



Cefin Brown BSc (Hons) CSci CChem MRSC
Director of Research & Quality Development
The Mentholatum Company Limited



Colin Brown BSc (Hons) CSci CChem MRSC

Director of Research & Quality Development

The Mentholatum Company Limited



When is a Medicine Not a Medicine?

Journey - So Far.....

Analytical Chemist

Syntex Pharmaceuticals

Scientist in formulation development (pharmaceuticals)
and clinical trial supplies

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

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, predominantly graduate and post-graduate scientists

Chemists, biochemists, pharmacists and microbiologists

On the Leadership Team for the company

BSc (Hons) CSci CChem MRSC

When is a Medicine Not a Medicine?

What is a Medicine?



Gel must be a medicine

No other reason why ibuprofen is
an for its NSAID properties

Medicine by Function

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

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

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





Ibuprofen Gel must be a medicine

There is no other reason why ibuprofen is present than for its NSAID properties

Limb 2 - Medicine by Function

.....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.....

Pain relieving cold spray



Pain relieving cold spray



(cools skin and deeper tissue by evaporation of solvents)



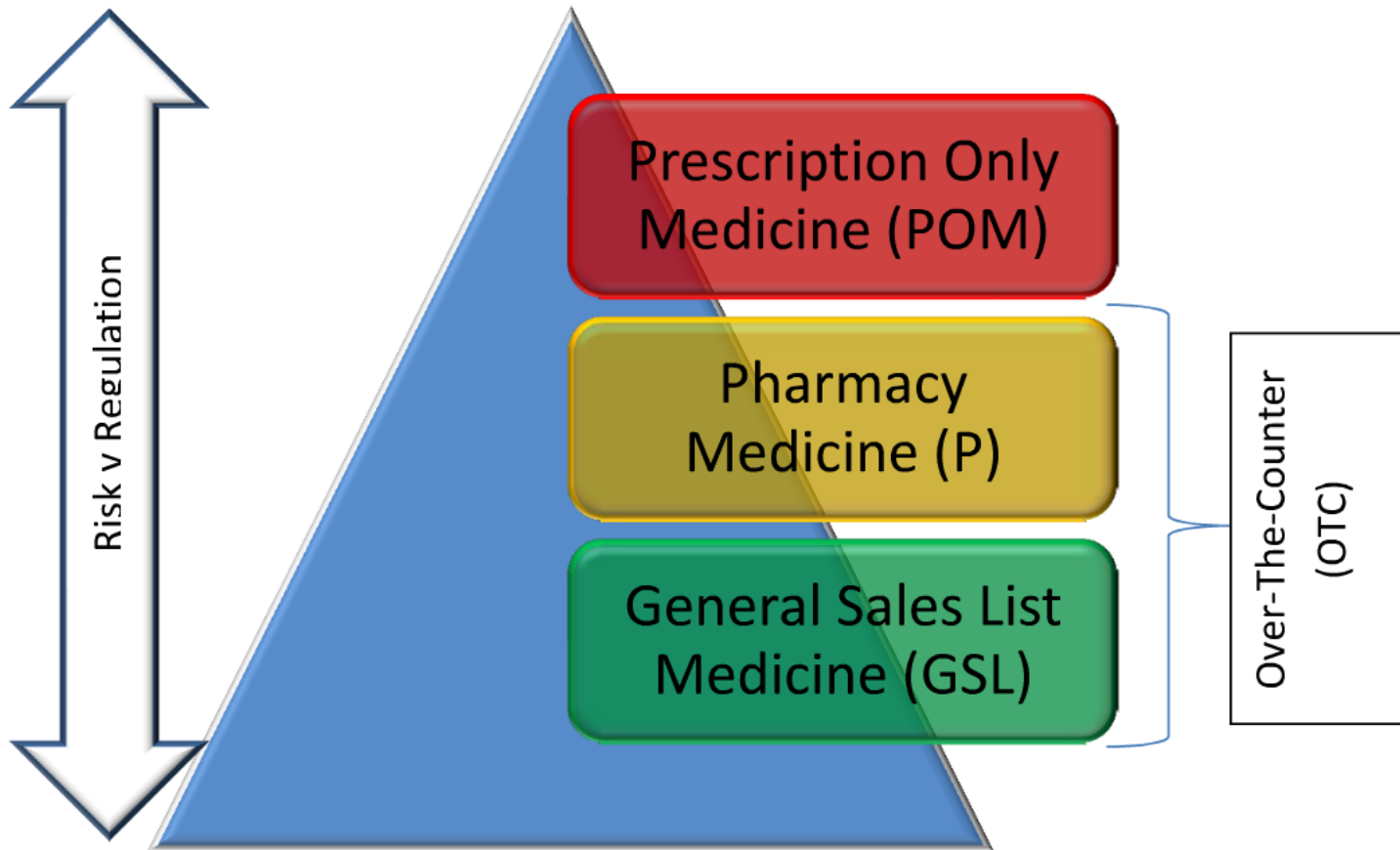
Contains menthol - can have pharmacological action

Present as fragrance

Lots of products contain menthol, but aren't medicines



Medicines - Legal Status



When is a Medicine Not a Medicine?

