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PIONEERING WHAT MATTERS

High Viscosity Spinal Cement & Delivery System
Technical Monograph

Confidence™
SPINAL CEMENT SYSTEM

Control Through Viscosity | Control Through Delivery | Control Through Simplicity.

Confidence™
SPINAL CEMENT SYSTEM

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Technical Monograph

1. Bone Cements: Basic Chemistry and Composition

Brief History

Bone cement (polymethylmethacrylate – PMMA) was discovered in 1902 by German chemist Otto Röhm. It was first used clinically in the 1950's, to help fix femoral and hip prostheses. In the 1960's, it was also used in the dental market.

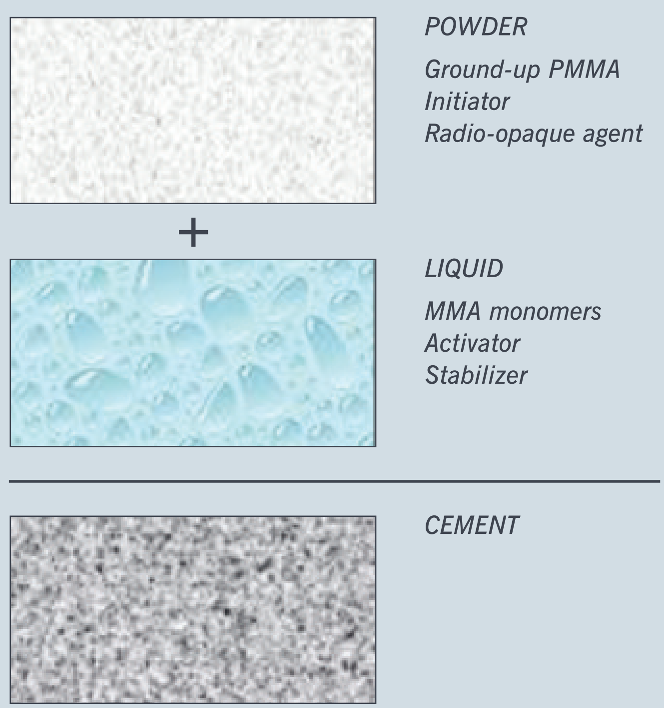
After optimization of its handling properties, PMMA finally received FDA clearance for total hip and knee surgery in the early 1970's. In 1976, it was cleared for pathological fractures and general prosthetic fixations.

Chemistry – Keywords & Principles

Bone cements are made of PMMA. PMMA is a synthetic "resin", a glass-like hard material. It is formed when thousands of identical molecules referred to as monomers – in this case, the monomer being called a "methylmethacrylate" (MMA) – bind to each other to form a long chain called a polymer (hence, the polymethylmethacrylate, PMMA). The chemical reaction in which monomers attach to each other to form a polymer is called **polymerization**.

In 1943, chemists discovered that PMMA could be ground up, mixed with a solution containing MMA to form a workable dough which would polymerize back into a hard PMMA plastic after a certain time. This polymerization happened when two additional types of chemicals (initiators and activators) were added to the mix. Over the next 60 years, further refinements included adding radio-opaque markers and MMA stabilizers to prevent auto-polymerization of the MMA solution.

In summary, the formula to prepare a PMMA bone cement looks like:



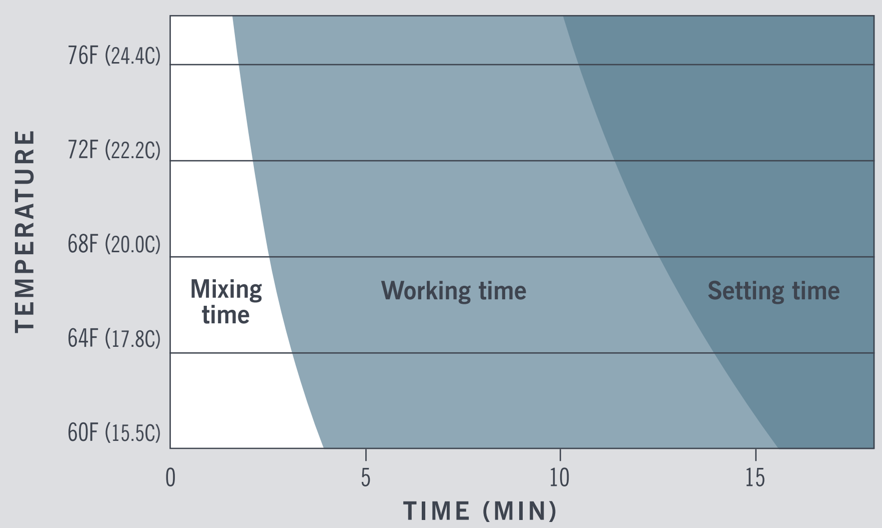
Bone Cement Timings

Chemists soon discovered that the preparation of bone cements included 3 separate phases (as shown in Figure 1):
1) an **initial mixing phase**, as the liquid and the powder are mixed together; 2) a **dough/working phase**, during which the cement remains malleable, and 3) a **setting phase**, at which point the dough hardens. The timings associated with these 3 phases were characterized and defined as follows:

