Extrapolation of evidence related to dressings for pressure ulcer prevention may compromise patient safety

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This paper, written by an international group of experts in the bioengineering and clinical aspects of the design, use and evaluation of dressings for pressure ulcer prevention, addresses a central question commonly faced by the medical device industry, clinicians and patients. The question being whether evidence obtained for a specific product can be extrapolated to other products, which are similar or lookalikes, and are made by different manufacturers. Specifically, this question is of fundamental importance to wound care clinicians and particularly in the area of dressings used in the prophylaxis of pressure ulcers (also called pressure injuries in the US and Australia). The authors thoroughly discuss recent developments and litigation in the medical device industry, relevant regulation routes in the pharmaceutical industry aimed at ensuring patient safety, and examples from the automotive industry to describe the great danger in extrapolating bioengineering and medical evidence obtained for one dressing product to other products by different manufacturers. The contents of this paper demonstrate why the question clinicians must ask before selecting a prophylactic dressing is: "Will I choose a dressing based on marketing hype and cost or, alternatively, based on published scientific, bioengineering and ultimately clinical evidence?"

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In 2016, a federal jury in Dallas, Texas, in the US, ordered Johnson & Johnson and its DePuy Orthopaedics unit to pay more than $30mn in damages for patients harmed by the defective ASR metal-on-metal hip implants and $1bn in punitive damages. The jurors ruled that these metal-on-metal hip implants were defectively designed, inflicting a risk of metallosis. No clinical trials were conducted with the product before it was launched. The justification provided by the company to gain approvals for commencing clinical use of this ASR implant was that it is similar to already approved metal-on-metal hip prosthesis models.

This case places a spotlight on a central question, commonly faced by the medical device industry, clinicians and patients, of whether evidence obtained for a specific product can be extrapolated to other products, which are similar or lookalikes, and are made by different manufacturers. This question is of fundamental importance to wound care clinicians and particularly, in the area of dressings used in the prophylaxis of pressure ulcers (also called pressure injuries in the US and Australia).

An appropriate starting point for such a discussion should be the situation in the sister market to medical devices, which is the pharmaceutical industry. The pharmaceutical industry has developed unique, thorough and rigorous processes for extrapolating clinical evidence of efficacy from one product to another when it comes to generic medications. In the US, for example, by law, the Food and Drug Administration (FDA) is the regulatory body that is authorised to approve generic versions of brand-name drugs without requiring (new) research to be conducted in order to specifically prove them safe and effective,

as was done for the original, patented drug. Nevertheless, for obtaining such an approval, the generic drug is required to meet a multitude of strict and objective criteria. Specifically, a generic drug must demonstrate that it: (1) contains exactly the same active ingredients; (2) is identical in strength, dosage form and route of administration; (c) is bioequivalent; (d) has precisely the same indications for clinical use; (e) meets the same batch requirements for identity, strength, purity, and quality; and (f) it is manufactured according to the same FDA regulations (Howland, 2009).

A key aspect of generic drug development is the aforementioned concept of bioequivalence (Meyer, 2001). According to this concept, if a drug product contains an active ingredient that is chemically identical, manufactured according to an unchanged protocol and is delivered to the target site in the human body at the same rate and extent as another drug product, then it is considered to be clinically equivalent and can be substituted for the original drug product. This then facilitates the availability of drugs at lower prices for healthcare providers and patients and overall lowers health costs, as generic drugs are produced by multiple companies that typically compete on costs over production and sales of an identical end product.

The concept of bioequivalence is so fundamental in the pharmaceutical industry that it is repeated in numerous forms when defining the specifications of a generic drug. For example, the FDA requires that both over-the-counter and prescription generic drugs have exactly the same active ingredients and that they be of the same quantity as the brands they claim to copy. The FDA further requires that the generic drug have the same purity and stability, come in exactly the same form e.g. a tablet, a patch, a gel or liquid etc., and be administered in precisely the same way (for example, as a pill, applied as topical cream to the skin or administered as an injection). Moreover, manufacturers of a generic drug must demonstrate that the drug is also "bioequivalent" to its corresponding brand by showing that it delivers the same amount of active ingredients into the bloodstream over the same time scale as the original brand.