When it's a Medical Device.....

A medical device achieves its therapeutic effect principally by a physical action

EU Medical Devices Directive - Definition

MDD defines a medical device as: "Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: - diagnosis, prevention, monitoring, treatment or alleviation of disease, - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, - investigation, replacement or modification of the anatomy or of a physiological process, - control of conception, **and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;**

In deciding whether a product falls under the MDD, particular account shall be taken of the principal mode of action of the product.

Typically, the medical device function is achieved by physical **means** (including mechanical action, physical barrier, replacement of or support to organs or body functions ...).

The principal intended action of a medical device may be deduced from the scientific data regarding mechanism of action and the manufacturer's labelling and claims.

EU Medical Devices Directive - Definition

MDD defines a medical device as: "Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: - diagnosis, prevention, monitoring, treatment or alleviation of disease, - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, - investigation, replacement or modification of the anatomy or of a physiological process, - control of conception, **and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;**

In deciding whether a product falls under the MDD, particular

does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

In deciding whether a product falls under the MDD, particular account shall be taken of the principal mode of action of the product.

Typically, the medical device function is achieved by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions ...).

The principal intended action of a medical device may be deduced from the scientific data regarding mechanism of action and the manufacturer's labelling and claims.



McCain

PEAS

1kg NET

- Classic vegetables
- ✓ Source of fibre
- ✓ Farm grown for you





Could be a medical device if it claimed to have a medical purpose;

e.g. if the label claimed that frozen peas had pain relieving properties

.....and achieved that effect principally by a physical action (e.g. cooling)

Medical Device Classifications

TABLE 3. QUALITY SYSTEM BY CE CLASS¹

Classification	Class I	Class I	Class IIa	Class IIb	Class III
Type	Nonsterile	Sterile			
Implementation	N/A	Implement company quality system			
Documentation	Technical file prepared to demonstrate compliance with MDD			Design dossier prepared in compliance with MDD	
Application	N/A	Submit QMS and technical file to notified body			
Accreditation	N/A	CE Mark for the device and certificate for the company for a successful audit issued			
Registration	Register with Competent Authority		No registration for most EU member states		
CE Mark	Prepare declaration of conformity before affixing the CE Mark				
Auditing	Self-certified CE Mark	Yearly unannounced audits to ensure compliance with EU regulations			
Approval time	< 1 month	3–4 months	3–5 months	3–6 months	6–9 months
Validity period	Does not expire	3 years			
Cost (€)	< 4,000	< 12,000	12,000–24,000	< 40,000	> 40,000

MDD = Medical Devices Directive; QMS = quality management system; N/A = not applicable

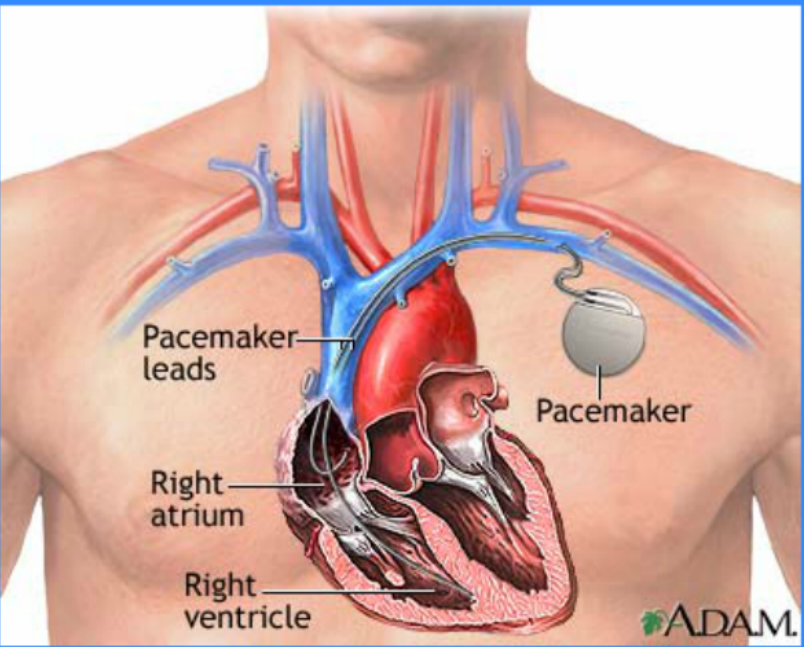
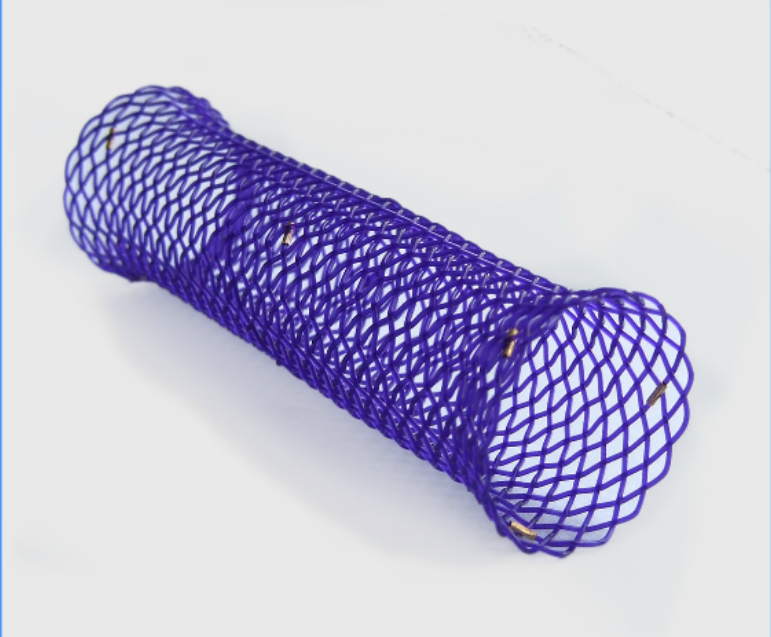
¹. Europe CE Approval Process for Medical Devices. Emergo website. www.emergogroup.com/resources/europe-process-chart. Accessed January 22, 2015.

