK Daily Laboratory and Pathology News @ darkdaily.com

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Introduction

Formalin is highly irritating to the upper respiratory tract, eyes, and skin, and is a known carcinogen.

Formalin has been used as a tissue preservative in operating rooms and pathology laboratories for over one hundred years. Formalin is a solution of about 4% formaldehyde and water (known as 10% NBF) and is ubiquitous in clinical laboratories, pathology laboratories, and in operating rooms. It is an inexpensive reagent and effective at what it does.

Unfortunately, it is hazardous. According to the U.S. Department of Labor's Occupational Safety & Health Administration ("OSHA"), formalin/formaldehyde is a moderate fire and explosion hazard when exposed to heat or flame and when mixed with certain chemicals. More problematic are its health hazards. Formalin is highly irritating to the upper respiratory tract, eyes, and skin, and is a known carcinogen. "In humans, formaldehyde exposure has been associated with cancers of the lung, nasopharynx and oropharynx, and nasal passages."¹ It is also considered to be mutagenic.

In addition to those problems, modern healthcare institutions often have multiple clinics, hospitals, operating rooms, and laboratories at separate geographic locations. This requires that surgical tissue samples, large or small, be transported over significant distances in formalin-filled containers, greatly increasing the risk of potentially dangerous formalin spills.

This white paper will look at the risks of formalin use, trends in formalin use and disposal, and how laboratory and operating room workflow is affected by it. Alternate methods for storing and preserving pathology specimens will be introduced along with descriptions of changes to workflow, benefits in terms of healthcare worker safety, and the safety and economic benefits of these changes. Two case studies, one of a major metropolitan hospital that has adopted two systems that modify or eliminate traditional formalin usage, and the other a major hospital in Italy, will be presented.

Chapter 1:

When Traditional Tissue Handling Methods Fall Short of Today's Requirements for Anatomic Pathology Labs

Formalin, despite its known health hazards, remains a key component of the histopathology and pathology laboratory.

Formalin, despite its known health hazards, remains a key component of the histopathology and pathology laboratory. Over the years alternative fixatives have been studied, such as Bouin and Hollande, and newer products such as GreenFix, UPM and CyMol. A study published in *The European Journal of Histochemistry* compared these fixatives “to evaluate alternative fixation for morphological diagnosis and nucleic acid preservation for molecular methods.”²

Each had their advantages and disadvantages, but ultimately none provided right combination of acceptable qualities to replace formalin. The point of that study, however, was to evaluate whether any of those reagents could replace formalin in terms of test validation. The focus was not safe use or ease of disposal. Due to issues of cost, re-validation and the need to evaluate long-term effects of alternate fixatives on tissue preservation, it is unlikely that total elimination of formalin is likely or even possible. In most cases, the pathologist or histologist has been trained to interpret characteristic tissue morphology that is created by formalin fixation. Laboratory scientists and pathologists looking to replace formalin fixation have several factors to consider:

- Toxicity of the fixative (both short-term and cumulative)
- Component volatility

- Flammability
- The effects of over-fixation on tissues
- Storage requirements if specimens cannot be left in fixative
- Compatibility of the fixative with instrumentation
- The practical, legal and financial requirements of disposal after use³

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A more practical and realistic goal is to evaluate methods and approaches to minimize the use of formalin while still maintaining a high level of fixative effectiveness and flexibility, while decreasing healthcare workers' exposure to formalin.

Anatomic Pathology Workflow

The workflow of most pathology labs are similar. The tissues removed from the patient need to be processed in the laboratory in order to create diagnostic slides that can be viewed under the microscope by pathologists. Very often, molecular and IHC tests are performed on the slides or from paraffin blocks that are created during the workflow process.

Gross Examination

Tissues biopsied from the patient are transported from the operating room to the pathology department. Traditionally the specimen is placed into a container filled with formalin then transported to the pathology laboratory. The pathologist or pathology assistant will describe the physical appearance of the tissue sample. Small representative samples of the tissue are placed into small plastic cassettes that hold tissue while it is processed. The processed tissue is then embedded into a paraffin block.

The problem is that if a high-volume laboratory or hospital processes thousands of anatomical samples yearly, they are utilizing literally thousands of gallons of formalin...

Fixation

If the tissue was not transported in a fixative (such as formalin), it typically will be fixed in formalin as a step during processing. According to the University of Utah Medical Library, “The purpose of fixation is to preserve tissues permanently in as life-like a state as possible. Fixation should be carried out as soon as possible after removal of the tissues (in the case of surgical pathology) or soon after death (with autopsy) to prevent autolysis.”²⁴

There are five groups of fixatives—aldehydes, mercurial, alcohols, oxidizing agents, and picrates—but formalin is considered to be the most effective for all uses.

Additional steps include: tissue processing, embedding, sectioning, staining, and coverslipping.