1. **Mixing time: time required to thoroughly mix the powder and liquid and ensure that it forms a workable dough.**
2. **Dough/Working time: time during which the viscosity (thickness) of the dough is suitable for use.**
3. **Setting time: time during which the dough hardens to form the final, hard PMMA.**

These 3 times are dependent on temperature: **the higher the temperature, the faster the mixing, working and setting times**. Figure 1 below shows how these 3 times decrease as a function of temperature. In this example, at 60F (15.5C), the mixing time is approximately 4 minutes and the working time, an additional 12 minutes (for a total of 16 minutes before setting). At 75F (23.8C), the mixing time is now only ~ 2 minutes and the working time, 9 minutes (for at total of 11 minutes before setting), thus, the warmer the temperature, the shorter the mixing/working times.

***FIGURE 1:** Theoretical example of mixing, working and setting time as a function of temperature.*



Bone Cement Viscosity

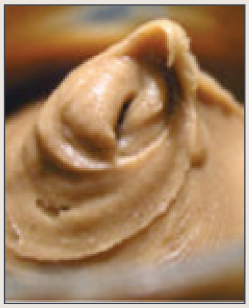
The mixing, working and setting times discussed above are based on the fact that the **viscosity of the mixed material changes with time,** as the dough enters the final stage of setting. **Viscosity is a measure of the resistance of a fluid to deformation by stress**. Commonly perceived as "thickness" or resistance to flow, viscosity may be thought of as a measure of fluid friction.

In other words, water is thin and shows no resistance to flow, thus water has a very low viscosity. At the opposite end of the spectrum, peanut butter is perceived as "thick", or having a high viscosity. Figure 2 below provides some examples of viscosity:

Figure 2: *Examples of: a) Low viscosity solution (milk), the fluid easily deforms with stress; and b) High viscosity solution (peanut butter), the fluid resists deformation by stress.*

FIGURE 2A

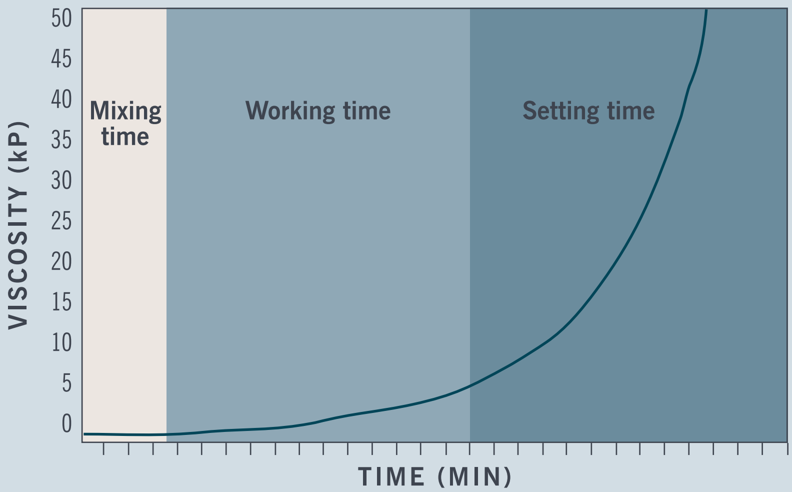
FIGURE 2B



In the case of cements, when the MMA solution is first added to the PMMA powder, the mix is watery and has very low viscosity. As the mixing time increases, the mix becomes more viscous or doughy and workable. The viscosity of the mix remains more or less stable during the working time and then increases exponentially during the setting time, when the dough effectively sets and hardens.

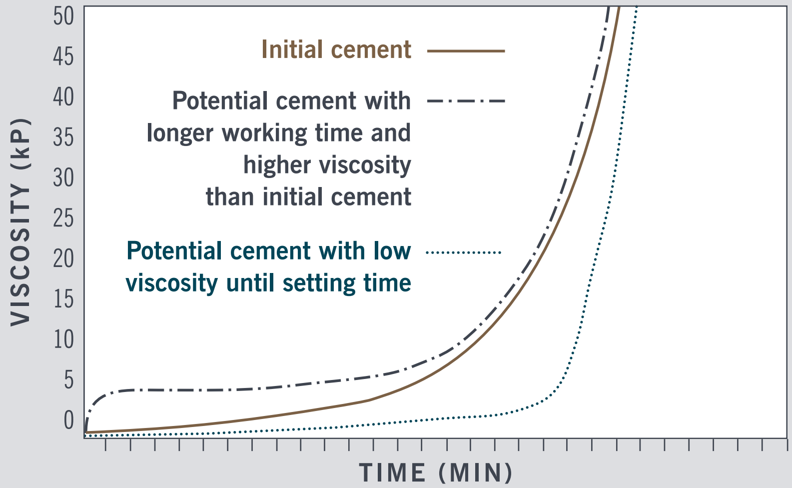
To better understand this phenomenon, the mixing, working and setting times can also be presented as a function of the dough's thickness or viscosity, as shown below in Figure 3. In this case, the solid line represents the viscosity of the dough as time progresses.

