Colin Brown
Director of Research & Quality Development
The Mentholatum Company Limited

Developing Medicines

Helping People to Get Well, Feel Well and Stay Well

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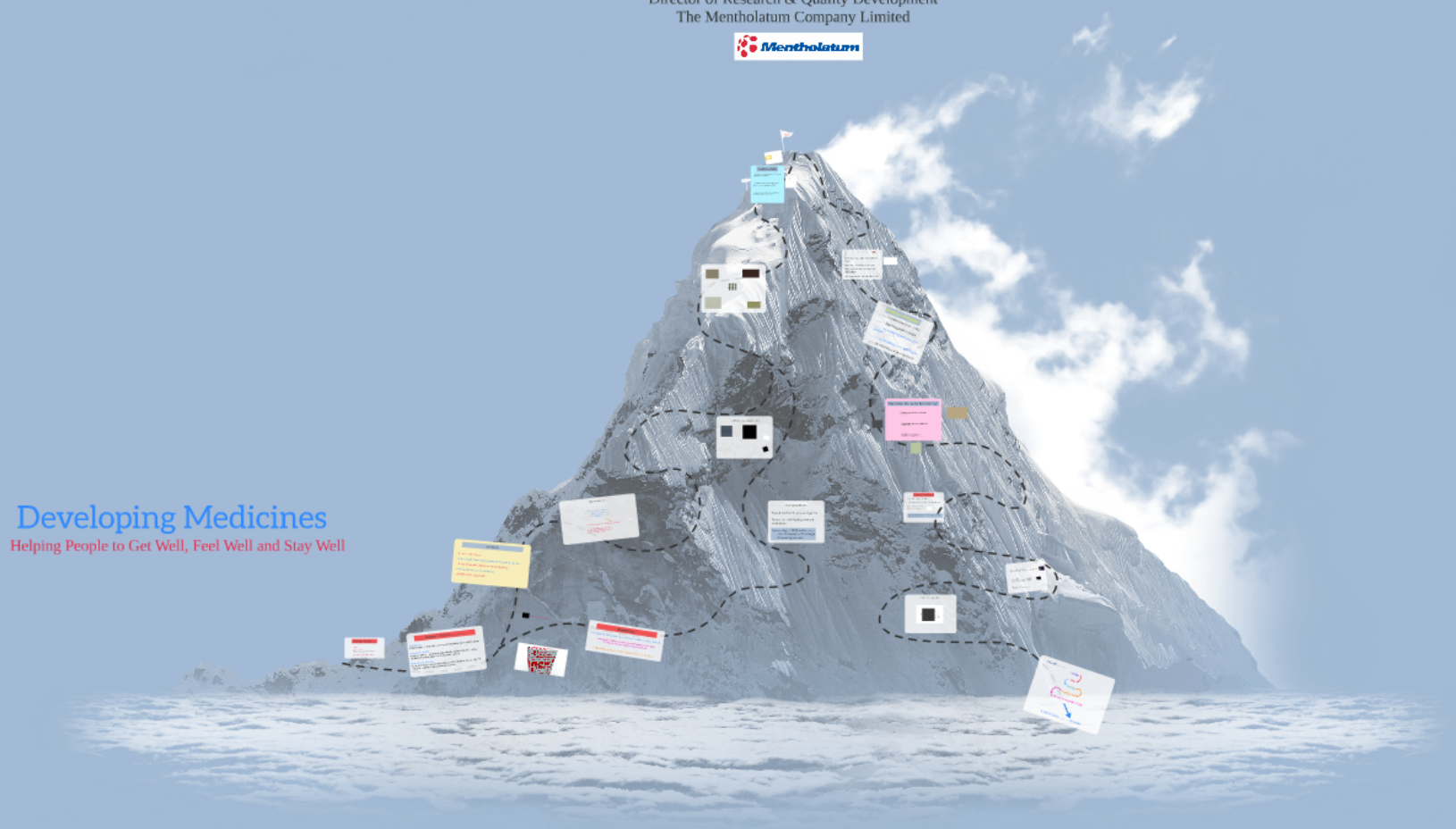

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Helping People to Get Well, Feel Well and Stay Well

Journey - So Far.....

Chemist

Syntex Pharmaceuticals
Scientist in formulation development, pharmaceutics and clinical trial supplies

Syntex Acquired by Quintiles (CRO) - no change to role

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Scientist in formulation development, pharmaceutics and clinical trial supplies

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Journey - So Far.....

Mentholatum

R&D Manager - product development, analytical chemistry, regulatory affairs

Returned to Quintiles

Associate Director - pharmaceutical production, technical transfer, process validation, project management, business development

Returned to Mentholatum

Director of R&QD - product development, analytical chemistry, QC, QA, QP, validation, regulatory affairs, pharmacovigilance

Summary

30+ years in the industry

Team of 25 staff, predominately graduate and post-graduate scientists

Chemists, biochemists, pharmacists and microbiologists

On the Leadership Team for the company

BSc (Hons) CSci CChem MRSC

What is a Medicine?

2nd 'Limb' of the Regulation ("medicine by function")

.....anything intended to treat or prevent a medical condition.....

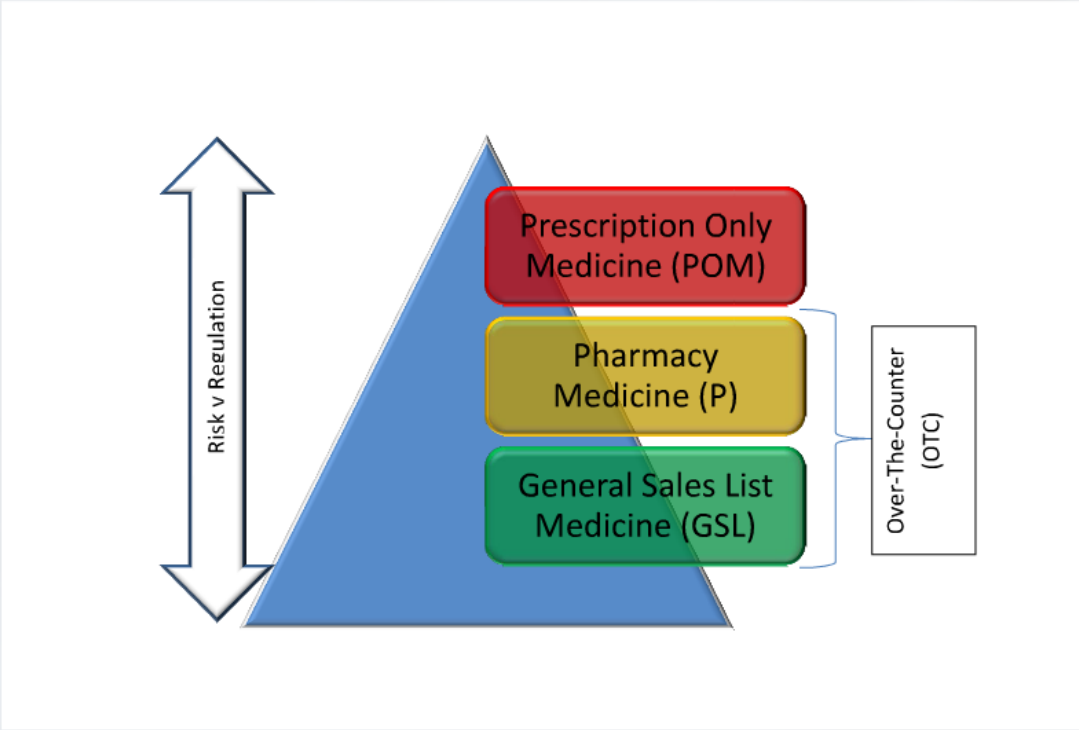
.....anything that possesses a pharmacological action.....