When it's a Medical Device.....

A medical device achieves its therapeutic effect principally by a physical action



When it's a Medical Device.....



A medical device achieves its therapeutic effect principally by a physical action



Data Requirements

The **AMOUNT** of data depends on the legal status of the product (medicine, medical device, other)

The **TYPE** of data depends on the legal status and the country in which authorisation is being sought

The legal status depends on the regulations in a particular country (a medicine in one country may not be a medicine in another)

Mentholatum deliberately straddles the "regulatory borderline" between legal statuses

Mentholatum markets products in over 70 countries = complexity

Regulations!

The development and production of healthcare products is highly regulated

Regulatory quality systems and standards do not differentiate between classifications of medicines - only one standard

However, unlike POMs, healthcare products can be advertised to the public



- Marketing Claims!

SNAKE-OIL LINIMENT

RELIEVES INSTANTANEOUSLY
AND CURES HEADACHE, NEURALGIA, TOOTHACHE, EARACHE, BACKACHE,
SWELLINGS, SPRAINS, SORE CHEST, SWELLING of the THROAT, CONTRACTED CORDS
and MUSCLES, STIFF JOINTS, WRENCHES, DISLOCATIONS, CUTS and BRUISES.

It Quickly takes out the Soreness and Inflammation from Corns, Bunions, Insect and Reptile Bites.

The best External Preparation for BYCICLISTS and ATHLETES. It makes the Muscles supple
and Relaxes the Cords. Loosens the Joints and gives a feeling of Freshness and Vigor to the whole System.

SNAKE-OIL LINIMENT CURES ALL ACHES AND PAINS.

If you are suffering from Rheumatism, ALWAYS take LA-CAS-KA internally for the Blood and
use SNAKE-OIL LINIMENT externally. When used together we GUARANTEE A CURE in every
instance or MONEY REFUNDED.

If You Are Afflicted With DEAFNESS

Get Our Specially Prepared

PURE Rattlesnake Oil

We need.....



Evidence to Support Claims



Which Requires.....Scientists

Chemists

QC, Validation, QA, QP,
Product Development, Regulatory
Affairs

Pharmacists

Product Development, QP,
Pharmacovigilance, Regulatory Affairs

Microbiologists

QC, QA, QP, Regulatory Affairs

Biochemists

QC, QA, Regulatory Affairs

Chemists

QC, Validation, QA, QP,
Product Development, Regulatory
Affairs

Pharmacists

Product Development, QP,
Pharmacovigilance, Regulatory Affairs

QC, Validation, QA, QP,
Product Development, Regulatory
Affairs

Pharmacists

Product Development, QP,
Pharmacovigilance, Regulatory Affairs

Microbiologists

QC, QA, QP, Regulatory Affairs

Biochemists

Pharmacists

Product Development, QP,
Pharmacovigilance, Regulatory Affairs

Microbiologists

QC, QA, QP, Regulatory Affairs

Biochemists

QC, QA, Regulatory Affairs

Everyday Challenges

Medicines are Regulated!