Further Processing

For the purposes of this white paper, the important steps occur between surgery and gross examination and processing, because those steps involve formalin. However, to give context to validation issues, it should be noted that, increasingly, tissue specimens can undergo a variety of molecular-based and immunohistochemical (antigen)-based tests that can be performed on samples taken from paraffin blocks.

The problem, as noted, is that if a high-volume laboratory or hospital processes thousands of anatomical samples yearly, they are utilizing literally thousands of gallons of formalin, with its inherent hazards. In addition, hospitals, health systems and laboratories are increasingly spread out over regional distances (sometimes nationally), which require tissue samples to be transported, increasing exposure and the risk of spillage. In addition, any changes to standard procedures, i.e., eliminating formalin altogether or using a different type of fixative, requires that the tests be validated for clinical utility by the laboratories.

Chapter 2:

Challenges in the Movement of Pathology Tissue Specimens

Even within a single institution, there is transport time from removing the specimen from the patient and moving it to the laboratory.

Almost immediately after removal from the body, tissue specimens begin to degrade. The primary factors involved in tissue degradation are warm and cold ischemia, i.e., time and temperature, or the time between the chilling of the tissue, organ or body part after excision.

Even within a single institution, there is transport time from removing the specimen from the patient and moving it to the laboratory. In facilities with greater geographic distances, such as hospitals and surgery centers at separate facilities from the laboratory, the time it takes to transport the specimen becomes a factor.

This is why tissues are traditionally placed into a fixative, to halt the process of degradation. But, as described above, fixatives such as formalin pose a health and safety risk to healthcare providers.

Time

Even use of formalin does not cause “instant” fixation of tissues. The rule of thumb is, under ambient and passive exposure, it takes one hour for formalin to penetrate 1 millimeter into tissues. Although finding data regarding the amount of time a tissue specimen can remain viable at room temperature unfixed is hard to come by, “not very long” is the most common response. Numerous studies have been conducted on different types of tissues examining preanalytic ischemic times for specific antigen and protein expression data. A study by Neumeister et al. (2012), for example, focused on breast cancer tissue, concluding that “Key breast cancer biomarkers show no evidence of loss of antigenicity, although this dataset assesses the

Creating even more time pressure on histologists and pathologists are DNA and RNA degradation times.

relatively short time beyond the 1-hour limit in recent guidelines. Other proteins show changes in antigenicity in both directions.”⁵ They also conclude that size and heterogeneity of the tissue plays a significant role.

Creating even more time pressure on histologists and pathologists are DNA and RNA degradation times. A 2004 study by Spruessel et al. reported that, “Initial changes of gene and protein expression profiles were already observed 5-8 min after colon resection. Fifteen minutes after surgery, 10%-15% of molecules, and after 30 min, 20% of all detectable genes and proteins, respectively, differed significantly from the baseline values.”⁶

Temperature

As suggested above, room temperature specimens have a very short period of viability for the majority of laboratory uses. If fresh specimens are not examined immediately, they are typically fixed as soon as possible. Even in various fixatives, time is a factor. Geoffrey Rolls points out in his article, “Fixation and Fixatives”, “For light microscopy initial fixation is usually carried out at room temperature and this may be followed by further fixation at temperatures up to 45°C during tissue processing.”⁷

A study published by Yildiz-Aktas et al. (2012) evaluating cold ischemic time on IHC results for ER/PR and HER2 expression in breast tumors said, “Non-refrigerated samples are affected more by prolonged cold ischemic time than refrigerated samples. Cold ischemic time period of as short as one-half hour may occasionally impact the immunohistochemical (IHC) staining for progesterone receptor. Significant reduction in IHC staining for hormone receptors, and HER2, however, generally does not result until 4 h for refrigerated samples and 2 h for non-refrigerated samples. The

ASCO/CAP guideline of cold ischemic time period of <1 h is a prudent guideline to follow.”⁸

Safety

Any system that would minimize or eliminate the amount of fixative/formalin would be desirable.

Transporting specimens in formalin, obviously, expands the risk of exposure and spills. Containers for transport need to be well sealed, resistant to vibration and shock that may cause leakage or breakage. In the amounts typically found in the laboratory, OSHA has designated formalin spills under the category of Manageable Chemical Spill, which is short of Immediately Dangerous to Life and Health (IDLH). What this means, from a practical point of view, is that most formalin spills in a laboratory or transport environment (i.e., courier vehicle), can be cleaned up by someone who is not hazmat trained. However, it is flammable, potentially explosive, as well as carcinogenic and mutagenic. Standard procedure in most hospital or lab environments would include cordoning off the spill area during clean-up, and potentially evacuating personnel to avoid exposure to fumes. Any system that would minimize or eliminate the amount of fixative/formalin would be desirable.