.....anything that possesses a pharmacological action.....

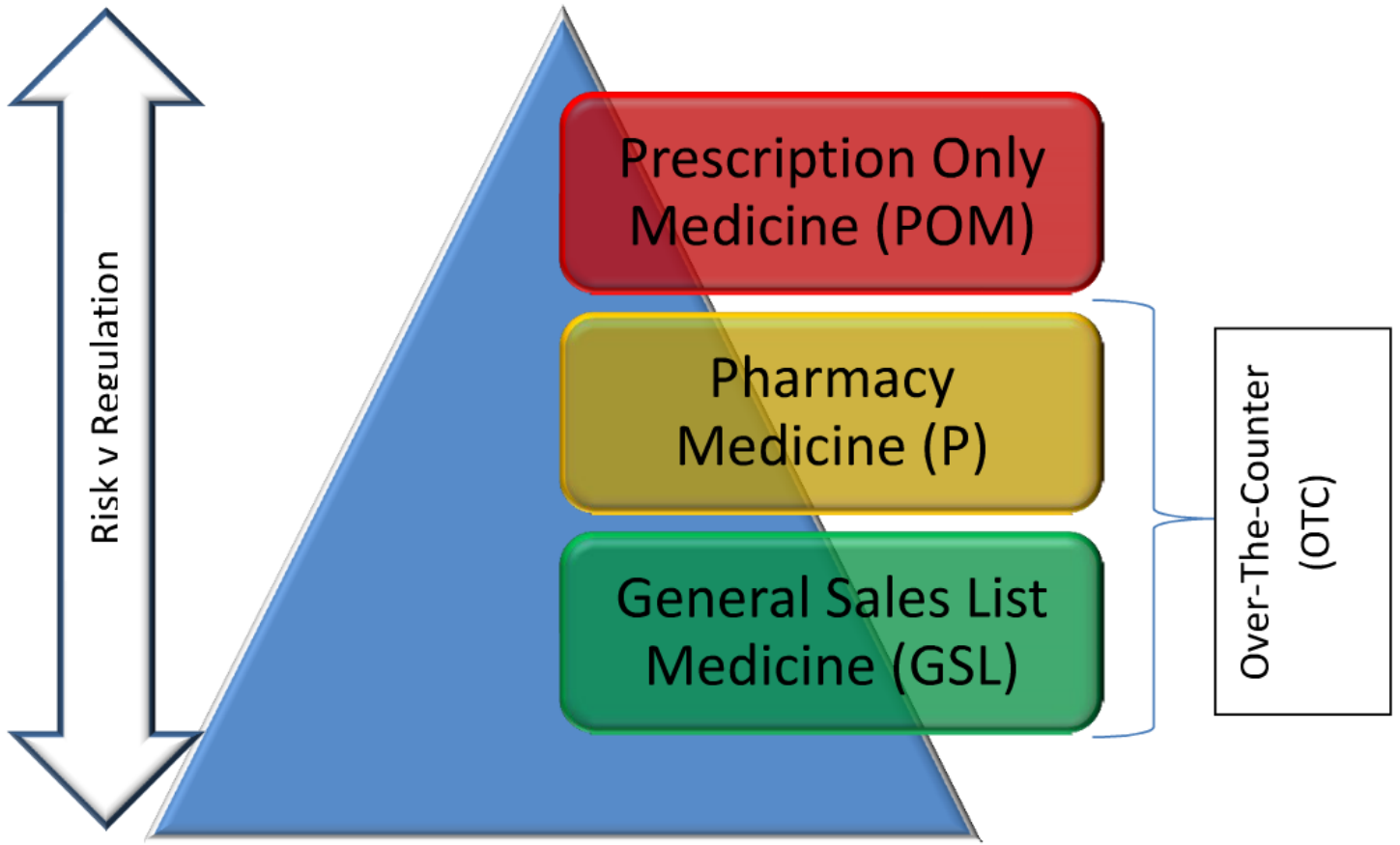
1st 'Limb' of the Regulation ("medicine by presentation")

.....anything that is presented to the consumer as being capable of treating or preventing a medical condition.....

Medicines - Legal Status

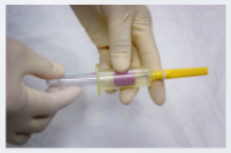


Medicines - Legal Status


Risk v Regulation
Prescription Only Medicine (POM)
Pharmacy Medicine (P)
General Sales List Medicine (GSL)
Over-The-Counter (OTC)

Syntex Pharmaceuticals - POM
(cardiovascular disease, antiretrovirals, stroke, immunosuppressants)

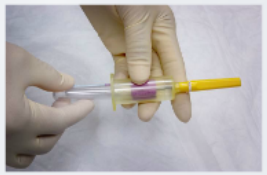
Quintiles - POM
(all therapeutic areas, all routes of administration, all dosage forms)



Mentholatum - OTC
(topical pain relief, joint and muscle care)

Syntex Pharmaceuticals - POM
(cardiovascular disease, antiretrovirals, stroke, immunosuppressants)

Quintiles - POM
(all therapeutic areas, all routes of administration, all dosage forms)



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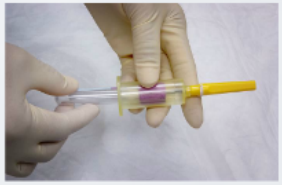

Mentholatum - OTC
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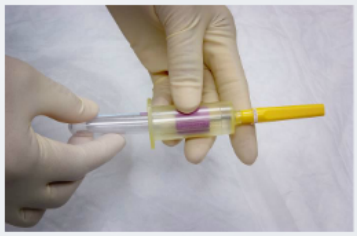
Quintiles - POM
(all therapeutic areas, all routes of administration, all dosage forms)



Mentholatum - OTC
(topical pain relief, joint and muscle care)

Regulations!

Thankfully, the development and production of medicines is highly regulated

Unfortunately, regulatory requirements and standards don't really differentiate between classifications of medicines

Unlike POMs, healthcare products CAN be advertised to the public

- Marketing Claims!


new
fat free
beauty enhancing
Earth-Friendly
Rapid Releasing
great
HYPOALLERGENIC
new!
& IMPROVED
lighter
makes you a better person

We need.....


Studies
Data
Testing
Intelligence
Evidence to Support Claims

Evidence to Support Claims

Which Requires.....Scientists

What Makes Me Get Up Each Morning?