It is noteworthy that the analysis to determine the level of a drug as being generic is quantitative in nature. For example, the maximum drug concentration in blood plasma is the parameter used to characterise the drug absorption rate, and the area under the plasma drug concentration-time curve is calculated in order to characterise the extent of drug absorption in the body (Howland, 2010). Meta-analysis of 2,070 bioequivalence studies found that the average difference in absorption between generics and their branded prototypes was about 4%, which is the same variation normally found between two batches of the same brand-name drug (Davit et al, 2009). Such a methodological approach and level of rigour of systematic studies justify the existence of a generic drug market. The criteria used to evaluate generic drug bioequivalence studies support the objective of the FDA in approving generic drug formulations that are therapeutically equivalent to their innovator counterparts.

The fundamental driving force that allows the generic pharmaceutical industry to exist and flourish is the abbreviated mechanism for approval of generic copies of all drugs, which states that pre-clinical and clinical testing does not have to be repeated for generics. This implies that pharmaceutical companies with expertise in generic drugs, such as Teva, the Israeli company, which is the largest generic manufacturer in the world, do not need to invest in reproducing all the research and development efforts after a patent of an original drug has expired. The end result is that once a patent expires, medical insurance companies, institutes and consumers can use drugs at reasonable costs as opposed to returning investments in Research and Development (R&D) to the industry forever.

However, this model in its entirety is based on the concept of bioequivalence and the quality in measuring bioequivalence, which facilitates availability. It is also worthwhile to note that the requirements for producing a generic drug add to numerous other strict FDA requirements that require the precise description of analytical procedures in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria (including elaboration where there are aspects of the analytical procedures that require special attention) (FDA, 2015).

In contrast to the strict regulatory processes for development and testing generic drugs, the medical device industry operates in essentially a grey zone. Specifically, whereas a drug (or at a minimum the active component in a drug) is made of a specific, unique chemical composition, with a formula that is exclusive and chemically defined for achieving a certain clinical effect, medical devices may use diverse design principles and variations and still claim

the same effect. This, by definition, prevents direct evaluation of the level of similarity between competing medical devices or equipment, as done in the pharmaceutical industry when a drug is claimed to be 'generic'.

Notable differences between pharmaceuticals and medical devices

In the pharmaceutical industry, all raw materials, components and processes are highly regulated to ensure quality, as every slight deviation from the chemical formulation that has originally proven to be efficient in randomised clinical trials (RCTs) may compromise the eventual clinical efficacy. Critical material attributes (CMAs), which are physical, chemical, biological, or microbiological properties or characteristics of an input material (i.e. which is a component in a drug) should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Likewise, critical process parameters (CPPs) are process parameters whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality. Examples of CMAs in a drug that is made according to a certain chemical formula can be the blend uniformity, particle size, density, moisture and flow properties, dissolution, degradation products and residual solvents. Example CPPs can be the temperature and humidity during production, the quality of the air and level of sterility along the production line. Once the drug has been produced, for instance, in a tablet form, there can be additional relevant CMAs, such as the tablet weight, breaking strength, its thickness and volume, the solid fraction, friability and appearance.

All these CMAs and CPPs are measurable and quantifiable, for the purpose of monitoring, recording and making standardised and objective comparisons for internal and external quality control. A characteristic to the pharmaceutical industry is that a holistic quality control approach is employed to test the quality of raw materials, processes and end-product, and conduct all these tests in quantitative means, so that products are reproducible (generic) across facilities, manufacturers and companies. The result of this holistic quality control approach supports the rationale that if two pharmaceutical equivalents provide identical plasma concentration-time profiles in humans, there is no need to demonstrate that these two identical dosage forms will exhibit a difference in safety and clinical efficacy. Medical devices are, unfortunately, fundamentally different from drugs in this aspect.

The well-regulated conditions that apply in the pharmaceutical industry in the USA (as well as in other Western countries) stand in stark contrast to the arena of medical devices and equipment. Indeed, all companies who wish to market devices in the USA are required to register with the FDA and are subject to periodic audits. However, the process by which the FDA deals with devices that claim a certain clinical effect — based on the fact that there are already previous devices that achieve this effect — differs considerably from the (theoretically analogue) process used to determine if a drug is 'generic'. Specifically, if a company claims that a device is achieving a certain effect that is similar to that being achieved by other devices, an application needs to be made to obtain a so called 510(k) Clearance. The purpose of a 510(k) submission is to demonstrate that a device is "substantially equivalent" to a predicate device, that is, a device that has been previously cleared by the FDA.