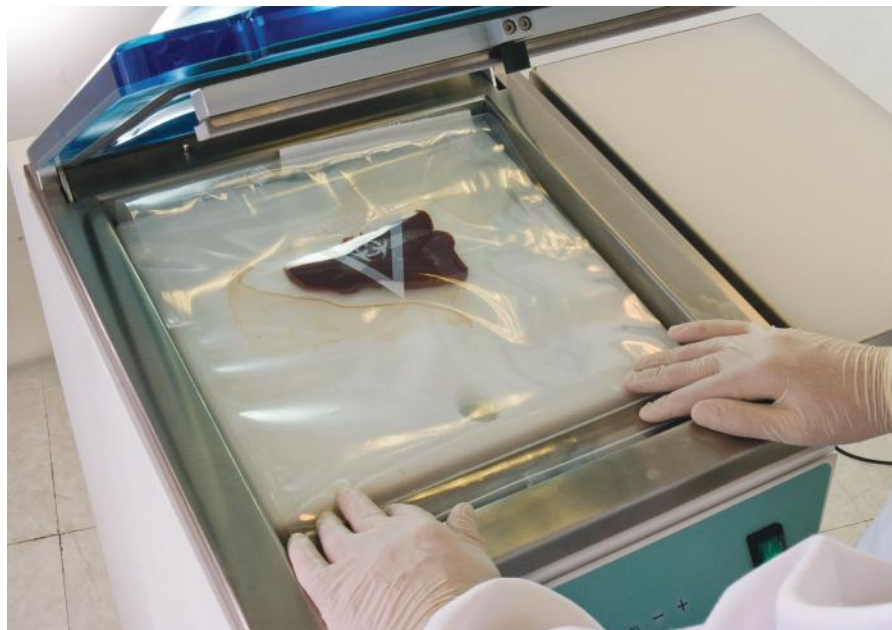
Chapter 3:

The Benefits of New Pathology Tissue Management Technologies and Methods

As mentioned, formalin is a reliable, well-documented fixative. It is also hazardous, and any method that can decrease the amount of formalin used while maintaining current clinical viability would be welcome, both for healthcare provider safety and for decreased disposal efforts and costs.

Two new approaches, both utilizing under-vacuum sealing, include:

- Delaying the introduction into formalin/fixative for controlled short-term transport and storage
- Standardizing formalin/fixative amounts based on weight and specimen type



Delaying (or Eliminating) Formalin Use During Specimen Transport—Milestone’s TissueSAFE

In this controlled environment, most tissue types are preserved ‘as fresh’ for up to 72 hours.

It is well known that tissues, once removed from the body and kept at room temperatures, begin to degrade quickly. Quick freezing or refrigeration is one option, although not suitable for all tissues or applications.

A new alternative, however, for short-term storage of pathology tissues is a combination of vacuum storage and refrigeration.

Milestone Medical (Sorisole, Italy) has developed a system for sealing tissue specimens in a medical grade vacuum bag, which is then stored refrigerated for a limited time. This system is called TissueSAFE.

Immediately after excision the specimen is moved from the operating room to an adjoining room where the TissueSAFE system is located. The tissue is placed in a specimen bag and sealed under vacuum. Specimen bags can be labeled with critical case information. The tissue sample is then placed into a carryable “coolbag” for short distances or into a refrigerated transfer box. In this controlled environment, most tissue types are preserved “as fresh” for up to 72 hours. Once the specimen is delivered in this state to the laboratory, it is removed from the sealed bag, examined, and prepared for diagnostic testing, either on the fresh specimen or following fixation of the tissue.

TissueSAFE benefits include:

- No transport of formalin
- Minimizes formalin in the operating room
 - » Reduce nursing staff exposure to formalin fumes
 - » Reduce or eliminate costly formalin spills

The SealSAFE system is similar to the TissueSAFE system except that it utilizes a specimen bag to which formalin can be added, then the specimen bag and the tissue it holds is vacuum-sealed.

- Specimens are held “as fresh,” enabling improved visualization during grossing
- Tissues do not dry out
- Autolytic (degradation) process is slowed
- Tissue cools quicker in vacuum than in air
- Pathology department selects fixative type, fixation start time and duration, while improving documentation of this workflow step

Researchers at the Città della Salute e della Scienza of Torino (Italy) evaluated the TissueSAFE system. The authors state, “From a pathological standpoint no morphological or immunohistochemical drawbacks were encountered in a local series (more than 2000) of UV (under vacuum) processed cases.”⁹ Based on that study and others, the Italian Group of Mammary Pathology (GIPaM) of the Society of Pathology (SIAPEC) recognized the UV methods of tissue preservation and transport.¹⁰

Standardizing Formalin – Milestone’s SealSAFE

The SealSAFE system is similar to the TissueSAFE system except that it utilizes a specimen bag to which formalin can be added, then the specimen bag and the tissue it holds is vacuum-sealed. The generally accepted ratio of formalin used to tissue weight is 10:1. Unfortunately, this really is more dogma than scientific fact. A 2012 study by Buesa and Peshkov¹¹ found that a 2:1 ratio at 45°C was adequate. In working with the Milestone SealSAFE system and experimenting with the formalin to tissue weight ratio, Dr. Richard J. Zarbo, MD, Senior Vice President and KD Ward Chair of Henry Ford Health System’s Pathology and Laboratory Medicine, has presented data indicating that a 1:1 ratio is adequate.^{12,13}

Studies have validated both systems for histology, histochemistry, and DNA and RNA-based molecular tests.