In the UK, medicines are licensed by MHRA and must

be safe

be efficacious

demonstrate appropriate quality

Everyday Challenges

Increasing costs, risks and burden of proof

Increasing technological advances

Increased consumer awareness and expectations

Increasing regulation and compliance



Integrity of Equipment

Data Integrity

*Planned
Preventative
Maintenance &
Calibration*

Training

Regulatory Dossiers

*Substantiation of
Claims*

Advertising

Validation of Instruments

Trending

Pharmacovigilance

Out of Specification

Stability Data

Clinical Evaluations

Storage & Distribution

Microbials

Country-Specific Data

Supply Chain Management

Labelling

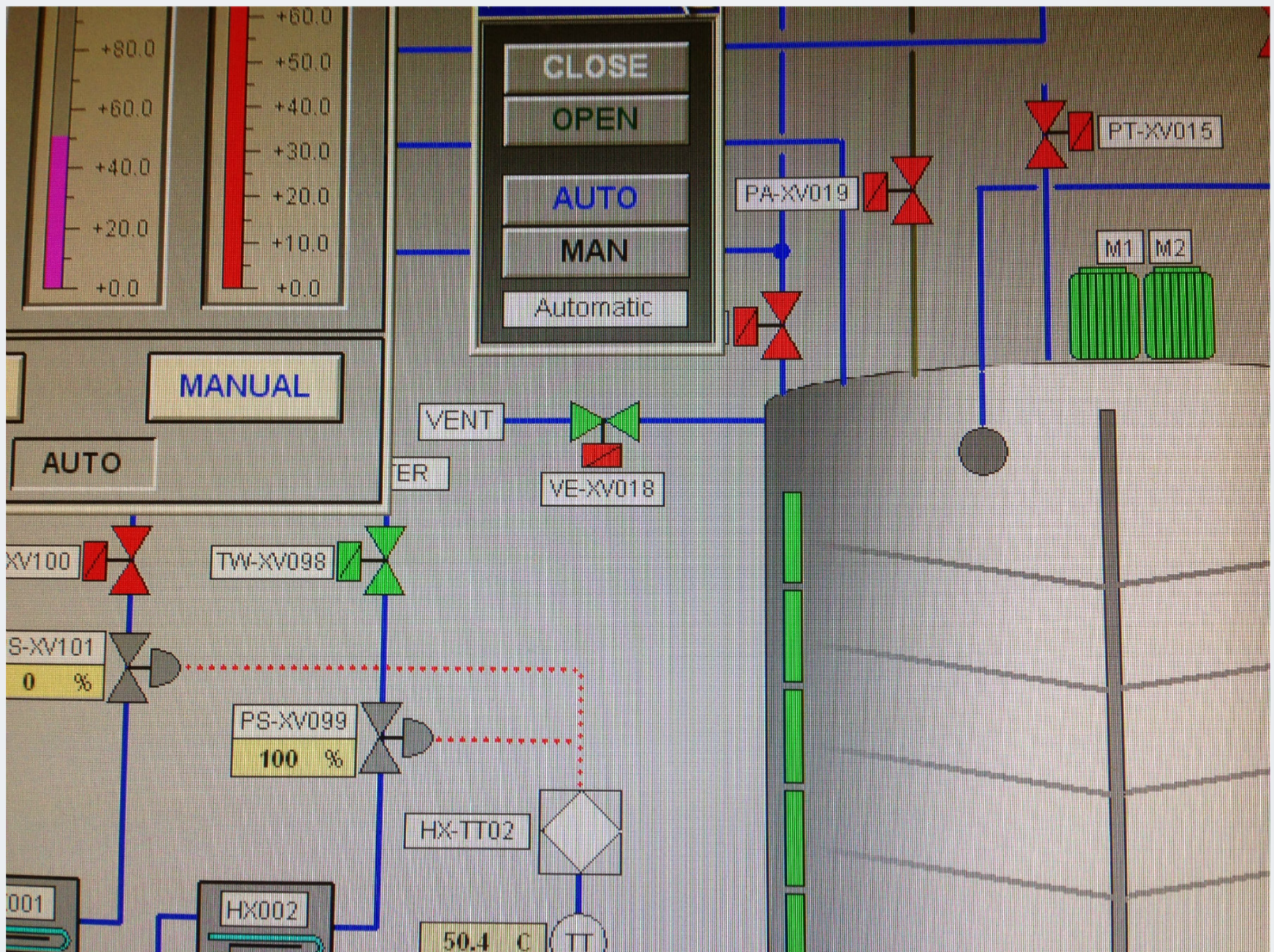
Analytical Method Development & Validation

Process Qualification

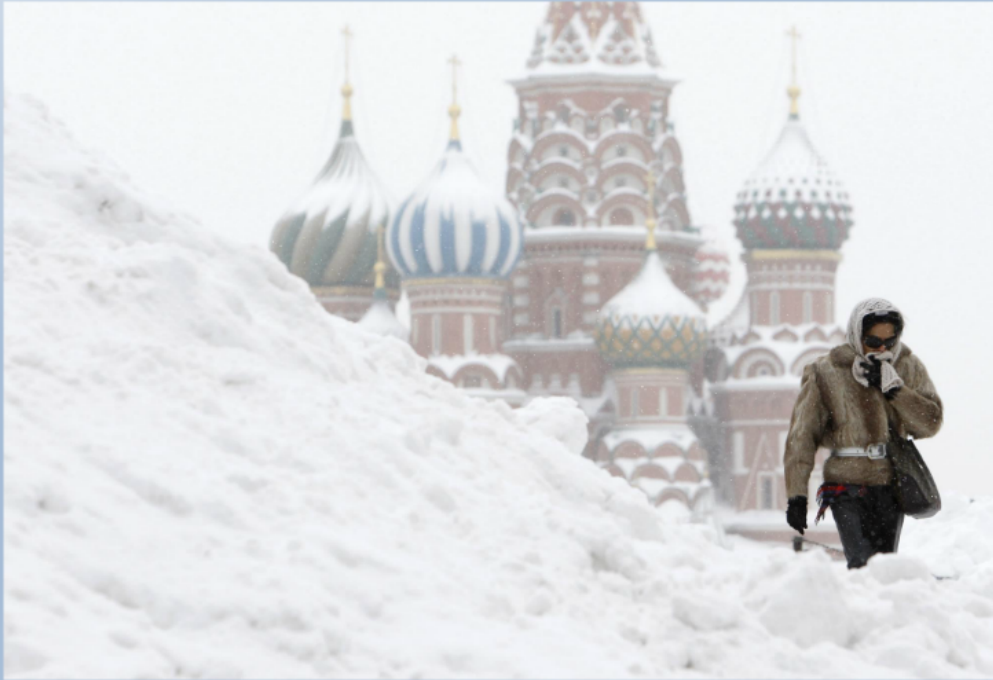
Non-Conformance

*Risk
Management*









EARTH



DUBAI



SUN



WWW.FACEBOOK.COM/DUBAILOVERS

ICH Stability Zones

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IV	Hot humid/tropical zone
Zone IVb	ASEAN testing conditions hot/higher humidity