Consumer Healthcare makes a difference to peoples' lives

These products enhance the quality of life of those in pain

Consumers can feel better, be independent and lead normal lives

kes Me Get Up Each

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to peoples' lives

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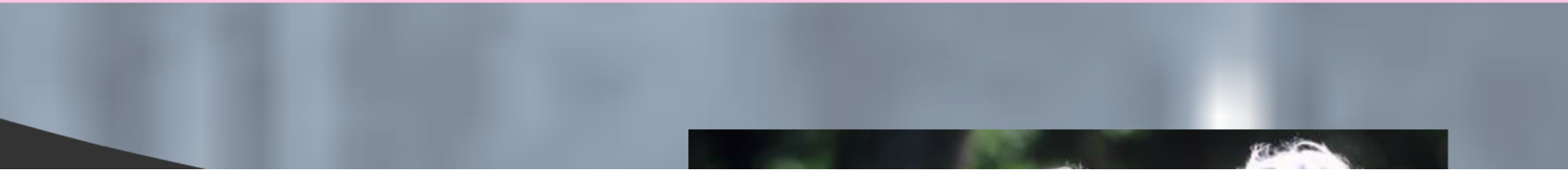


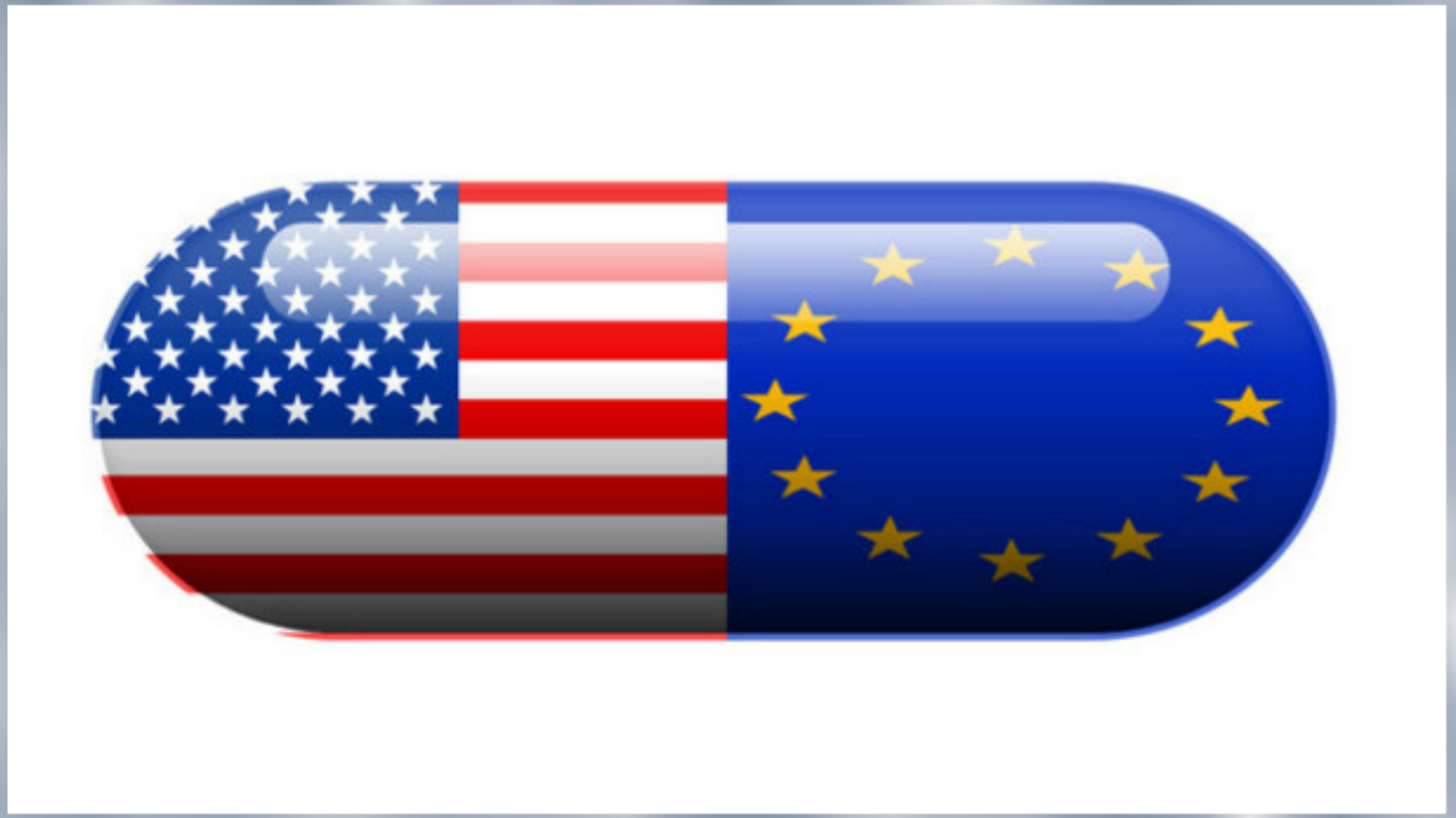
Everyday Challenges

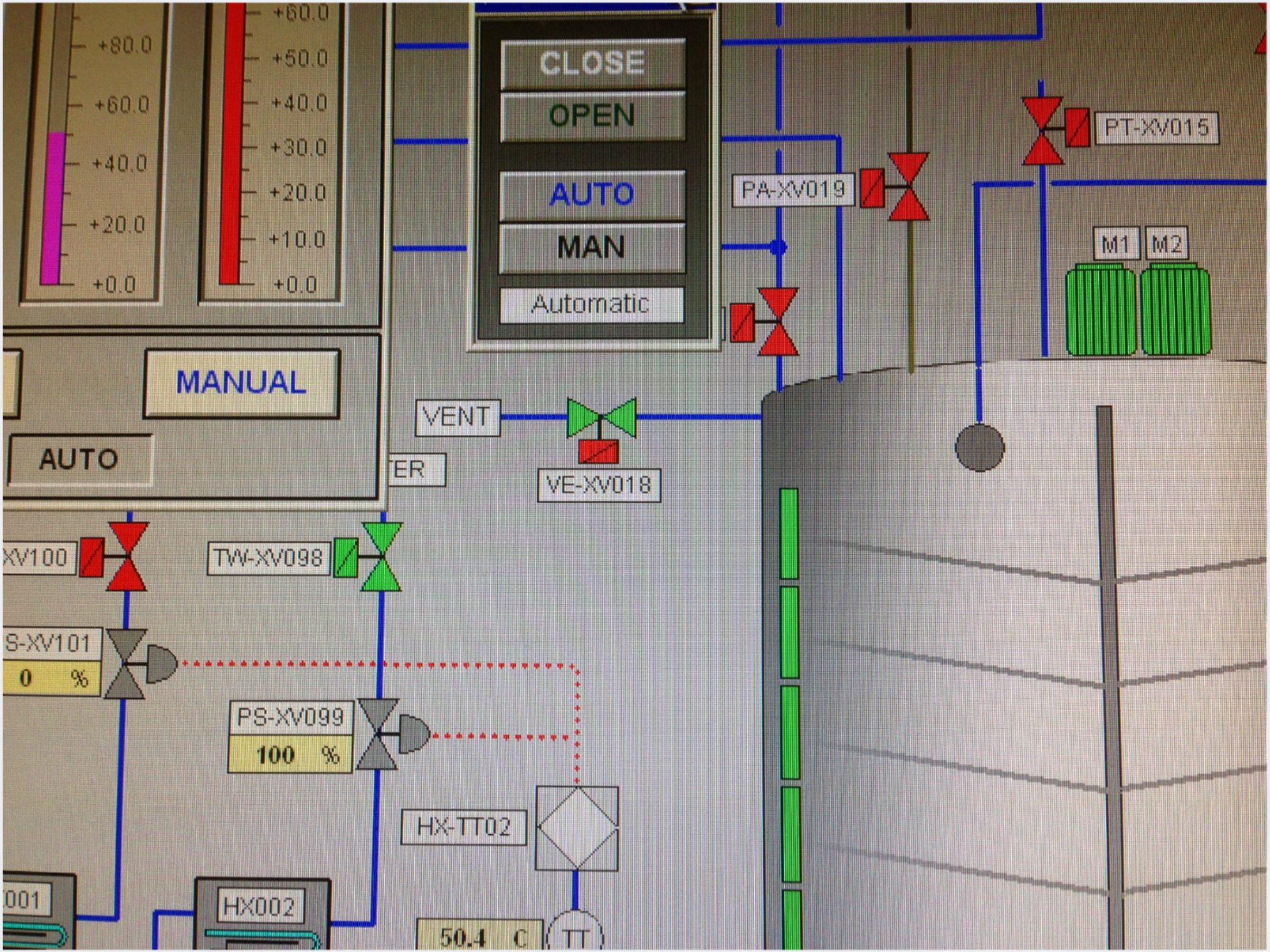
Increasing costs, risks and burden of proof