Using specially designed vacuum bags, the tissue is placed in the bag, then placed into the SealSAFE cavity. The device automatically weighs the tissue specimen. The laboratory assigns a preset ratio of formalin to tissue weight (1:1, 1:2, 1:2.5, 1:3, etc.), then fixative is dispensed into the bag while under a closed case, keeping splashing or fumes from the technologist or nurse performing the procedure. The final step seals the specimen bag, under vacuum, within the closed and ventilated cavity. The same bag can be opened and resealed up to three times from the operating room to final storage, if samples need to be taken for different types of testing.

SealSAFE benefits include:

- Standardization and quality – the same amount of formalin to tissue is always used
- Less formalin – vacuum bags reduce formalin volume
- Safety – closed and ventilated system – reduces formalin exposure
- Improved archiving – prints labels with pertinent patient information
- Cost savings – decreased formalin volumes and use of bags versus rigid containers reduces costs of biohazard material disposal
- Enables flexibility in fixative choice – formalin, formalin substitutes, alcohols, and molecular fixatives.

Studies have validated both systems for histology, immunohistochemistry, and DNA and RNA-based molecular tests.^{12,13}

Chapter 4:

Case Studies

Henry Ford Health System Laboratory, Detroit, Michigan

Henry Ford Health Systems' laboratories have been experimenting for quite some time with approaches to eliminating or decreasing the amount of formalin used.

Henry Ford Health System operates six hospitals in the Metropolitan Detroit area, including its 802-bed flagship hospital, Henry Ford Hospital. It also operates 32 Henry Ford Medical Centers throughout four counties, and three free-standing medical centers with 24-hour emergency care. The system employs 23,000 people, 3,214 allied health professionals and records 3.2 million outpatient visits annually with more than 104,000 hospital admissions.

The health system operates one of the largest hospital-based laboratories in the U.S., processing more than 12 million specimens annually. Around 2006 the health system restructured their laboratories into the Henry Ford Production System utilizing Lean principles. The laboratories involved are ISO 15189:2007 accredited for quality and competence, the first for a U.S. integrated laboratory system and the only ISO 15189 accredited labs in the State of Michigan.

Henry Ford Health Systems' laboratories have been experimenting for quite some time with approaches to eliminating or decreasing the amount of formalin used. Dr. Richard J. Zarbo, MD, Senior Vice President and KD Ward Chair of Henry Ford Health System's Pathology and Laboratory Medicine, says, "The goal was to eliminate formalin from an operating room, specifically at our newest hospital, which is located 25 miles from the core lab. We have three community hospitals that don't gross examine tissues or process them locally. All tissues are sent to a centralized histology core laboratory."

The nurses at that hospital, West Bloomfield Henry Ford Hospital, would take the excised specimens to another room and place them into formalin in containers. Those containers would be sent to the local site's pathology department, which would then ship them via courier to the main core laboratory in Detroit.

*TissueSAFE
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transfer.*

“The opportunity here was to remove a toxic and potentially carcinogenic chemical from the OR so that nurses wouldn't be exposed to this,” says Dr. Zarbo. “This was something we basically presented to nurses as a new process that would have advantages for them. When you're changing somebody else's work, it's always a good idea to present it in terms of what's in it for them. They would be taking on a different role. Instead of putting specimens in containers with formalin, they were going to be using a new device to seal specimens without formalin.”

In this case, Dr. Zarbo refers to Milestone's TissueSAFE, a high vacuum biospecimen transfer system. TissueSAFE completely eliminates the use of formalin for tissue transfer. After a tissue sample is obtained, it is placed into the designated specimen bag and sealed under vacuum within the TissueSAFE system. The sealed bag is labeled, then placed into a carryable “coolbag” or into a refrigerated transfer box. Radio Frequency Identification Device (RFID) smart cards can also be placed into the transfer box, if the laboratory chooses; this allows labs to continuously monitor and document tissue temperature throughout the transfer from OR to local pathology lab to core lab and histology lab.

“Our pilot program was, one, to see if we could get people external to the laboratory—our suppliers—to adopt a new technology that was advantageous to them, but also helped us achieve our goal. Number two was to see how many specimens we could collect in this manner,” says Dr. Zarbo.