Long Term Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21°C ± 2°C	45% rH ± 5% rH	12 Months
Zone II	25°C ± 2°C	60% rH ± 5% rH	12 Months
Zone III	30°C ± 2°C	35% rH ± 5% rH	12 Months
Zone IV	30°C ± 2°C	65% rH ± 5% rH	12 Months
Zone IVb	30°C ± 2°C	75% rH ± 5% rH	12 Months
Refrigerated	5°C ± 3°C	No Humidity	12 Months
Frozen	-15°C ± 5°C	No Humidity	12 Months

Accelerated and Intermediate Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
<i>Accelerated Ambient</i>	<i>40°C ± 2°C</i>	<i>75% rH ± 5% rH</i>	<i>6 Months</i>
<i>Accelerated Refrigerated</i>	<i>25°C ± 2°C</i>	<i>60% rH ± 5% rH</i>	<i>6 Months</i>
<i>Accelerated Frozen</i>	<i>5°C ± 3°C</i>	<i>No Humidity</i>	<i>6 Months</i>
<i>Intermediate</i>	<i>30°C ± 2°C</i>	<i>65% rH ± 5% rH</i>	<i>6 Months</i>





.....by improving product quality
by developing next generation products
by embracing novel technologies
by improving patient compliance

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



Collaborations - Objective Data

rag

Collaborations

Extend reach and increase expertise

Interaction with leading research institutions

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

Consumer Healthcare

NOT about saving patients' lives
 NOT as glamorous as so-called ethical pharmaceuticals

****Not linked to the marketing team discussed earlier
 ****Not linked to the public health/ethics or health economics team

BUT consumer healthcare is definitely professionally challenging and rewarding

Medical Device Classification

Device Name	Classification	Regulation
Medical Device 1	Class I	CE Marking
Medical Device 2	Class II	CE Marking
Medical Device 3	Class III	CE Marking

Collaborations

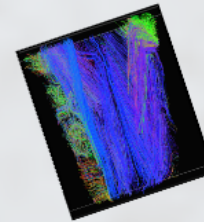
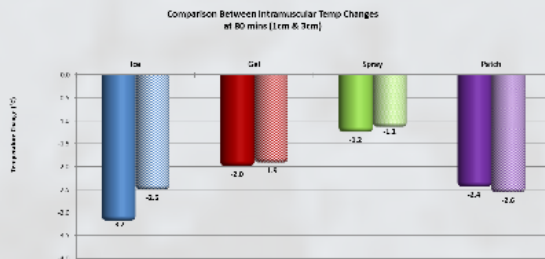
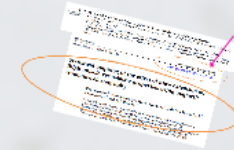
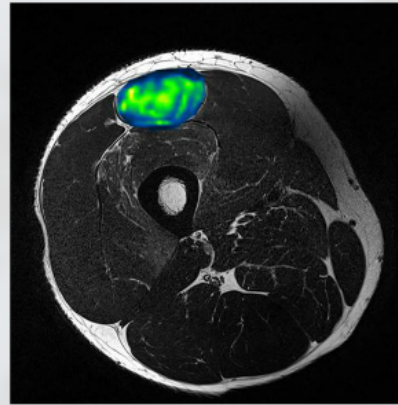
Extend reach and increase expertise