Figure 3: *Graphical representation of a cement's increase in viscosity as a function of time.*



However, as bone cement research progressed over the last 50 years, it became clear that the viscosity of the dough during the actual working time could be optimized. Using Figure 3, this would mean that the height of the solid line could be altered. Figure 4 below shows 3 theoretical cements with low (·······), medium (——) and high (—·—) viscosity at working time.

Figure 4: *Theoretical graph showing the possible ways to optimize cement viscosity. The dashed line (—·—) represents a cement with a higher viscosity at the dough/work time, as compared to the initial cement shown with the solid line. This material has a longer working time at an increased viscosity and represents a more favorable material for clinical use than the initial cement (solid line). The dotted line (·······) represents a potential cement that remains very fluid until its setting time. This cement could be very difficult to work with in a clinical setting.*



Having the right viscosity during the "working time" is critical for the usability of any cement: too low a viscosity makes it impossible to control the location of the cement, which could allow leakage outside of the bony regions. Too thick of a cement may be difficult to deliver.

Clinical Use of PMMA Cements

The clinical advantage of a PMMA cement was clear since its discovery: the dough-like substance could be prepared in an operating room, and applied to the site. The dough would then harden in vivo to help stabilize a bony fracture or orthopedic prosthesis.

PMMA cements are biologically inert and biocompatible, with now more than 50 years of clinical history. Their mechanical properties are well characterized and stable over time, and cements can be tailored with specific *viscosity* and *working time*, for optimal clinical use.

Bone cement is therefore an implant that is prepared in the operating room, as the mixing of a powder and MMA solution are needed to make the final material. **It is not a glue and does not form adhesive chemical bonds, but requires a mechanical interlock**, also known as interdigitation, to keep bone fragments together. The ideal cement will form an intricate network of interdigitation. More information on interdigitation can be found in Section 2.

2. CONFIDENCE SPINAL CEMENT SYSTEM – Overview

The CONFIDENCE SPINAL CEMENT SYSTEM is a novel proprietary formulation of PMMA that is reliable and easy to use, and is characterized by:

1. **High viscosity, for controlled delivery**
2. **Long dough/working time**
3. **Controlled delivery system through a novel hydraulic pump**
4. **Bony interdigitation**

The chemical composition of CONFIDENCE SPINAL CEMENT SYSTEM is as follows:

POWDER	
Polymer	*PMMA: 69.4%*
Radio-opaque agent	*Barium sulfate: 30.1%*
Initiator	*Benzoyl peroxide: 0.5%*

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LIQUID	
Monomers	*MMA: 98.5%*
Activator	*DmpT: 1.5%*
Stabilizer	*hydroquinone: 20 ppm*

CONFIDENCE SPINAL CEMENT SYSTEM Viscosity

Viscosity affects the clinical usage of PMMA cements. A recent publication by Baroud et al[1] demonstrated that **cements with higher viscosity spread more uniformly than cements with lower viscosity, thus significantly reducing the risk of leakage**. Viscosity is therefore critical, and the CONFIDENCE SPINAL CEMENT SYSTEM has an optimized viscosity to promote a long dough working time as compared to other cements in the market, as seen in Figure 5.

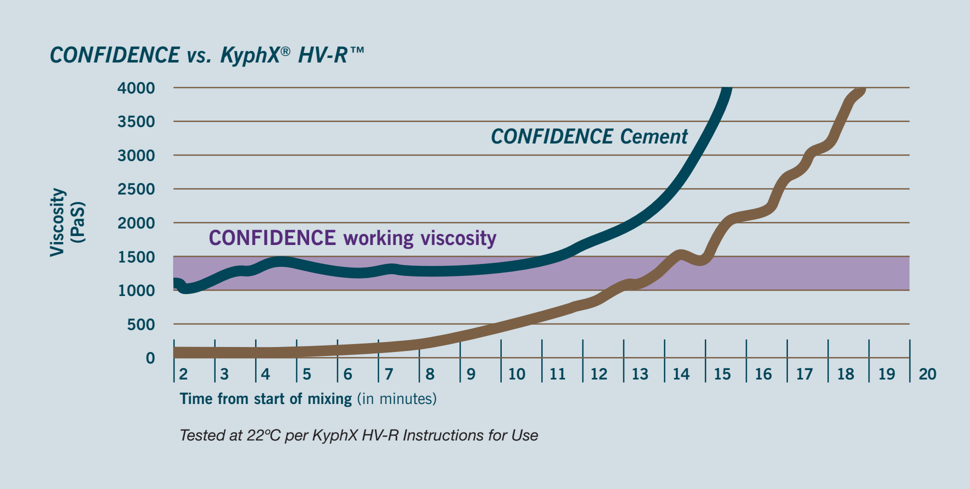
Figure 5: *Viscosity as a function of time, as determined at 22C (72F), for cements of the CONFIDENCE SPINAL CEMENT SYSTEM (▬▬) as well as the KyphX product (▬▬).*