The third part of the pilot validation was, Dr. Zarbo said, “If we treated specimens in this fashion shipped formalin-free under vacuum at 4 degrees centigrade, compared to if they were placed in formalin upfront, what would the morphology of that specimen look like under the microscope for the pathologist. Would it include artifacts that would preclude the pathology from making a diagnosis?”

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There is an incredible amount of savings related to safety and exposure to carcinogens, and elimination of costly formalin spills, so in that regard it’s fairly priceless for employees.”

Dr. Zarbo points out that their goal was not to be completely formalin free, because it was still used in the core laboratory for fixation and processing. “The opportunity was to remove formalin from the peripheral community hospitals and ship these specimens in a formalin-free manner in order to eliminate that upfront formalin process and reduce the formalin exposure.”

Several factors needed to be evaluated: ultimate economics, both front end and back end; what temperatures the specimens needed to be transported at; how long the vacuum-sealed, refrigerated specimens would last and still be optimal for microscopic examination, i.e., for 24, 48 or 72 hours?

Dr. Zarbo says, “We found that we could do this over a period of both 24 and 48 hours with virtually all tissue types acceptable for diagnosis. We initially evaluated over 100 specimens.”

Direct financial savings in-process are limited, as formalin is a low-cost reagent. Upfront, Dr. Zarbo notes that the savings from the small pilot hospital were fairly minimal. “We were able to calculate that we used 135 fewer gallons of formalin over a period of a year. That savings is only roughly \$1700, but there is an incredible amount of savings related to safety and exposure to carcinogens, and elimination of costly formalin spills, so in that regard it’s fairly priceless for employees.”

They could keep tissues for 72 hours at room temperature under vacuum with just 1:1 formalin with no degradation of the tissue.

After completing validation of the Milestone TissueSAFE system, Henry Ford Hospital began validating another Milestone system, SealSAFE. SealSAFE allows for either fresh specimen vacuum sealing, as with TissueSAFE, or fixative dispensing into the specimen vacuum bag at a specified volume to weight ratio. “We believed this device could further reduce our use of formalin in the gross lab whose protocol was to cut all specimens fresh from the main ORs.” Dr. Zarbo says, “Using SealSAFE, we were able to do another experiment and find out how much formalin you really need to put in the vacuum bag to preserve a fresh specimen after dissection. The rule of thumb, and nobody knows where this came from, that we’ve all been taught, is the formalin-to-weight ratio is 10:1, in other words, ten times formalin to the weight of the specimen. That’s an awful lot of formalin.”

So using the SealSAFE system, they tested various ratios of formalin to weight: 3:1, and 2:1 and finally down to 1:1. Dr. Zarbo says, “We did the same thing for a series of large specimens, colons, gall bladders, small intestines, thyroid, uteri, and we did, in this particular validation, both 2:1 and 1:1. We held these tissues in vacuum bags at room temperature for 24, 48 and 72 hours. Every day we would go back and take a piece of that specimen and give it to the pathologist after processing (blind) to see if there was degradation that diminished their ability to make a morphological diagnosis. And, in fact, there was none.”

They could keep tissues for 72 hours at room temperature under vacuum with just 1:1 formalin with no degradation of the tissue. Dr. Zarbo says, “So we’ve proved you can use a minimum amount of formalin to store your tissues, which is where a portion of savings now come into play downstream.”

There were two other areas of savings. First, residual large specimens were typically stored in very large, rigid buckets. Dr. Zarbo said, “We were able to, by using the plastic bags sealed with the SealSAFE,

reduce the amount of occupied shelf space by 43%. That opened up more space in the lab. So what? In labs with 80,000 surgical cases, like we have, that's an awful lot of space you save."

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With our volume, that was a savings of \$51,000 per year. Now you have achieved a significant savings for the institution.”

Second, for most institutions, and Henry Ford Hospital is consistent with this, there is considerable expense in disposing of tissues that are preserved in formalin. For Henry Ford Hospital, the facilities disposal people responsible for disposing of the tissue are obligated to open the containers and decant the formalin from the tissue. The tissue then goes to an incinerator and the formalin is sent to a special hazardous waste disposal site. Dr. Zarbo says, “That process costs the institution roughly \$1.70 per pound. If you have minimal formalin in your waste containers, then formalin is no longer required to be decanted and separated. Then you're disposing at \$0.75 per pound. With our volume, that was a savings of \$51,000 per year. Now you have achieved a significant savings for the institution.”

Some questions still remained—did the formalin-free system cause changes to the morphology of the specimens for advanced diagnostics? Would they be acceptable for molecular testing, immunohistochemical testing, and special stains? The simple answer is, YES—specimens stored and transported fresh, under-vacuum utilizing the TissueSAFE system did not affect the outcomes for advanced diagnostic testing. Dr. Zarbo says, “We most recently have completed a molecular validation as well as the routine histology, special stain and IHC. There were no effects. We tested the samples in vacuum up to three hours, because that's how long it takes to transport specimens from our community hospital. What we found was excellent preservation of RNA and DNA. The molecules and length of molecules are less than in fresh immediately frozen tissues, but they were still excellent.”