Interaction with leading research institutions

Sponsorship of PhD studentships

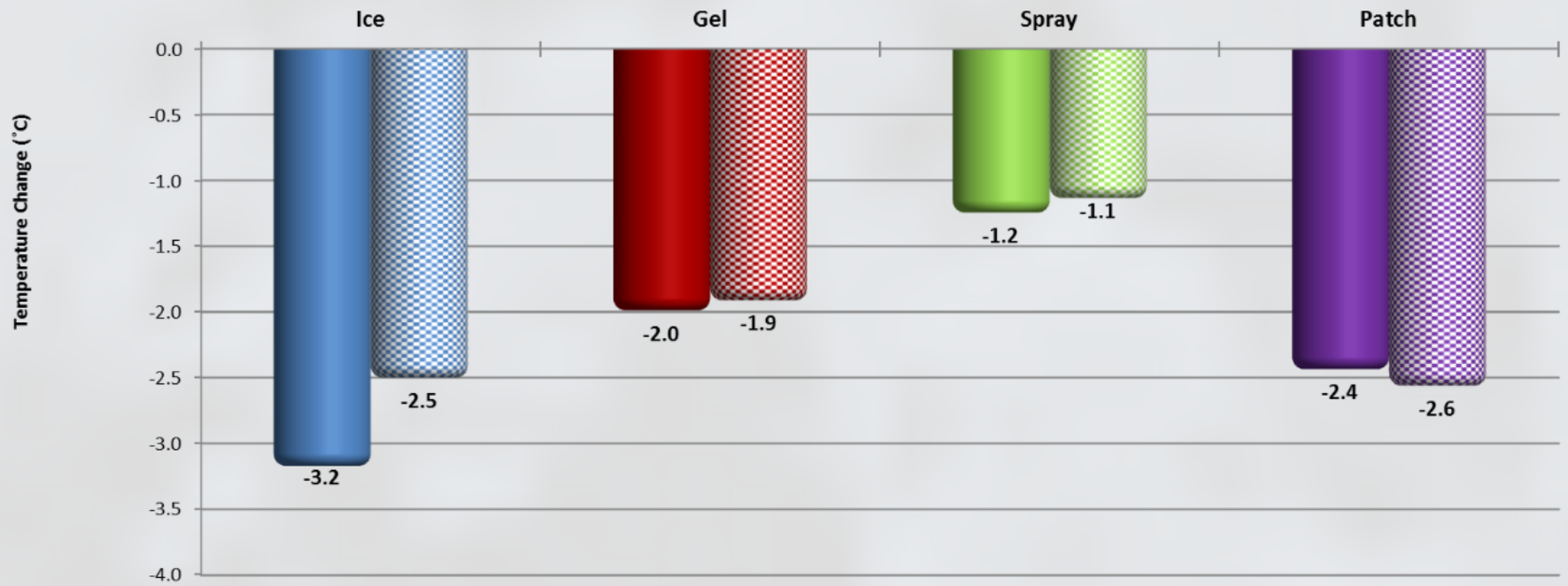
- 3 at University of Edinburgh
- Pioneering research