Increasing technological advances

Increased consumer awareness and expectations

Increasing regulation and compliance




+80.0
+60.0
+40.0
+20.0
+0.0
+60.0
+50.0
+40.0
+30.0
+20.0
+10.0
+0.0
CLOSE
OPEN
AUTO
MAN
Automatic
MANUAL
AUTO
VENT
VE-XV018
PT-XV015
PA-XV019
M1
M2
TW-XV098
S-XV101
0 %
PS-XV099
100 %
HX-TT02
HX002
50.4 C
TT

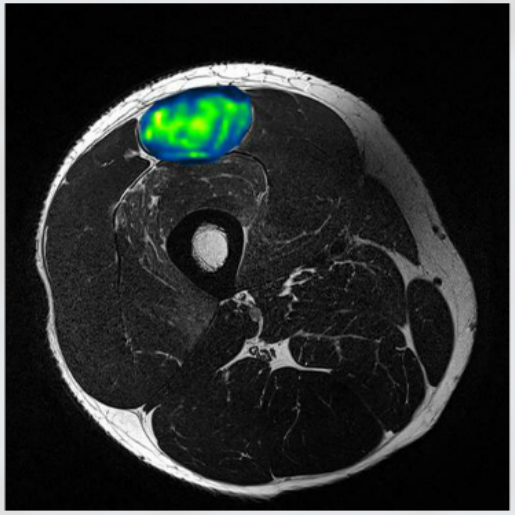
Collaborations

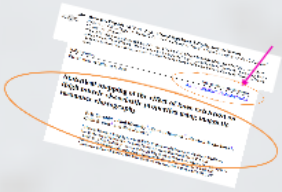
Extend reach and increase expertise

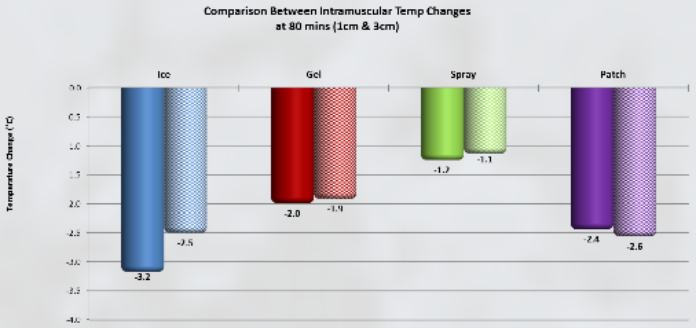
Interaction with leading research institutions

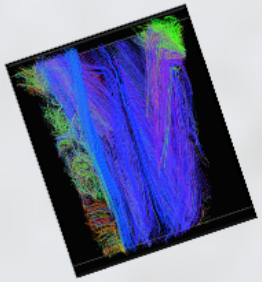
Sponsorship of PhD studentships
- 3 at University of Edinburgh
- Pioneering research