As shown herein for the CONFIDENCE SPINAL CEMENT SYSTEM:

- *The viscosity of the cement reached 1000 PaS within the first 2 minutes following mixing. This viscosity is similar to that measured for peanut butter[2].*
- *The viscosity of the cement remained constant for 9 minutes thereafter.*
- *The cement was workable under high viscosity conditions[3] for a total of 11 minutes.*

For the KyphX product:

- *After the first 2 minutes of mixing, the product had still a viscosity lower than 100 PaS. It required 6 minutes for the product to reach approximately 100 PaS, or ten times less viscosity than the cement from the CONFIDENCE SPINAL CEMENT SYSTEM.*
- *From 6 to 13 minutes, the viscosity of the cement continuously increased.*
- *The cement reached 1000PaS after 13 minutes and maintained high viscosity working conditions for only 3 more minutes.*



The in vivo cement fill pattern provides a visual clue as to why cement viscosity truly matters. Typically, liquid cements will tend to disperse in the bone and can lead to greater rates of cement leakage, while high-viscosity cements offer greater control and will tend to stay where injected. Examples of cement fill patterns are shown in Figure 6 below.

Figure 6: *Cement fill pattern with different types of cement viscosity. A) Cement fill following vertebroplasty. A diffuse volume of cement can be observed across the vertebral body; B) Cement fill pattern following kyphoplasty. While less diffuse than vertebroplasty, some horizontal spreading of the cement can be seen. In addition, limited bony interdigitation is visible, a possible consequence of the balloon compaction of surrounding trabecular bone; C) Cement fill following vertebral body augmentation with CONFIDENCE SPINAL CEMENT SYSTEM. Controlled placement of the cement and interdigitation to form a mechanical bond between the cement and the bone was achieved.*

FIGURE 6A

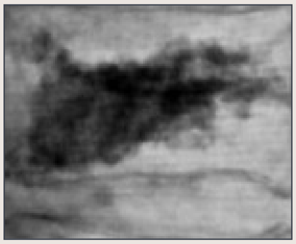


FIGURE 6B

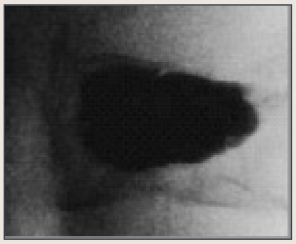
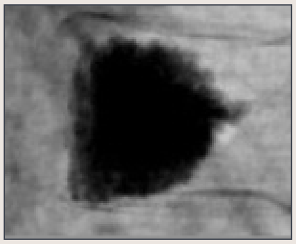


FIGURE 6C



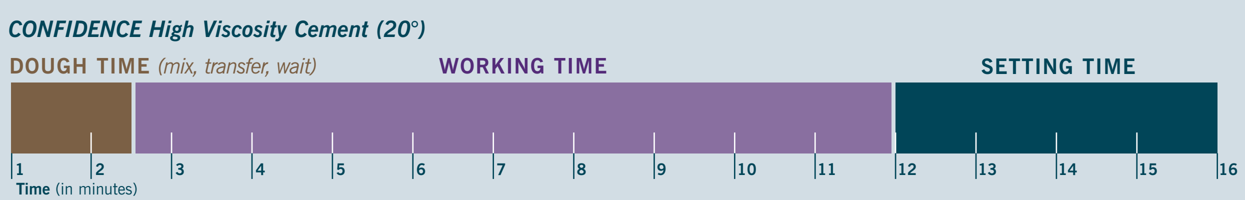
CONFIDENCE SPINAL CEMENT SYSTEM Timings

As discussed above, optimizing the different cement times is critical:

- **The mixing time should be as short as possible, to prevent wait time in the operating room**
- **The dough/work time should be long enough to allow optimal cement injection in the fracture site**
- **The setting time should be fast**

CONFIDENCE SPINAL CEMENT SYSTEM was designed with these principles in mind. As shown in Figure 7 right, it has a **very short mixing time**, followed by an **optimal dough/work time** and a **short setting time**.