Henry Ford Health System's conclusion was that the SealSAFE and TissueSAFE systems provided measurable upfront savings and significant backend disposal savings, while significantly decreasing healthcare provider exposure to formalin.

Dr. Zarbo points out that he doesn't see getting rid of formalin use completely any time soon. This fixative has been around for over a hundred years and all the pathology tissue-based lab tests and diagnostic criteria are validated on formalin fixation. However, decreasing the use of formalin, especially in transportation and disposal, was a positive thing both economically and for safety. The nursing staff involved found the TissueSAFE system easy to work with. "We're a Lean enterprise, so we do everything according to standardization and visualization. Once we got that done the nurses actually liked it. They accepted it very well."

In short, a major metropolitan health system, evaluated the TissueSAFE system for use in one of their suburban hospitals to determine if they could eliminate formalin from the operating room, minimize the formalin exposure to nurses and other staff, decrease and eliminate formalin for the approximately 25-mile transport distance to the core laboratory facility. In addition, they evaluated the SealSAFE system to minimize the amount of formalin necessary to maintain fixed stored specimens, that may be revisited for morphological testing. Furthermore, they then evaluated the upfront and backend costs and savings created by decreasing the amount of formalin used and the savings associated with formalin-fixed tissue disposal.

Henry Ford Health System's conclusion was that the SealSAFE and TissueSAFE systems provided measurable upfront savings and significant backend disposal savings, while significantly decreasing healthcare provider exposure to formalin. In addition, they provided valuable data verifying that excised tissue samples transferred and stored formalin-free under vacuum maintained their morphological, antigenic and molecular properties for both traditional gross examination and advanced diagnostics like molecular testing, IHC and special stains.

University Hospital Le Molinette, Turin, Italy

Today, the University Hospital Le Molinette is using nine TissueSAFE systems spread throughout several surgical centers.

The University Hospital Le Molinette, in Turin, Italy, is the largest hospital in the Piedmont region. In 2008, the pathology team, led by Professor Gianni Bussolati, then later by Dr. Anna Sapino, began to investigate the possibility of moving away from formalin to an alternative non-toxic reagent. However, they were unable to identify any formalin replacement that was commercially available and that did not cause problems with morphological changes in fixed tissue. At that point, the researchers partnered with Milestone, an Italy-based company known for manufacturing medical technology. The goal was to look for a method to reduce the use of formalin while still maintaining viability for a broad range of clinical tests.

Dr. Anna Sapino, currently the Director of Pathology, says, “Histopathological diagnosis is essential for management of patients; however, pathologists are being challenged with increasing demands of molecular tests for personalized treatments, the accuracy of which is dependent on adequate tissue preservation. In addition, pathologists are expected to facilitate procurement, preservation, and distribution of tissues to qualified biomedical researchers. Nowadays the procedures of tissue preservation, transport and fixation are neither standardized nor optimal to maintain the integrity of proteins and nucleic acids.”

Teaming with Milestone led to the development of the TissueSAFE system. Today, the University Hospital Le Molinette is using nine TissueSAFE systems spread throughout several surgical centers. “Since 2008 at our Institution (Città della Salute e della Scienza of Torino) we have collaborated with Milestone to introduce an alternative method by which specimens are sealed under vacuum (UV) by using the TissueSAFE in the surgical suite and then cooled for transport to the pathology lab,” said Dr. Sapino. “From a

pathological standpoint no morphological or immunohistochemical drawbacks were encountered in a local series (more than 2000) of UV processed cases. In a survey on the feasibility, compliance and quality assurance of UV procedure for transferring surgical specimens, the UV procedure was met with favor by the staff.”

*In response to
this success...
a group of
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tendered a
proposal to
Italy’s national
health system
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They have now adopted using the TissueSAFE system for any surgical specimen larger than 2 centimeters. Over the course of five years they have collected more than 25,000 samples.

As a result of the University Hospital Le Molinette’s experience, it became a case reference for other surgical staff and pathologists throughout Italy and in other European countries, most notably France, Holland and Spain. In addition, in response to this success as well as an accidental exposure to formalin during a post-surgical mechanical ventilation, a group of pathologists tendered a proposal to Italy’s national health system to adopt the TissueSAFE and SealSAFE systems, designed to provide the following benefits:

- Elimination of liquid fixatives (formaldehyde, glyoxal, alcohol, etc.) from operating rooms
- Reduction of the current number of containers with liquid fixatives
- Control of tissue fixation times in the anatomic pathology laboratory
- Continuous control of tissue temperatures
- Under Vacuum storage and controlled temperature (4°C) of each type of tissue with excellent preservation of its histological and biomolecular characteristics for no less than 60 hours
- The possibility of being able to transfer surgical tissue samples via pneumatic tubes

- Preservation under vacuum of fixed material, even at room temperature

As these examples indicate, a large number of healthcare institutions across Europe have successfully adopted the TissueSAFE and SealSAFE systems resulting in significant decreases in formalin usage. Along with increased safety, pathology laboratories have found improved workflow and marked cost savings.