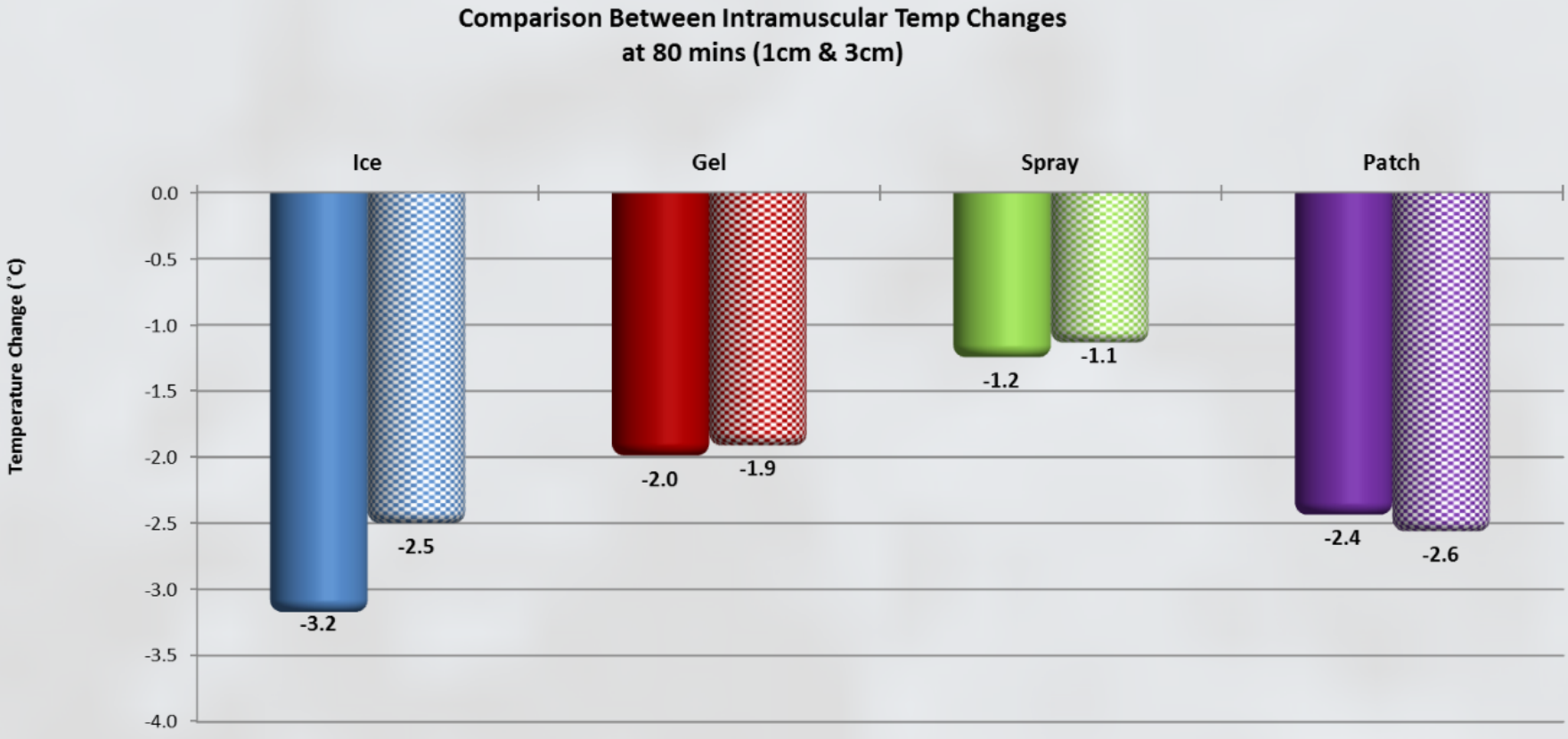
Collaborations - Objective Data

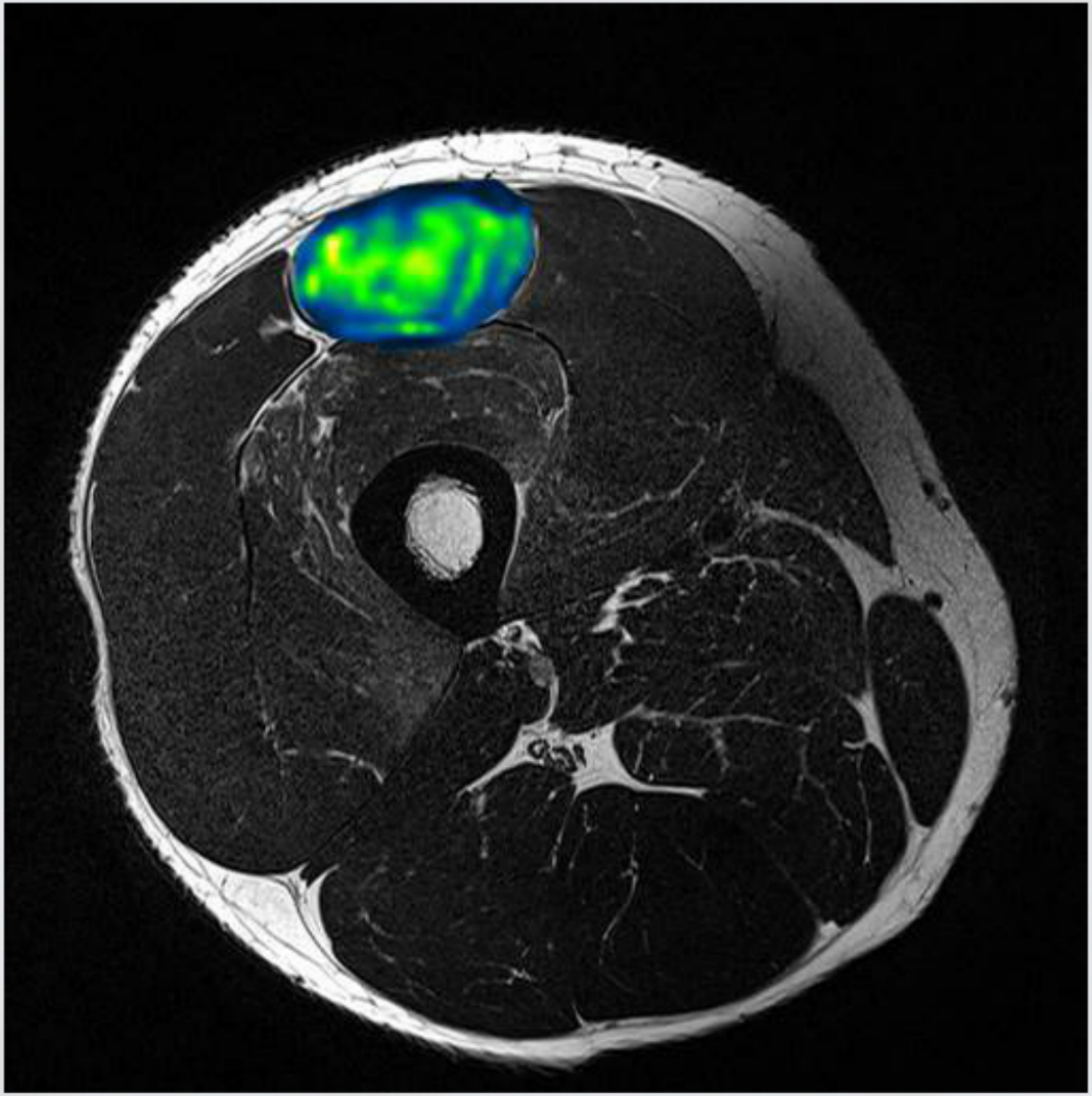


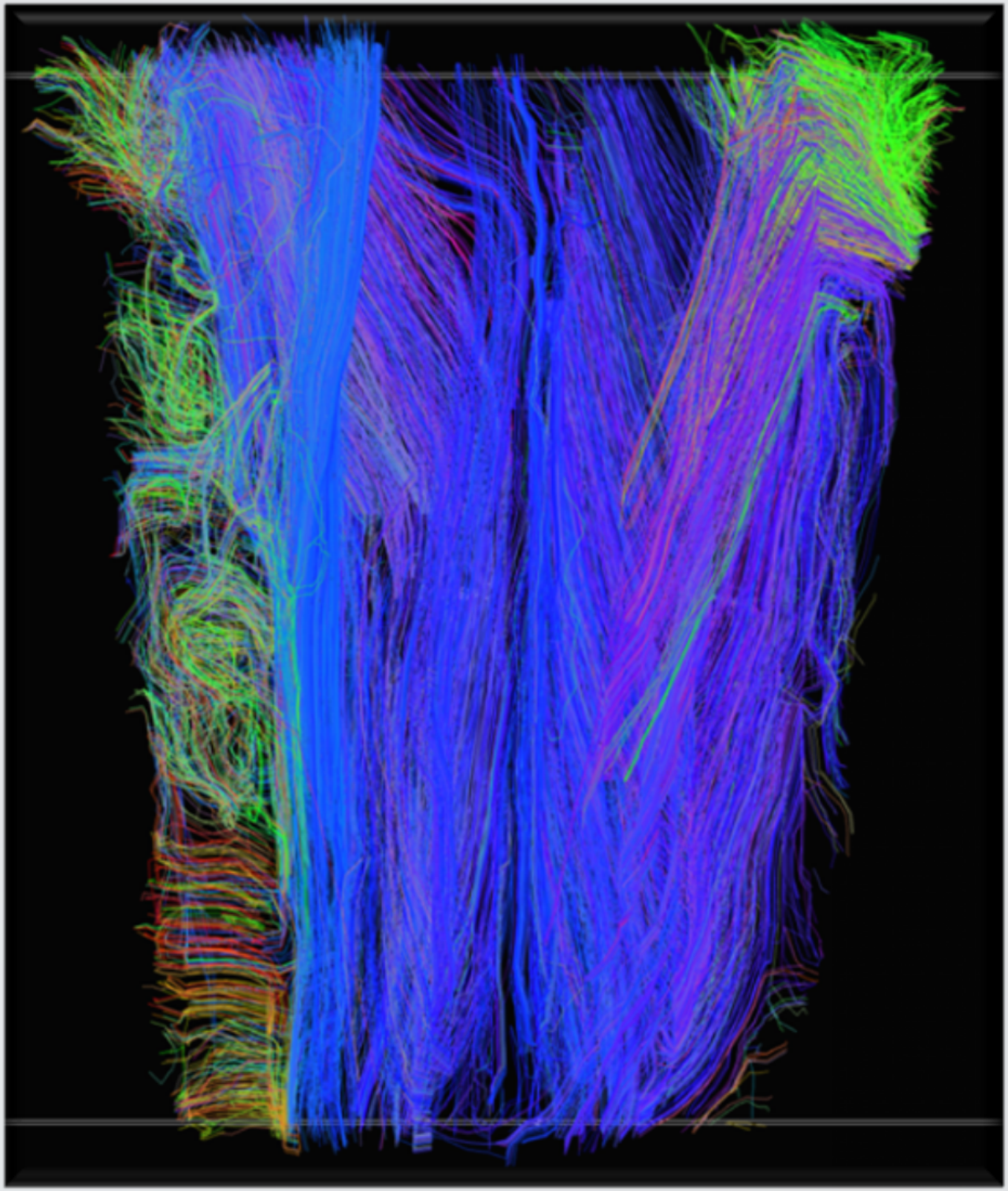







Comparison Between Intramuscular Temp Changes
at 80 mins (1cm & 3cm)
Temperature Change (°C)
Ice
Gel
Spray
Patch
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-3.2
-2.5
-2.0
-1.9
-1.2
-1.1
-2.4
-2.6





Mechanical properties and force output of quadriceps muscle following eccentric exercise

Paul Kennedy[1], Lewis MacGregor[2], Eric Barnhill[1], A Cooper[1],L Hiscox[1], Colin Brown[3], Jürgen Braun[4], Ingolf Sack[4], Edwin van Beek[1], Angus Hunter[2],Curtis L. Johnson[5], Neil Roberts[1]

1: Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, UK. 2: School of Sport, University of Stirling, Stirling, UK. 3: The Mentholatum Company, East Kilbride, Glasgow, UK. 4:Charité University, Berlin, Germany 5: Beckman Institute, University of Illinois at Urbana-Champaign, USA

Introduction

Unaccustomed intense eccentric exercise is known to produce increased passive muscle tension, reduced force output, muscle soreness and increased Creatine Kinase (CK) concentration in blood plasma[1]. Damage to muscle fibre structures and subsequent release of Ca2+ ions into the cytoplasm causing injury contracture are thought to be the mechanism leading to increased tension. The aim of this study is to assess the mechanical properties of the quadriceps following eccentric exercise using Magnetic Resonance Elastography (MRE), and to confirm injury via Maximum Voluntary Contraction (MVC), CK blood concentration and subjective pain assessment. T2 weighted imaging is used to detect hyper-intense signal, which suggests oedema is present. The cross-sectional view of the thigh also allows the distribution of muscle damage to be observed via MRE and T2 imaging.

Method

20 healthy male subjects (mean age 24.1± 4.3yrs) underwent MRI scanning and functional testing 24 hours before and again 48 hours after completion of a standardised eccentric exercise protocol, when the effects of EIMD are expected to peak[2]. Functional testing is undertaken on three further occasions over the next 9 days following the exercise protocol to track recovery. Multi-frequency MRE data at 25Hz, 37.5 Hz, 50Hz and 62.5Hz vibration frequency, and high resolution T2 weighted data are acquired during each scanning session. MR imaging is carried out on a 3T Siemens Verio scanner using a 32 channel receiver coil (InVivo). Functional testing is undertaken using a BioDex isokinetic dynamometer (Figure 1).

Figure 1: Subject seated in Biodex dynamometer. The leg rests on a mechanical arm and is secured with a Velcro cuff.