The 510(k) applicant compares and contrasts the subject and predicate devices, explaining why any differences between them should be acceptable. Importantly, human data are usually not required for a 510(k) submission; this decision is made at the discretion of the FDA. Laboratory testing is almost always a requirement, but by definition, such testing does not and cannot demonstrate clinical efficacy. Hence, the FDA does not "approve" 510(k) submissions, but rather, it "clears" them (and therefore it is not legal to advertise a 510(k) cleared device as "FDA-approved"). The fundamental difference between the aspects of regulation in the pharmaceutical and medical device/equipment worlds — despite the intended use of both drugs and devices to protect and save lives, is anomalous. However, the differences in regulation very likely originate from the simple fact that there is only one possible way of producing a drug — based on its chemical formula, but probably infinite ways for engineering design of a device.

As explained above, unlike the pharmaceutical industry, the medical device industry does not apply a strict, mandatory policy of measurable, reported CMAs and CPPs. As a result, in the medical device industry, it is far more difficult to determine whether similar products, or products that make the same claims of a clinical effect, or lookalike products, are actually equivalent in effectiveness. In fact, the FDA (and other regulatory bodies worldwide) do not even attempt to test this question, hence the 510(k) procedure for 'clearance'.

In the wound prevention and care industry, in particular, this opens the path for cheap production of lookalikes for nearly every successful technology or product. For example, in the domain

Table 1. Numbers of published journal articles reporting the clinical efficacy of different brands of prophylactic dressings.

Article type	Mepilex® Border	Allevyn Life	Aquacel® Foam	Optifoam®
Meta-analysis/systematic reviews	2	0	0	0
Randomised controlled trials	4	1	0	0
Non-randomised clinical/cohort study (prospective)	7	0	0	0
Non-randomised clinical/cohort study (retrospective)	25	2	1	0
Case reports/case series	8	2	1	0
Expert opinion	23	0	0	0
NICE Guidance	1	0	0	0
Total	**70**	**5**	**2**	**0**

of support surfaces, a high-quality wheelchair cushion, which has undergone rigorous testing for safety, impact force damping, durability and tolerance to environmental conditions and product aging according to International Standards (ISO 16840, 2015) may then be copied and made from inferior materials that do not comply with the same standards and will, in fact, cause accelerated wear-and-tear. However, the two cushions may still be indistinguishable in appearance and for the end consumer, or even for expert decision-makers, identifying differences in compositions and materials would be extremely difficult and likely not even feasible without rigorous laboratory testing (which end-users are not expected to make and should not perform).

If a policy of evaluating CMAs and CPPs would have been applied, similar to the one for generic drugs, the lookalike cushion would fail to be called 'generic', but unfortunately, this is not the standard practice concerning medical devices. The cheap version may push the original high-quality product out of the market based on cost alone. This also places an undue responsibility on clinicians to decipher and interpret marketing material designed to give the lookalike product the illusion of clinical evidence and validity.

In a world where healthcare decisions are now predominantly money-driven (with progressively decreasing attention to the voices of clinicians and scientists), and because regulatory bodies, such as the FDA, do not oblige device and equipment companies to comply with a policy that is analogous to the well-developed policy for claiming generic drugs, the price argument typically overweighs the existence of published high-quality evidence of clinical efficacy. As a result, patients are unfortunately often prescribed compromised or sometimes even inadequate products.

The case of prophylactic dressings

The past decade has seen an increasing research and practice focus on the use of multilayer soft silicone dressings used in the prophylaxis of hospital-acquired pressure ulcers. There is now a significant body of high-quality evidence for the clinical, bioengineering and cost effectiveness of one brand of this class of dressings in preventing pressure ulceration, however, unfortunately, prophylactic dressings fall under an even greyer zone within the grey zone of standards and regulation of medical devices. With reference to the above discussed example of wheelchair cushions, in the case of dressings used for prophylaxis of pressure ulcers, there is not even a current standard that exists, neither internationally nor at a national level, essentially because this is a relatively new technology in the clinical setting.