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Chapter 5:

Conclusion

Because of its potential health hazards and disposal costs, it is important that healthcare institutions and laboratories make every effort to eliminate use of formalin when possible...

Concerns over formalin use in clinical laboratories, as well as its use in various manufacturing processes, are not new. The U.S. Court of Appeals for the District of Columbia oversaw a case in 1987 between the US Environmental Protection Agency (“EPA”), OSHA, College of American Pathologists (“CAP”), Formaldehyde Institute, DuPont, and labor unions about the problem of occupational hazards. Worldwide, the organization most involved in the assessment of carcinogenicity of reagents is the World Health Organization’s (“WHO”) International Agency for Research on Cancer (“IARC”). The IARC classifies formalin as a Group I, i.e., known carcinogens, along with substances such as asbestos and benzene.¹⁴

It is unlikely that use of formalin will ever be completely eliminated in the anatomic and surgical pathology laboratory. As a fixative, formalin is highly functional and inexpensive. Because of its potential health hazards and disposal costs, it is important that healthcare institutions and laboratories make every effort to eliminate use of formalin when possible while still maintaining high quality healthcare services, or maximize methods that will minimize the amount of formalin used as well as providing technologies that guarantee healthcare worker safety.

Izak B. Dimenstein wrote, “The harmful effects of formaldehyde in anatomical pathology should be kept in perspective without underestimating them but also without overreacting. Monitoring, PPE, and measures for limitation of formaldehyde exposure substantially diminish its harmful effects. While using formalin, appropriate working practices include minimizing formaldehyde evaporation

as the safety rationale. Formalin can remain for a long time as the ubiquitous fixative reagent in anatomical pathology.”¹⁵

“
The harmful effects of formaldehyde in anatomical pathology should be kept in perspective without underestimating them but also without overreacting.”

This paper provided an overview of the problems inherent with working with formalin as a fixative in anatomic and surgical pathology and described the workflow of the typical anatomic pathology laboratory and how formalin is traditionally utilized. It examined two new methods to minimize or eliminate the use of formalin for tissue transport systems, and addressed the limitations and benefits of those systems. This paper also provided a case study of how a major metropolitan healthcare system has changed its workflow utilizing the Milestone Medical TissueSAFE and SealSAFE systems in order to significantly decrease the amount of formalin used during transport, and the resulting decrease in healthcare worker exposure to formalin and financial savings to the institution as a result of decreased formalin disposal. It also provided a case study of how a major hospital in Turin, Italy helped develop the TissueSAFE and SealSAFE systems, which not only became standard usage for the hospital, but led to adoption of those systems throughout Europe and in the Italian national health system.

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Appendices

A-1

About Milestone Medical

Milestone Medical is a world leader in tissue specimen management systems, macro digital imaging systems and rapid xylene-free tissue processors. Milestone headquarters are based in Sorisole (Bergamo), Northern Italy. Milestone Medical North American headquarters are located in Kalamazoo, Michigan. Founded in 1988 as a company specializing in advanced microwave instrumentation for analytical and organic chemistry labs, it established a Medical division in 1994 to transfer its expertise in laboratory grade microwaves to the world of histopathology. Visit their website at www.milestonemedssrl.com.

A-2

About Mark Terry



Mark Terry is a freelance writer and editor specializing in clinical diagnostics, telemedicine, and biotechnology. He worked for 18 years in clinical genetics prior to turning to writing, and has published over 700 magazine and trade journal articles, 19 books, and dozens of white papers and book-length market research reports related to the clinical lab industry. He is a member of the Association of Health Care Journalists and the Association of Genetic Technologists. For more information, visit his website at www.markterrywriter.com.

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About DARK Daily

“Dark Daily is a concise e-news/management briefing on timely topics in clinical laboratory and anatomic pathology group management. It is a solution to the dilemma facing anyone in the laboratory profession.

DARK Daily is a concise e-news/management briefing on timely topics in clinical laboratory and anatomic pathology group management. It is a solution to the dilemma facing anyone in the laboratory profession. New developments, new technology, and changing healthcare trends make it imperative to stay informed to be successful. At the same time, the Internet, cell phones, blackberries, laptop computers and wireless devices are overwhelming any one individual's ability to absorb this crushing Tsunami of data.

DARK Daily is a quick-to-read, easy-to-understand alert on some key development in laboratory medicine and laboratory management. It has no counterpart in the lab world. Why? Because it is produced and written by the experts at THE DARK REPORT and The Dark Intelligence Group, who know your world, understand your needs and provide you with concise, processed intelligence on only those topics that are most important to you!