The exercise protocol is tailored to each subject based on their peak eccentric and concentric force output. A work target is determined and 12 sets of eccentric contractions are completed in as few reps as possible.

MRE phase unwrapping and mathematical inversion is carried out using custom software previously described[3]

Results

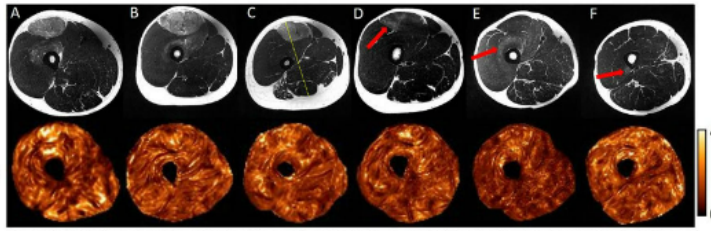


Figure 2: T2 weighted and magnitude stiffness elastograms from a selection of subjects who displayed oedema (A-F). The yellow line through image C depicts the plane through which a sagittal scan was prescribed (Figure 3).

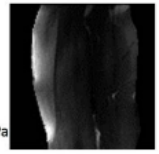


Figure 3: Sagittal slice exhibiting hyper-intense signal present throughout the RF muscle length.

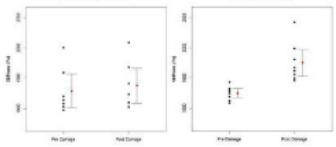


Figure 4 (above): RF stiffness measurements before and 48 hours after damage.

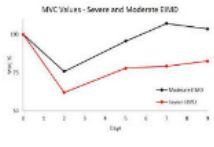


Figure 5 (above): MVC time course of moderate and severe EIMD groups

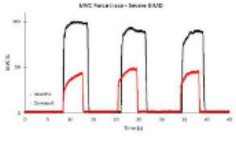


Figure 6 (above): MVC force trace at baseline and 48 hours after damage.

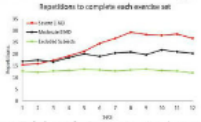


Figure 7 (above): Reps required to complete each set of the eccentric exercise protocol.

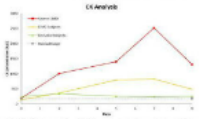


Figure 8 (above): CK concentration time course. Concentration peaks 7 days post exercise.

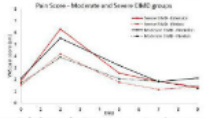


Figure 9 (above): Reps required to complete each set of the eccentric exercise protocol.

- A moderate and severe EIMD group were defined based on MVC values (>10% force loss=moderate EIMD) and T2 weighted images (T2 hyper-intensity=severe EIMD) (Figure 2). Group definition is supported by analysis of reps required per set (Figure 7)
- Rectus femoris (RF) muscle is found to significantly increase following eccentric exercise over both moderate (6% increase, *p=0.02*) and severe EIMD groups (45% increase, *p=0.005*) (Figure 4).
- Severe EIMD subjects exhibited a 14% (*p=0.01*) stiffness increase in the vastus intermedius (VI) muscle, consistent with localised hyper-intensity seen on the T2 images.
- Average force reduction following eccentric exercise is 24% (*p<0.001*) in the moderate EIMD group and 48% (*p>0.001*) in the severe EIMD group. MVC values recover to baseline levels after 7 days in the moderate EIMD group but fail to recover within the sampling window in the severe EIMD group (Figure 5).
- CK time course analysis shows a significant increase after 48 hours, peaking at 7 days post damage (*p>0.001*).
- Subjective pain measurements indicate a significant pain increase after 48 hours during flexion and extension (*p<0.01*).