Prophylactic dressings are essentially dressings that are applied to vulnerable anatomical regions in the body of a patient where pressure ulcers are common or may occur in the individual based on clinical judgment, such as the sacrum and heels. The dressing is typically multilayered (i.e. has more than 2 layers — each made of a different material), and is used to alleviate tissue loading at the skin and sub-dermally, at the specific sites of attachment in conjunction with the protective effect of the support surface.

The majority of evidence that has been published in the literature, including major multiple RCTs with hundreds of patients participating in each (Santamaria et al, 2015a, Santamaria et al, 2015b, Kalowes et al, 2016), refers to the Mepilex® 5-layer dressing technology by Molnlycke Health Care. Following the proven success of the Molnlycke Mepilex technology, the market is now swamped with different 'me-too' products.

To highlight the disparity of clinical evidence that exists between the Molnlycke Mepilex Border range of dressings used for the prevention of pressure ulcers and the competitor products making similar claims of clinical efficacy one only has to look at the huge imbalance in published peer-reviewed articles for the clinical performance of the various dressings claiming to provide protection against pressure ulceration. We have conducted that analysis using the PubMed and NICE databases, and have summarised the outcomes in *Table 1*.

Given the lack of a regulatory framework to determine the actual equivalence of dressings we strongly contend that clinicians must be guided by high-quality clinical evidence when making decisions about which dressing may be appropriate to use for pressure ulcer prevention as this is the only guide available to them regarding the actual performance of the dressing. As can be seen in *Table 1*, claims of similarity between the clinical efficacies of commercially available dressings clearly cannot be supported by published research evidence.

The Molnlycke Mepilex Border multilayered dressings essentially reduce deformations in skin and underlying soft tissues by multiple mechanisms, as follows: (a) these dressings are adequately elastic and flexible to deform and expand in compression, tension and shear under weight-bearing, which cushions and protects the tissues; (b) the alternating stiffness structure of the dressing which is composed of a softer layer between each two less soft layers (a sandwich-like composition) acts to absorb shear distortions internally in the dressings so that these deformations are taken off the tissues; (c) the outer surface of the dressing is smooth and has a very low coefficient of friction, which further reduces frictional forces on the surface, thereby causing less tissue distortion in shear internally; (d) the sacral dressing model (Mepilex® Border Sacrum) has a unique mechanical behaviour constituted by its specific material composition and structure, which effectively makes it flexible in response to forces acting in the lateral direction (of the buttocks cheeks) and at the same time, more resistant to forces acting longitudinally (along the line of the spine). This behaviour is known as anisotropy in engineering terms, and has been branded as 'deep defence' by the manufacturer. (e) The dressing manages moisture well, and its properties are nearly unaffected by the moisture level, which contributes to the endurance and stability of protective performances under different microclimate conditions (Call et al, 2015; Levy et al, 2015; Levy and Gefen, 2016; Levy and Gefen, 2017; Levy et al, 2017).

The Mepilex Border multilayered dressing technology has been thoroughly investigated from a bioengineering perspective in multiple studies, by different groups, using state-of-the-art experimental mechanical testing and computer modelling approaches, and the results have been published in several papers (Call et al, 2015; Levy et al, 2015; Levy and Gefen, 2016; Levy and Gefen, 2017; Levy et al, 2017). Taken together, these papers made a crystal clear point that each and all of the deformation alleviation features listed above will only work and be effective if the appropriate engineering design has been made. In other words, it is impossible to extrapolate from studies that have tested a certain dressing structure and composition, employing (borrowing the drug terminology) specific CMAs, on the performances of dressings with different CMAs. If a dressing has been designed to contain specific multiple materials, each shaped to a specific layer, and then connected and interfaced with the other materials/layers in a unique manner, the resulting dressing structure will determine the mechanical properties, behaviour and, hence, the protective clinical efficacy and endurance of this dressing alone.