You will find DARK Daily to also be an exceptionally valuable resource in laboratory and pathology management. Some of the lab industry's keenest minds and most effective experts will be offering their knowledge, their insights and their recommendations on winning strategies and management methods. Many of these experts are unknown to most lab directors. As has proven true with THE DARK REPORT for more than a decade, DARK Daily will be your invaluable—and unmatched—resource, giving you access to the knowledge and experience of these accomplished lab industry professionals.

A-4

About The Dark Intelligence Group, Inc. and THE DARK REPORT

“Membership is highly-prized by the lab industry’s leaders and early adopters. It allows them to share innovations and new knowledge in a confidential, non-competitive manner.

The Dark Intelligence Group, Inc., is a unique intelligence service, dedicated to providing high-level business, management and market trend analysis to laboratory CEOs, COOs, CFOs, pathologists and senior-level lab industry executives. Membership is highly-prized by the lab industry’s leaders and early adopters. It allows them to share innovations and new knowledge in a confidential, non-competitive manner. This gives them first access to new knowledge, along with the expertise they can tap to keep their laboratory or pathology organization at the razor’s edge of top performance.

It offers qualified lab executives, pathologists and industry vendors a rich store of knowledge, expertise and resources that are unavailable elsewhere. Since its founding in 1996, The Dark Intelligence Group and THE DARK REPORT have played instrumental roles in supporting the success of some of the nation’s best-performing, most profitable laboratory organizations.

The Dark Intelligence Group (TDIG) is headquartered in Austin, Texas. This location makes it very accessible for any laboratory organization seeking input, insight and support in developing their business operations, creating effective business strategies and crafting effective sales and marketing programs that consistently generate new volumes of specimens and increasing new profits. The Dark Intelligence Group, Inc. owns and operates two Web sites in the TDIG Website network:



<http://www.DarkReport.com>



<http://www.DarkDaily.com>

A-5

About the *Executive War College* on *Laboratory and Pathology Management*

Every spring since 1996, the lab industry's best and brightest gather at the *Executive War College on Laboratory and Pathology Management* to learn, to share and to network. Many consider it to be the premier source of innovation and excellence in laboratory and pathology management.

Each year, a carefully selected line-up of laboratory leaders and innovators tell the story of how their laboratories are solving problems, tackling the toughest challenges in lab medicine and seizing opportunities to improve clinical care and boost financial performance. The *Executive War College* is the place to get practical advice and solutions for the toughest lab management challenges. A unique case study format brings participants face-to-face with their most successful peers. They tell, first hand, how their laboratory solved intractable problems and successfully used new technology.

Many lab management secrets are shared, along with specific "what-not-to-do's" gained from hard-won experience! It's not pie-in-the-sky theory, but useful knowledge that can be put to use in any lab. The *Executive War College* offers superlative networking, with lab administrators and pathologists attending from countries as far away as the United Kingdom, Germany, Brazil and Australia. It makes the *Executive War College* a melting pot for all the best ideas, new lab technologies and management strategies now reshaping the laboratory industry. It's also become a recruiting ground used by headhunters and major lab organizations.

In the United Kingdom, The Dark Intelligence Group and the Association of Clinical Biochemists (ACB) have co-produced a meeting every February since 2003. Known as *Frontiers in Laboratory Medicine* (FiLM), it attracts laboratory leaders and innovators in the United Kingdom. Also featuring a case study format, this meeting pioneered the international laboratory side-by-side case study, where a North American laboratory and a United Kingdom laboratory prepare a comparison of best practices and an operational assessment of their two organizations.

In September 2005, a laboratory management meeting called *Executive Edge* was conducted in Toronto, Ontario, Canada, by The Dark Intelligence Group and QSE Consulting. It provided pathologists and lab directors in Canada with a customized meeting devoted to the strategic and operational issues of laboratory management in Canada.

A-6

About Dave Sanford & Joel Servais



David P. Sanford is General Manager of Milestone Medical's US operation in Kalamazoo, MI. Milestone is a world leader in tissue specimen management systems, macro digital imaging systems and rapid xylene-free tissue processors. His career has been focused in product development, manufacturing and sales into the anatomic pathology and histology marketplace since the late 1980's. He has been with Milestone since 2007.

Mr. Sanford attended undergraduate school at the University of New Hampshire's Whittemore School of Business and Economics, earning a Bachelor of Science degree in Business Administration with a minor in Marketing. He attended Michigan State's Eli Broad Executive MBA program.



Joel Servais is the Marketing Manager at Milestone Medical in Kalamazoo, MI. Responsibilities include support for product development, sales, and marketing initiatives. Additionally, his product management activities focus on digital imaging and specimen management portions of the portfolio. He has served as a design and marketing professional in the surgical and pathology market since 1991.

Mr. Servais attended Western Michigan University, earning a BFA in Design.



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