Conclusion

MRE is capable of detecting muscle stiffness increases following eccentric exercise. T2 hyper-intensity suggestive of oedema may increase passive mechanical properties as seen in the RF and VI muscle groups in the severe EIMD subjects. Significant stiffness increase is also detected in the absence of T2 hyper-intensity, indicating that there are several mechanisms contributing to stiffness increase after eccentric damage. The discovery of localised damage in the RF following this method of eccentric exercise is significant. The vastus lateralis muscle group is predominantly studied to assess muscle properties following exercise and disease[4], however our results suggest the main effect may be missed if the RF is not investigated.

References 1: Clarkson *et al*, Am. J. Phys. Med. Rehabil., 2001, 81(11):52-69 **2:** Green *et al*, NMR Biomed., 2012, 25(6):852-858
3: Barnhill *et al*, *Proc. Intl. Mag. Reson. Med.* 23 (2015), Prog. No. 3338. **4:** Denis *et al*, J Electromyogr Kinesiol, 2011, 21(2):334-341

Acknowledgements
The authors would like to thank all the volunteers and the CRIC radiography staff

ISMRM MERIT AWARD magna cum laude

2520. Mechanical Properties and Force Output of Quadriceps Muscle Following Eccentric Exercise

P Kennedy[1], L MacGregor[2], E Barnhill[1], A Cooper[1], L Hiscox[1], C Brown[3], J Braun[4], I Sack[4], E van Beek[1], A Hunter[2], CL Johnson[5], N Roberts[1]

[1]Clinical Research Imaging Centre (CRIC), University of Edinburgh, Edinburgh, United Kingdom; [2]School of Sport, University of Stirling, Stirling, United Kingdom; [3]The Mentholatum Company Ltd., Glasgow, United Kingdom; [4]Department of Radiology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [5]Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, United States

IOP PUBLISHING — PHYSIOLOGICAL MEASUREMENT

Physiol. Meas. **34** (2013) 1675–1698 — doi:10.1088/0967-3334/34/12/1675

Statistical mapping of the effect of knee extension on thigh muscle viscoelastic properties using magnetic resonance elastography

Eric Barnhill[1], Paul Kennedy[1], Steven Hammer[2], Edwin J R van Beek[1], Colin Brown[3] and Neil Roberts[1]

[1] Clinical Research Imaging Centre (CRIC), College of Medicine and Veterinary Medicine, The University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, UK
[2] Institute of Mechanical, Process and Energy Engineering, School of Engineering and Physical Sciences, Heriot-Watt University, James Nasmyth Building, Edinburgh EH14 4AS, UK
[3] Research and Development, The Mentholatum Company, East Kilbride G74 5PE, UK

Consumer Healthcare

NOT about saving patients' lives

NOT as glamorous as so-called ethical pharmaceuticals

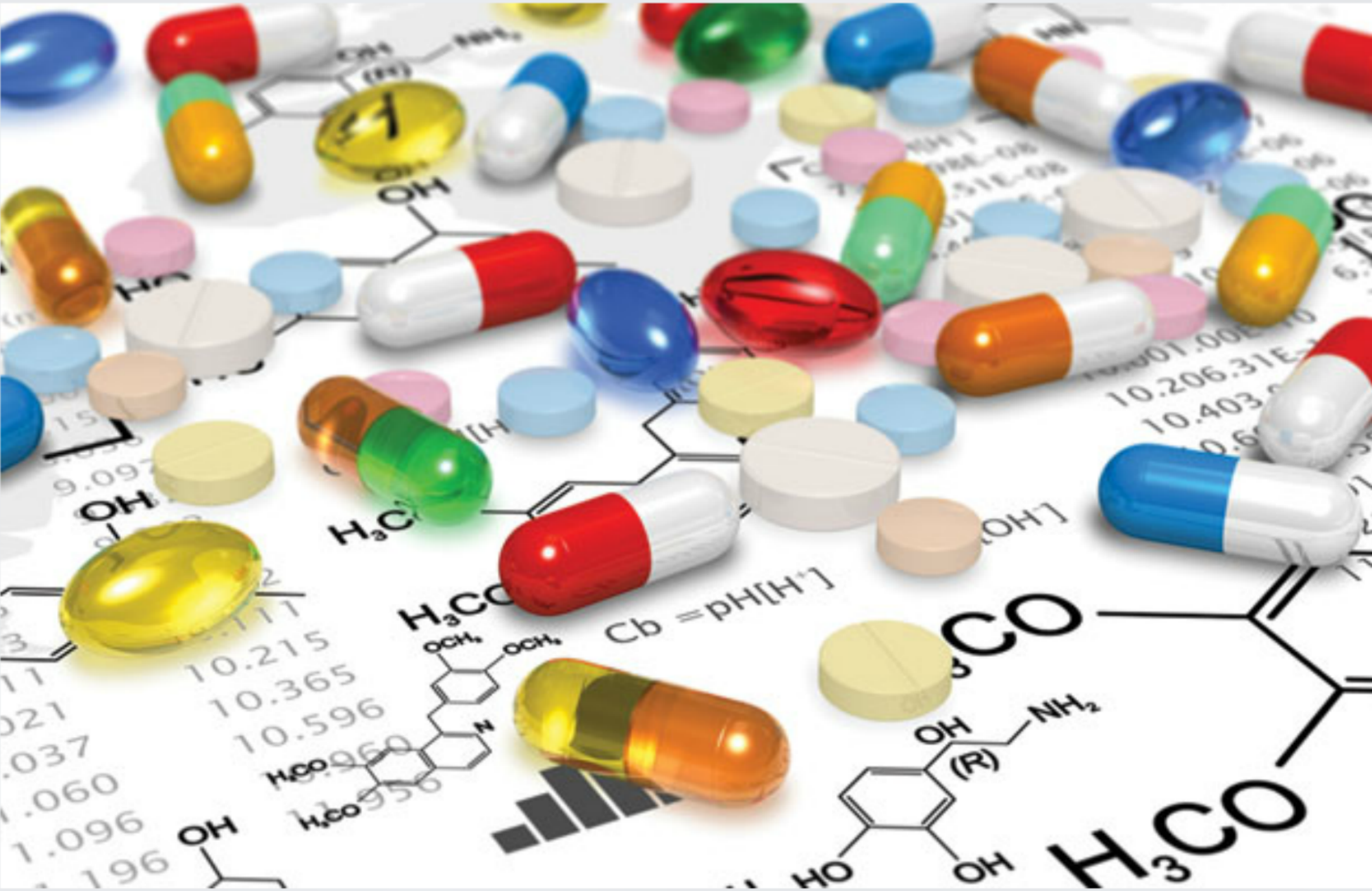
NOT involved in discovering new chemical entities