A good analogue to better explain the latter point would be safety systems in vehicles. Modern cars contain crumple zones, which are structural features designed to absorb the energy from the impact during a traffic collision by controlled deformation (i.e,. by crumpling) and, therefore, protect the passengers. Much like the protective mechanisms in prophylactic dressings, crumple zones work by managing the crash energy, absorbing it within the outer parts of the car rather than it being directly transferred to the occupants (which is analogue to the deformation energy associated with the bodyweight that is mostly being absorbed in the dressing and not in the tissues).

Advanced plastics and composite materials are used in crumple zones of cars, and are designed, primarily using computer modeling, to collapse on impact and absorb as much deformation energy as possible. It is clear that the effectiveness of the crumpling and the protective outcomes strongly depend on the details of the engineering design of the crumple zones, including both the material and structural aspects. Interestingly, cars are being rated for passenger safety – partially based on the ability of these crumple zones to absorb impact deformations and prevent the car from harming passengers. In most Western countries, it is mandatory for car manufacturers to advertise the rating that their car has achieved with respect to such safety tests.

The analogue of car safety makes a nice comparison as to where we would have liked to see the prophylactic dressing market advancing. In cars, the making of crumple zones, selection of materials and structures in a specific composition and design determines safety and eventually, if the car will be able to save the life of a passenger should an accident happen. Likewise, with regard to dressings, the selection of materials and structure in a specific composition and design determines the level of tissue protection, and

ultimately, if the dressing will be able to prevent a pressure ulcer and for how long.

Cars are not all 'born equal', they have different performance including safety performance and cars from different manufacturers, even though they typically have four wheels and may be able to drive from a point of origin to a destination, cost differently. Again, likewise, prophylactic dressings are not all born equal. Even though they may look similar, and manufacturers may make similar claims with regard to their prophylactic capacities, the clinical outcomes will eventually depend on the design details. This explains why, essentially, an RCT conducted with a certain prophylactic dressing cannot be extrapolated to other dressings, of other engineering designs, even if they have an FDA 510(k) clearance, particularly because the 510(k) does not test for clinical efficacy.

The clinical efficacy can only be determined by RCTs, which is how the pharmaceutical industry functions in the in the case of generic drugs. The formula is the same across manufacturers (and, therefore, RCTs do not need to be repeated). Whereas in the case of a prophylactic dressing, the engineering design is different across manufacturers, yet there is no regulatory requirement for the manufacturer to prove equivalence in materials, construction, or clinical efficacy when they claim that their dressing is as good as a well-tested dressing.

The above discussion linking generic drugs, the 510(k) route of the FDA and vehicle safety is meant to put the Johnson & Johnson failing ASR hip implant case in a more general context. Much like, with regard to hip implants, prophylactic dressings are fundamentally different from a generic medication with a single chemical formula. There could be more than one effective engineering design that alleviates tissue deformations, and each engineering design causes a specific reduction in peak tissue loads or load redistribution patterns. Hence, each engineering design will result in a different protective outcome and should be tested independently. It is fundamentally flawed to claim that a product that has not been tested in the same engineering evaluations and RCTs should have the same protective effect with respect to a product that has been successful in such testing and RCTs.

It is the design that determines the level of efficacy, and unlike generic drugs, there are no identical prophylactic dressing products across manufacturers. Accordingly, any equivalence claim that is being made, and is not being backed-up with the same level of bioengineering and clinical evidence, is misleading and compromising the safety of patients who are prescribed the lookalike or the me-too product.

Implications regarding patient safety

Clinicians who plan to use prophylactic dressings for pressure ulcer prevention must use the best available evidence when choosing which dressing to use, particularly when, as we have pointed out above, there is no standard available to make a straight-forward decision. The dressing must not only be chosen based on evidence but also considering its capacity to not cause harm. For example, its effects on the skin due to its ability to manage microclimate should be taken into account, as well as the degree of adhesion, which may cause stripping of skin cells as a result of repeated inspection of the skin under the dressing during daily skin inspection for possible tissue damage.

Unfortunately, the clinician is often confronted with an additional obstacle in dressing choice that relate to cost. As mentioned previously, hospitals are continually looking for opportunities to manage and reduce costs of consumable items, such as dressings. Value Analysis (VA) is defined as "a process that engages the clinical consumers of products and services in an evidence-based review to determine the clinical and financial impact of adding new products and technologies to the hospital product formulary" (Becker, 2005). These VA processes vary among healthcare organisations depending on the characteristics of the healthcare system and the level at which purchasing decisions are made, but VAs share the common goal of rationalising purchase decision making through a systematic and organised effort to minimise cost and optimise quality. This constitutes a process of determining the value or health outcome achieved per dollar spent.