Figure 7: *Different timings for the CONFIDENCE SPINAL CEMENT SYSTEM.*

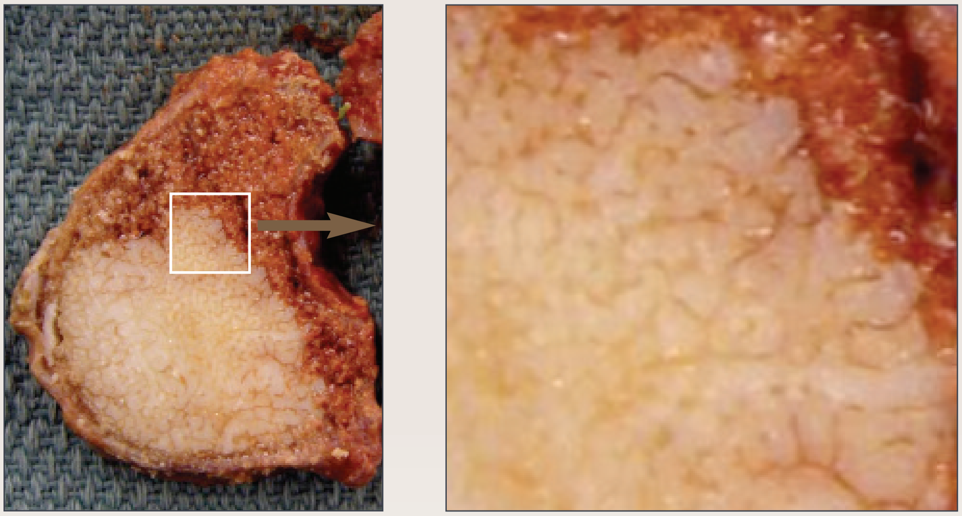


CONFIDENCE SPINAL CEMENT SYSTEM Interdigitation

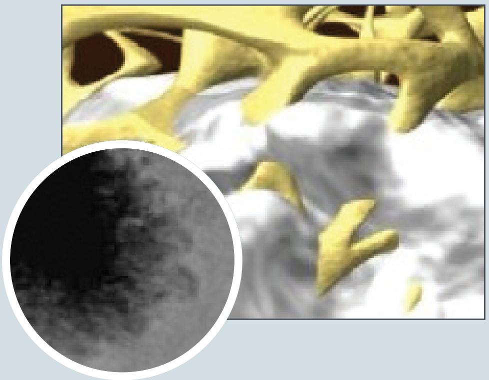
PMMA cements do not act as glue and rely on interdigitation to keep bone fragments together and stabilize bony fractures. Therefore, optimizing the degree of interdigitation of the cement throughout the bone trabeculae is critical to help maximize the clinical impact of the vertebral body augmentation procedures.

CONFIDENCE SPINAL CEMENT SYSTEM **was designed to further encourage interdigitation** of the cement throughout bony trabeculae. As shown in Figure 8 below, the cement is observed around the cancellous bone (bony interdigitation). This is particularly important in the case of osteoporotic patients. Indeed, osteoporotic patients tend to have much less cancellous bone, as large voids replace what was once filled with trabeculae. In these cases, using a cement that effectively interdigitates with the existing cancellous structures and thus creates a mechanical interlock with the surrounding bone is essential.

Figure 8: *Interdigitation of the CONFIDENCE SPINAL CEMENT SYSTEM throughout the bony trabeculae of the vertebrae.*



The high viscosity properties of CONFIDENCE allow for interdigitation, preserving the remaining trabecular structure of the vertebral body.



Trabecular structure

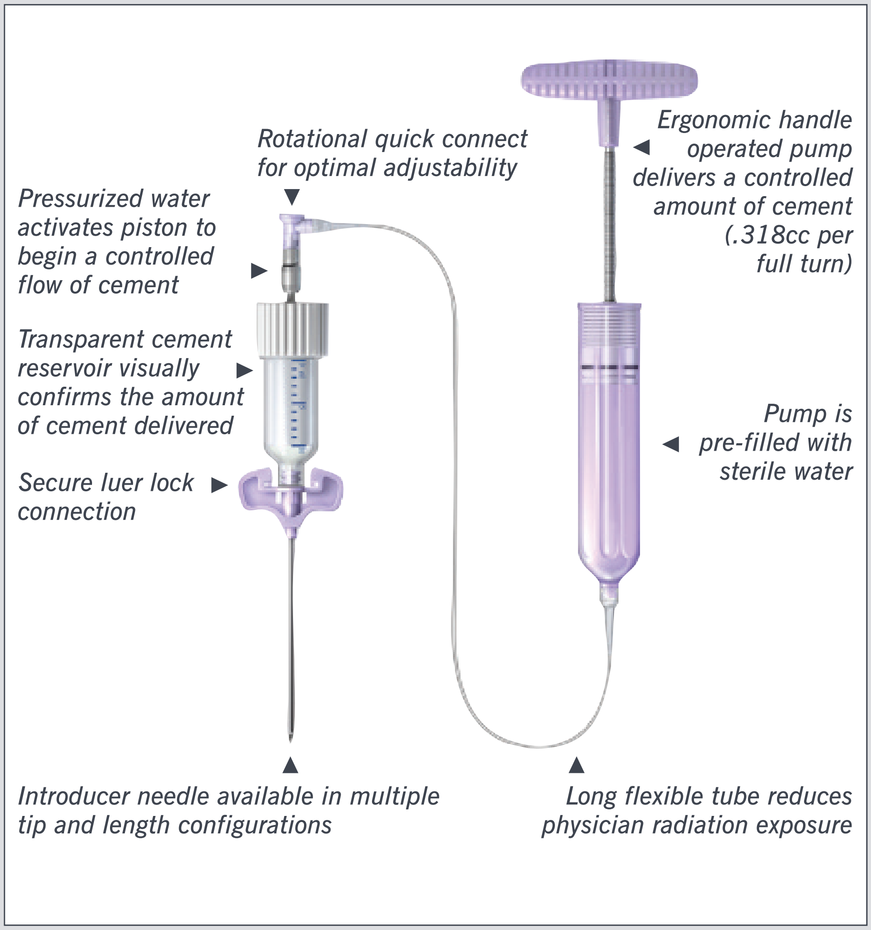
CONFIDENCE SPINAL CEMENT SYSTEM High Viscosity Cement