NOT involved in exotic formulations or novel modes of action

NOT as glamorous as so-cal

NOT involved in discovering new chemical entities

NOT involved in exotic formulations or novel modes of action


OH
H_3C
H_3CO
Cb =pH[H+]
OH
(R)
NH_2
HO
OH
H_3CO

NOT as glamorous as so-called ethical pharmaceuticals

NOT involved in discovering new chemical entities

NOT involved in exotic formulations or novel modes of action

BUT consumer healthcare is definitely professionally challenging and rewarding

Making a Difference

.....by improving quality of life

.....improving product quality

.....by developing next generation products

.....by embracing novel technologies

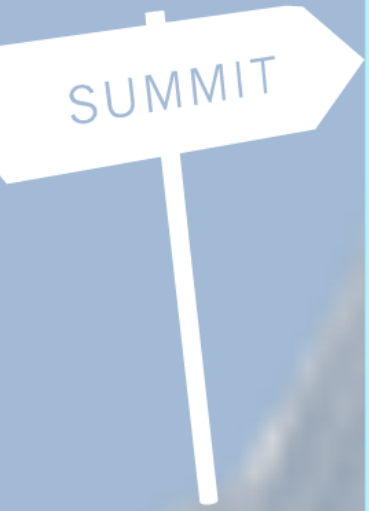
.....by improving patient compliance

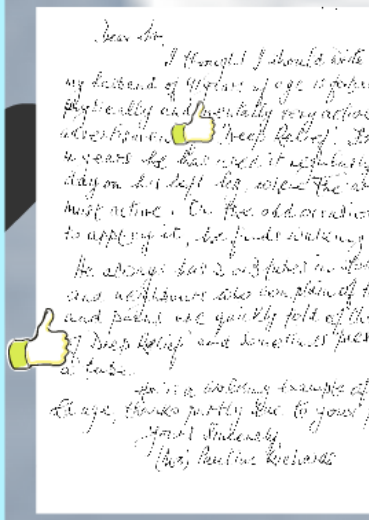
Testimonials

"My back is no longer painful and I can take my dog for a walk again"

"I applied your product to my joints and I can't believe how quickly it worked"

"I used to get sore joints after walking or gardening - but not any longer!"





Dear Sir,

I thought I should write to you as my husband of 91 years of age is fortunately, physically and mentally very active, is a great advertisment for 'Deep Relief'. For the past 4 years he has used it regularly every day on his left leg, where the arthritis is most active. On the odd occasion he forgets to apply it, he finds walking very painful.

He always has 2 or 3 tubes in store and friends and neighbours who complain of their aches and pains are quickly told of the benefits of 'Deep Relief' and sometimes presented with a tube.

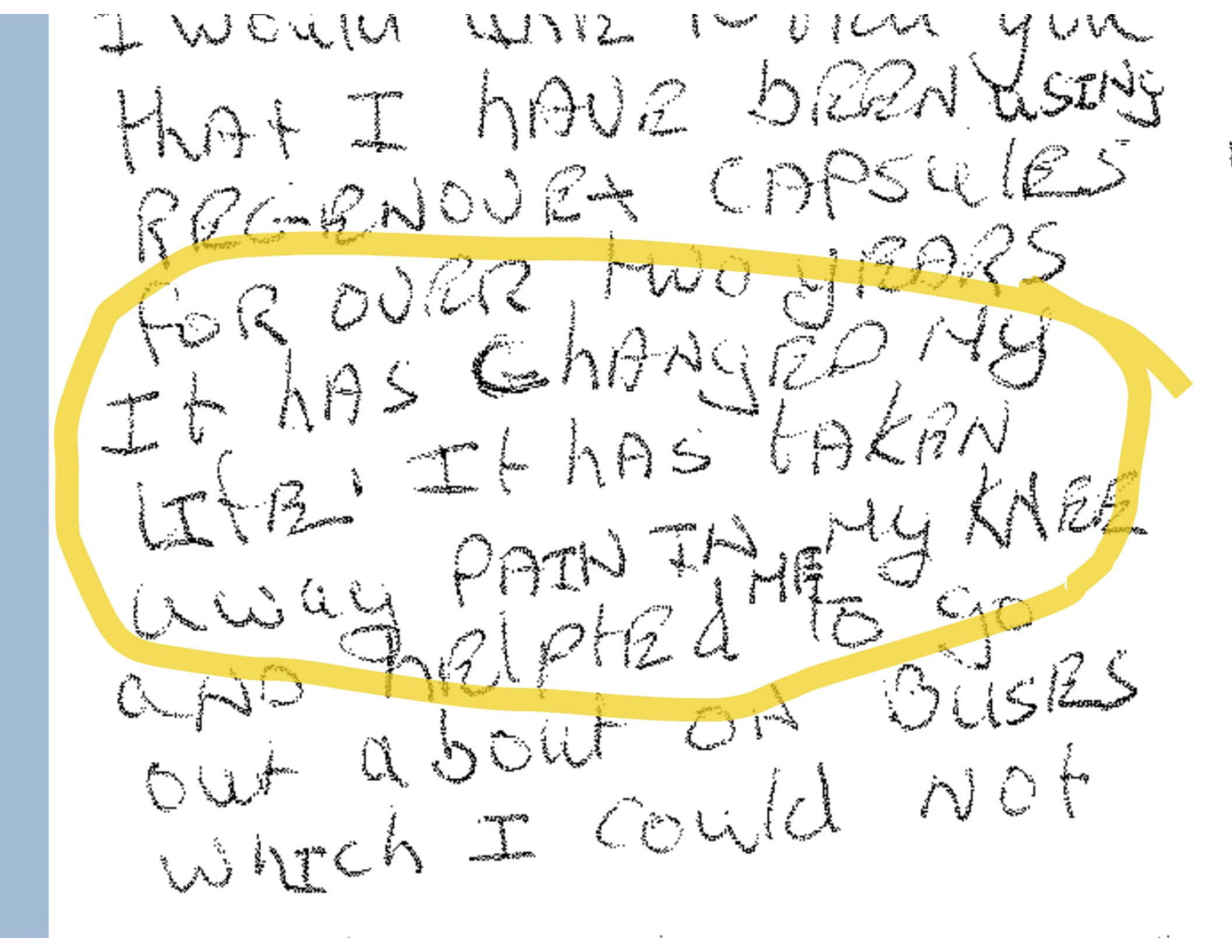
He is a walking example of an active old age, thanks partly due to your product

Yours Sincerely,

(Mrs) Pauline Richards

G74 5AA
World Cancer Research Fund (WCRF UK)
www.wcrf-uk.org/learn

DEAR SIR OR MADAM
I would like to tell you
that I have been using
REG-ENOURT CAPSULES
FOR OVER TWO YEARS
It has CHANGED MY
LIFE. It has TAKEN
AWAY PAIN IN MY KNEE
AND HELPED ME TO GO
OUT ABOUT ON BUSES
WHICH I COULD NOT
DO BEFORE. I HAVE
BEEN TELLING MY FRIENDS ABOUT
IT. HOPE THIS HELPS YOU
TO KNOW THE PRODUCT
IS VERY GOOD. THANKS
FOR MAKING REG-ENOURT
YOUR SINCERLY
HAZEL BARKER




Thank you for listening!

Thank you for listening!

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Director of Research & Quality Development
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Developing Medicines

Helping People to Get Well, Feel Well and Stay Well