In the current highly competitive healthcare market and reduced reimbursement, there is, unfortunately, a shrinking number of organisations utilising a true VA approach where the clinical evidence is weighed equally with the cost. Regrettably then, VA is really just a cost-cutting exercise that operates along the lines of simplistically comparing the costs of a number of competing multilayer dressings and selecting the cheapest one. The 'value' component of the value analysis must include the clinical performance of the dressing for its fundamental intended purpose, i.e. pressure ulcer prevention. The only source of this is in the published evidence. The Molnlycke Mepilex Border dressings are the only dressings that currently have robust cost-effectiveness data at both the individual hospital and national levels (Santamaria et al, 2014; 2015b; 2015c; Padula et al,

2017). Considering downstream costs of treatment in cases where a pressure ulcer developed, the aforementioned studies reported that the average net cost of applying the Molnlycke prophylactic dressings was overall less than half the cost of treating controls who did not receive this preventive intervention.

Dressings must be assessed using cost-effectiveness analysis and clinicians must be supported by hospitals to choose dressings that are both clinically and cost effective. The authors have the opinion that it is unethical to base dressing choice on price alone.

There are instances where the decision to change to another manufacturer of preventive dressings is made without input from the clinicians. The reason can be many, such as contractual issues (rebate capture and contract maximisation), cost cutting, marketing etc. In these cases, it is imperative that the clinician compute the baseline pressure injury/ulcer rate when using a 5-layer silicone dressing. The rate of pressure ulcer/injury formation following the change must be reported to value analysis. It is often heard in the healthcare sphere that "my hands are tied; the decision was made and is final".

Advocating for the patients when pressure ulcer rates are often publically reported should be factored into any conversation with the value analysis team. While their decision was likely made to save money, no money is saved when the entire pressure ulcer cost burden is computed. If the new dressings are not preventing pressure ulcers, those hospital-acquired pressure ulcers/injuries will not be reimbursed, will be reported to the state health department and to any other metrics the hospital uses (National Database for Nursing Quality Indicators [NDNQI], University Hospital Consortium) and may lead to legal claims against the hospital. Prevention has a price tag, but treatment is much more costly.

It may be helpful to present cost estimate for the number of new pressure ulcers that formed since the cheaper dressings were used. The cost of hospital acquired pressure ulcers varies by stage and amount of care rendered. In 2011, the mean cost for treating a hospital-acquired stage 3 or 4 pressure ulcer has been estimated at $14,000 (range $6,000 to $21,500) (Leaf Healthcare, 2016). The average settlement in a pressure ulcer lawsuit is $250,000. The average award from a jury is around $1mn. Even if the increased incidence of pressure ulcers is only 1%, over a year's time, that increase can equate to $1,605,000 in a 300-bed hospital (Leaf Healthcare, 2016).

A fundamental goal of all clinicians is to prevent harm to their patients and advocate for evidence-based quality care. The recent Declaration for Patient Safety, endorsed by multiple international healthcare organisations, including the European Wound Management Association and the European Pressure Ulcer Advisory Panel, specifically states that there should be "use of evidence-based medicines and medical technologies to decrease any potential harm" to patients (Health First Europe, 2017). There is now strong evidence that one brand of dressing can significantly reduce the rate of hospital-acquired pressure ulcers and associated costs, yet there are numerous competitor dressings making claims of clinical equivalence with little or no evidence. The question that clinicians must ask is: "Will I choose a dressing based on marketing hype and cost, or, alternatively, based on published scientific, bioengineering and ultimately clinical evidence?"

WINT

Declaration

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5 LAYERS
1 TRUTH.

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- Reduced Stage III, IV and unstageable pressure ulcers by on average, **one per quarter**
- Delivered a return on investment of **100% in less** than one year
- Could **save hospitals USD 200,000-600,000** per year

Mepilex Border Sacrum

Mepilex Border Heel

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