3. CONFIDENCE SPINAL CEMENT SYSTEM – Delivery System

Delivering highly viscous cements through thin needles represents a unique engineering challenge. The CONFIDENCE SPINAL CEMENT SYSTEM has addressed this technical challenge and is shown in detail in Figure 9.

Figure 9: *Drawing of the pump, showing the detail of the elements that account for the final device.*

The uniqueness of this hydraulic delivery system is that it allows the thick cement to move from its container through the needle and into the fracture site. This is achieved by using a design that maintains pressure in the cement reservoir. The pressure dissipates to a low level at the exit point of the needle tip.



How is this possible?

Three principles of fluid dynamics are required to understand how this change in pressure works.

1. **What goes in, comes out – the Continuity Principle.**
   In any given system, changing the diameter of the cylinder in which the fluid is flowing will inversely affect its velocity. Hence, the cement within the needle moves at a faster rate than that contained in the reservoir, because the needle has a smaller diameter than the reservoir.

2. **Pressure loss with flow – the Bernoulli Principle.**
   This principle dictates that for incompressible fluids, such as cement or water, an increase in the speed of the fluid occurs simultaneously with a decrease in pressure. The change in velocity and pressure as described by the principle above, explains the low pressure within the needle, as compared to that within the reservoir.

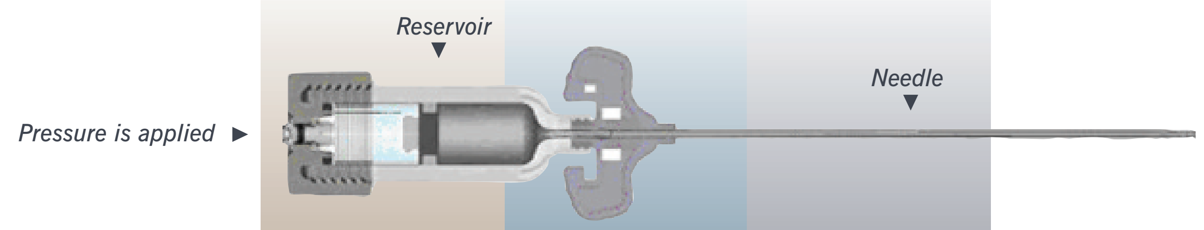
3. **Friction along the needle walls – The Darcy-Weisbach Principle.**
   In addition, the cement experiences resistance as it moves in the needle. In fact, the longer and thinner the path (i.e.; the needle), and the thicker the cement, the more resistance or friction the cement has to deal with as it is traveling through the needle. This resistance can be thought of as little brakes that would act along the way, slowing down the cement. Thus, as the cement advances in the needle, it not only loses pressure but also speed.

The CONFIDENCE SPINAL CEMENT SYSTEM, with its changing diameters and its long and thin needle, thus creates an environment where the pressure in the reservoir dissipates as the cement advances through the needle.

When cement is completely filling the needle (but is not flowing out), the system is in a state of equilibrium and is called “primed”. Once the delivery system is primed, small turns of the handle result in small increases in pressure in the reservoir, which translate in controlled amounts of cement being delivered out of the needle. For every full turn of the needle, about 0.3cc of cement are delivered.

The graph below (Figure 10) summarizes how the 3 principles described on page 9 explain the changes in pressure from the reservoir to the needle.