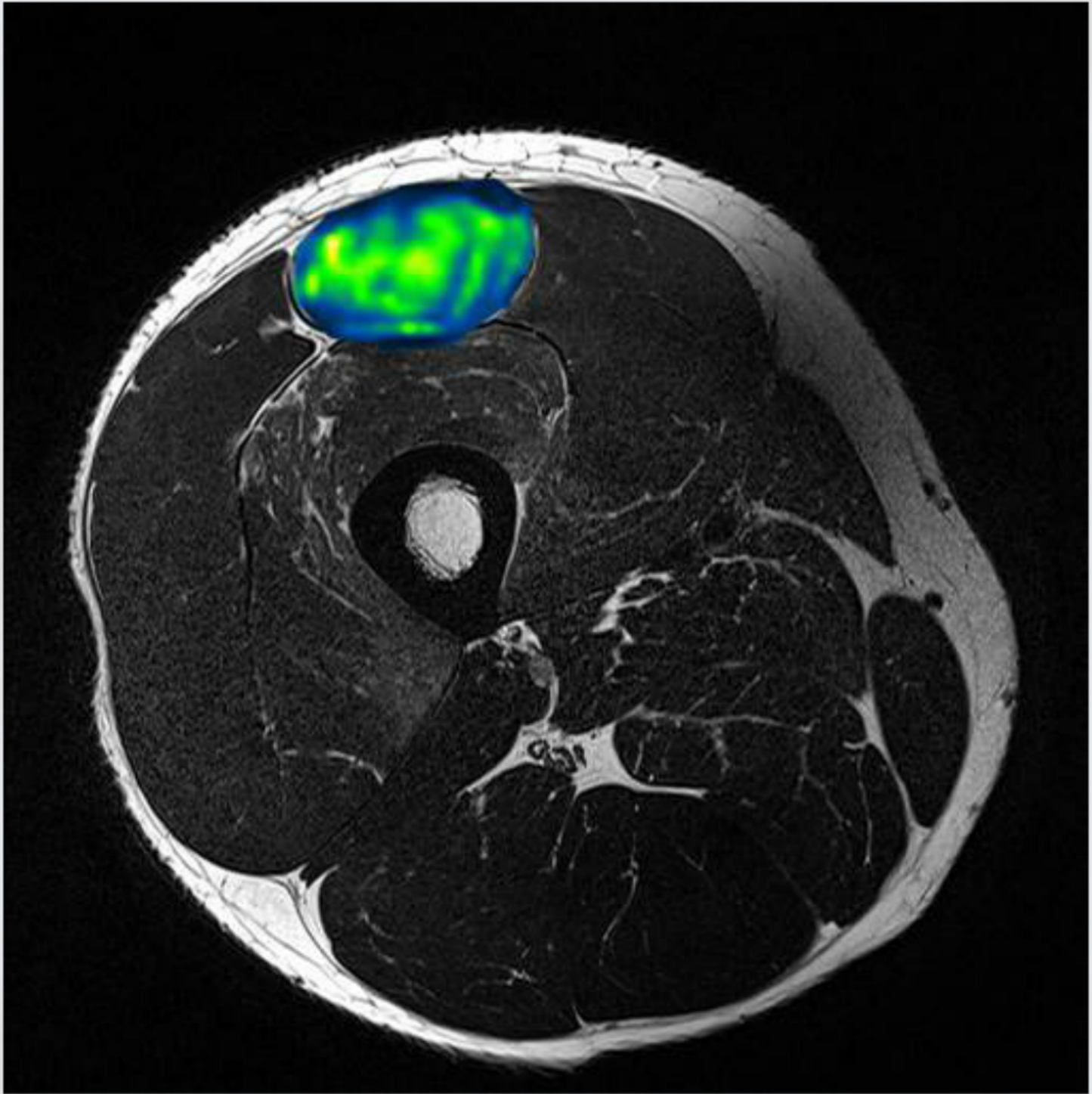
Collaborations - Objective Data

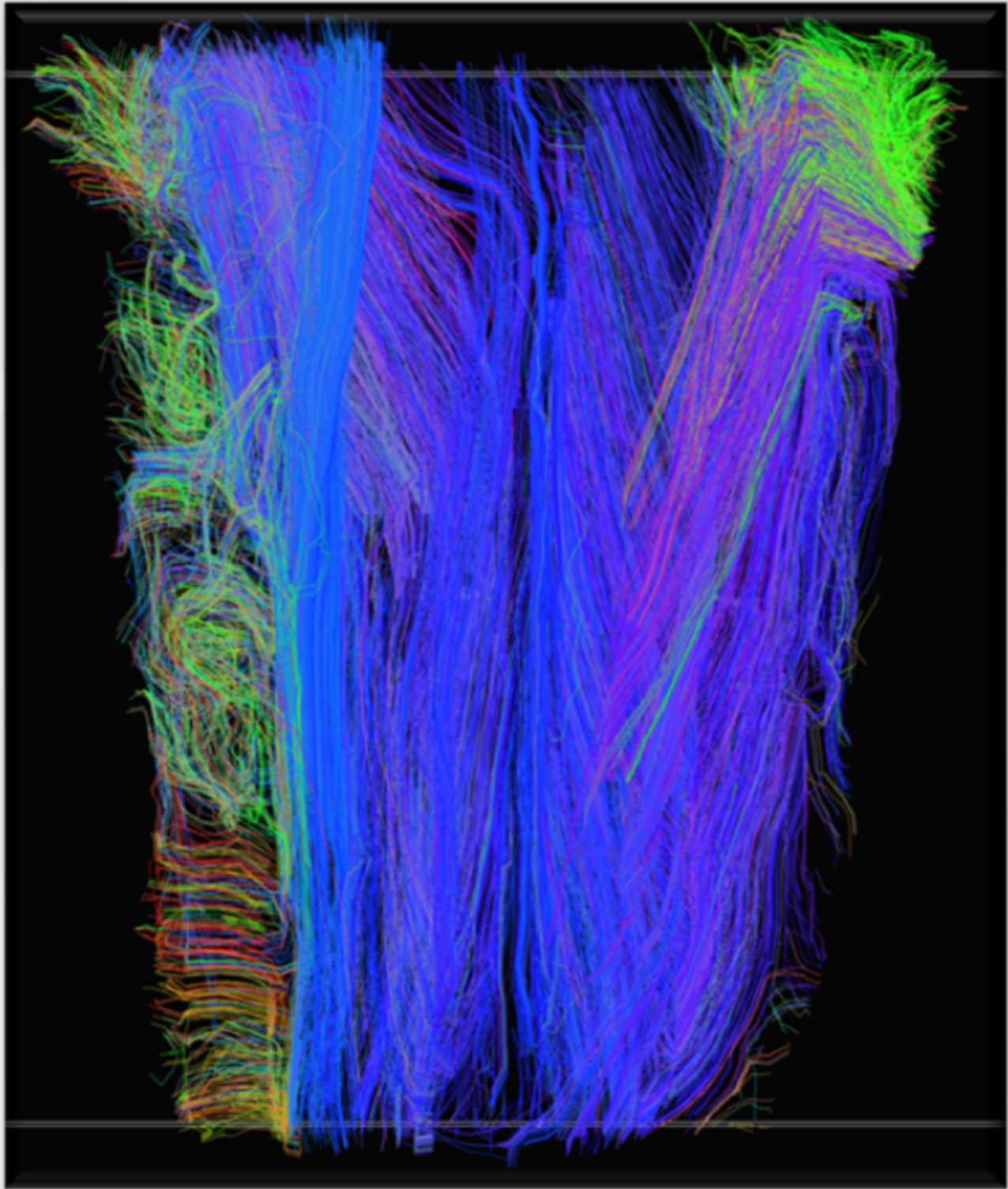




Comparison Between Intramuscular Temp Changes
at 80 mins (1cm & 3cm)







Mechanical properties and force output of quadriceps muscle following eccentric exercise

Paul Kennedy¹, Lewis MacGregor², Eric Barnhill¹, A Cooper¹, L Hiscox¹, Colin Brown³, Jürgen Braun⁴, Ingolf Sack⁴, Edwin van Beek¹, Angus Hunter², Curtis L. Johnson⁵, Neil Roberts¹

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 plasma¹. 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 peak². 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 described³