Figure 10: *The principles dictating pressures at various locations in the delivery system.*



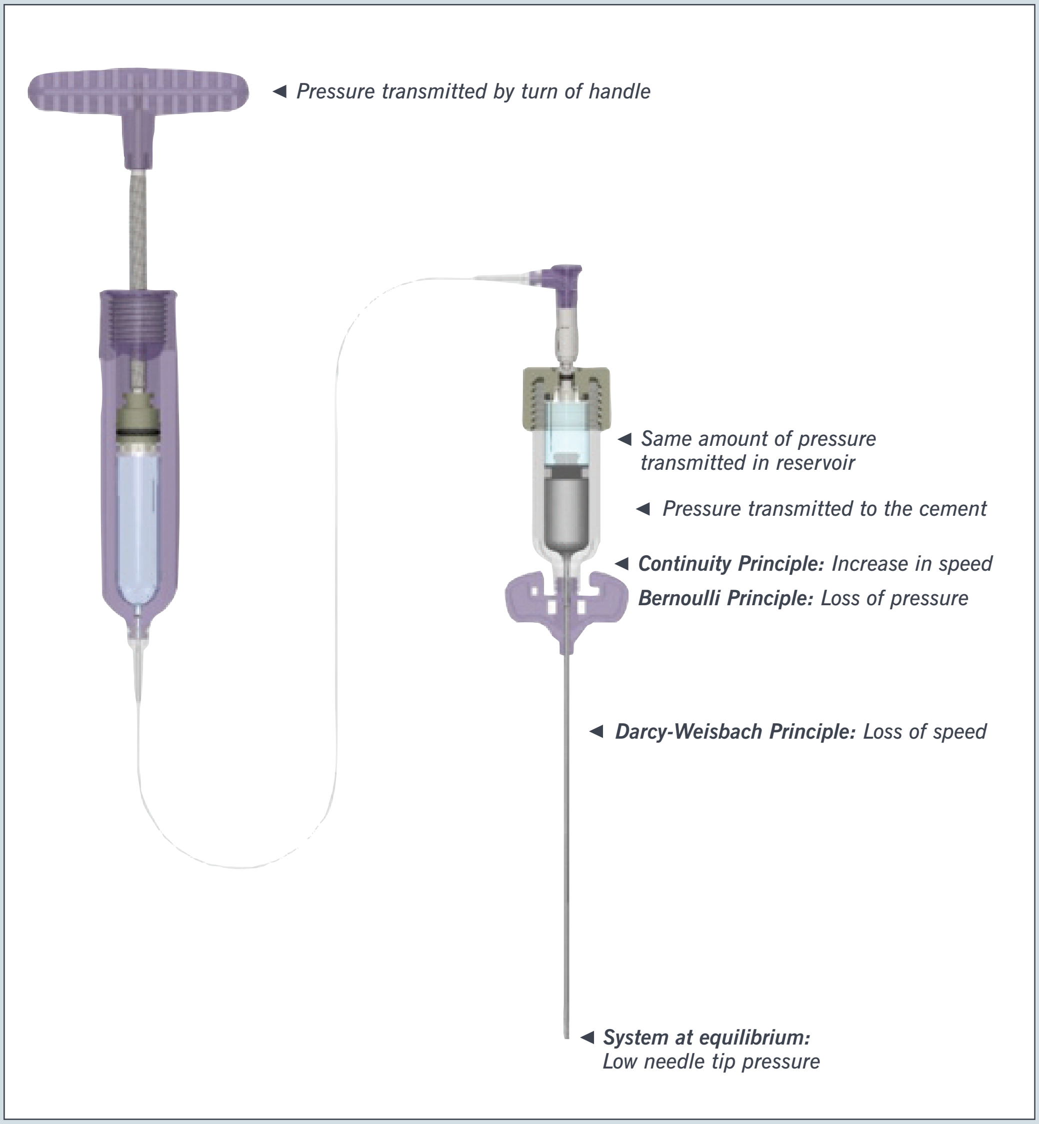
1. Continuity Principle	*Large diameter = low velocity*	*Small diameter = greater velocity*		
2. Bernoulli Principle	*Pressure on the cement*	*Increased velocity= lower pressure*		
3. Darcy-Weisbach Principle	*Pressure on the cement*	*Long thin needle = braking action*	*Reduced velocity and continued braking action*	*No velocity (Delivery system is primed)*

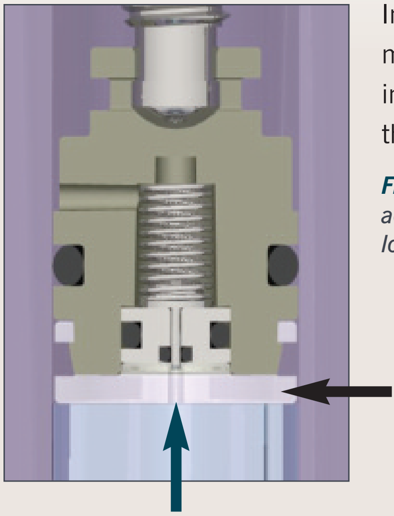
What does this mean for the CONFIDENCE SPINAL CEMENT SYSTEM?

In the reservoir, the cement experiences an increase level of pressure. This allows the cement to advance through the system.

Figure 11 below provides a graphical representation of the pressures experienced by the cement along the CONFIDENCE SPINAL CEMENT SYSTEM delivery system.

Figure 11: *Graphical representation of the pressures along the delivery system.*



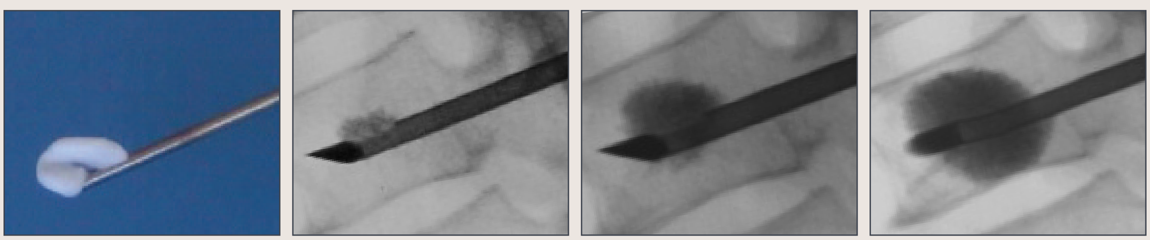


In addition to this hydraulic pump design, a built-in safety mechanism preventing excessive pressure in the reservoir is included in the CONFIDENCE SPINAL CEMENT SYSTEM. A representation of the pressure relief valve is shown below in Figure 12.

Figure 12: *Pressure relief valve (black arrow). When the relief valve is activated, water vents to the opposite side of the pump piston (blue arrow), lowering the pressure placed on the cement reservoir.*

Another aspect to the controlled delivery of the system stems from the novel side-hole needle. This needle tip design allows directional placement of the cement. The surgeon may rotate the side-hole needle to direct the flow of cement to the point of interest as shown in Figure 13 below.

Figure 13: *Side-hole needle design. Directionally controlled placement of the cement is achieved with this system.*



4. Conclusion

CONFIDENCE SPINAL CEMENT SYSTEM, a novel vertebral body augmentation system, is characterized by high viscosity and optimal mixing and working time. In addition, this cement interdigitates throughout bony trabeculae. The CONFIDENCE SPINAL CEMENT SYSTEM cement is delivered in a controlled flow system, which maintains low pressure at the tip of the needle while ensuring a controlled rate of cement distribution.

Confidence™

SPINAL CEMENT SYSTEM

INDICATIONS

The CONFIDENCE SPINAL CEMENT SYSTEM™ is intended for percutaneous delivery of CONFIDENCE Spinal Cements, which are indicated for fixation of pathological fractures of the vertebral body during vertebroplasty or kyphoplasty procedures. Painful vertebral compression fractures may result from osteoporosis, benign lesions (hemangioma), and malignant lesions (metastatic cancer, myeloma).

CONTRAINDICATIONS

The use of CONFIDENCE High Viscosity Spinal Cement is contraindicated in patients presenting with any of the following conditions:

- Use of CONFIDENCE High Viscosity Spinal Cement for prophylaxis (such as in metastatic or osteoporotic patients with no evidence of acute vertebral fracture)
- Coagulation disorders, or severe cardiopulmonary disease.
- Haemorrhagic diasthesis.
- Non-pathological, acute, traumatic fractures of the vertebra.
- Patient clearly improving on medical therapy.
- Spinal stenosis (> 20% by retropulsed fragments).
- Compromise of the vertebral body or walls of the pedicles.
- Compromise or instability of vertebral fractures due to posterior involvement.
- Anatomical damage of the vertebra that prevents safe access of the needle to the vertebral body.
- Vertebral body collapse to less than 1/3 (33%) original height.
- Vertebral plana (collapse >90%)
- Active or incompletely treated infection.
- Coagulopathy or inability to reverse anti- coagulant therapy (both during and approximately 24 hours post-procedure).
- Severe pulmonary insufficiency.
- Allergic reaction to any of the components of the CONFIDENCE High Viscosity Spinal Cement.

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LIMITED WARRANTY AND DISCLAIMER: DePuy Spine products are sold with a limited warranty to the original purchaser against defects in workmanship and materials. Any other express or implied warranties, including warranties of merchantability or fitness, are hereby disclaimed.

WARNING: In the USA, this product has labeling limitations. See package insert for complete information.

CAUTION: USA Law restricts these devices to sale by or on the order of a physician.

DePuy Spine is a joint venture with Biedermann Motech GmbH.

To order, call DePuy Spine Customer Service (1-800-227-6633).

www.depuyspine.com
www.confidencespinalcement.com

1 G. Baroud, M. Crookshank, M. Bohner, Spine 31, 2562 (2006).

2 Brookfield Engineering – Laboratory Viscometer Application Data Sheet at http://www.brookfieldengineering.com/education/applications/laboratory-peanut-butter.asp.

3 Defined as a viscosity greater than 1000 PaS and less than 2000 PaS.

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PIONEERING WHAT MATTERS

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