Results

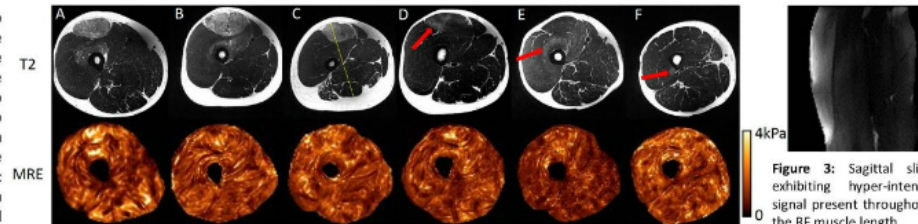


Figure 2: T2 weighted and magnitude stiffness elastograms of a selection of subjects who displayed oedema (A-F). The yellow line through image C depicts the plane through which a sagittal scan was prescribed (Figure 3).

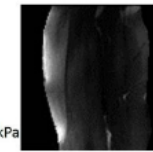


Figure 3: Sagittal slice exhibiting hyper-intense signal present throughout the RF muscle length.

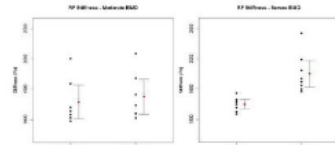


Figure 4 (above): RF stiffness measurements before and 48 hours after damage.

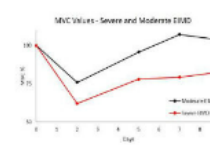


Figure 5 (above): MVC time course of moderate and severe EIMD groups

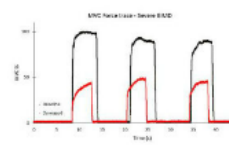


Figure 6 (above): MVC force trace at moderate and severe EIMD groups.

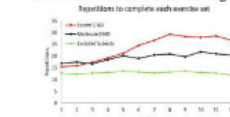


Figure 7 (above): Reps required to complete each set of the eccentric exercise protocol.

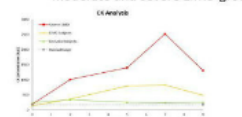


Figure 8 (above): CK concentration time course. Concentration peaks 7 days post exercise.

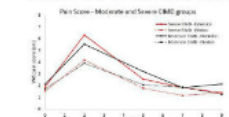


Figure 9 (above): Reps required to complete each set of the eccentric exercise protocol.

- 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 disease⁴, however our results suggest the main effect may be missed if the RF is not investigated.

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

P Kennedy¹, L MacGregor², E Barnhill¹, A Cooper¹, L Hiscox¹, C Brown³, J Braun⁴, I Sack⁴, E van Beek¹, A Hunter², CL Johnson⁵, N Roberts¹

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

IOP PUBLISHING

Physiol. Meas. **34** (2013) 1675–1698

PHYSIOLOGICAL MEASUREMENT

[doi:10.1088/0967-3334/34/12/1675](https://doi.org/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 Barnhill¹, Paul Kennedy¹, Steven Hammer², Edwin J R van Beek¹, Colin Brown³ and Neil Roberts¹

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-called

NOT involved in discovering new chemical entities

NOT involved in exotic formulations or novel modes of action



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

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



YES WE GET UP EACH DAY

Consumer Healthcare makes a difference
to peoples' lives

These products enhance the quality of life



to peoples' lives

These products enhance the quality of life
of those in pain

Consumers can feel better, be



Consumers can feel better, be independent and lead normal lives



Making a Difference

.....by improving quality of life

.....improving product quality

.....by developing next generation products

.....by embracing novel technologies

.....by improving patient compliance

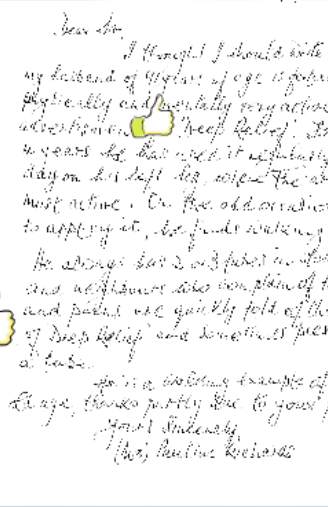

Testimonials

"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!"


SUMMIT




Dear Sir,
I thought I should write
my husband of 44 years, age 75, is
physically and mentally very active
adventurous. He's had 'Deep Relief' for
4 years he has used it regularly
day on his left leg, when he
must active. On the odd occasion
to apply it, he finds walking
he doesn't get a bit stiff in the
and pain is quickly felt off the
of 'Deep Relief' and sometimes 'free'
a base.
He is a walking example of
80 yrs, thanks partly due to your
'Deep Relief'
Yours faithfully
Mrs Pauline Richards

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 advertisement  '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



014 3AM

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-ENOVA 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 be fore. I have
been telling my friends about
it. HOPE this helps you
to know the product
is very good. THANKS
FOR MAKING REG-ENOVA
YOUR SINCERELY
HAZEL BARKER

Developing Medicines.....really *is* about....

Helping People to Get Well, Feel Well and Stay Well



Thank you for listening!

do be fore. I HAVE
DEAR MY FRIENDS
HELPING ME
IT. HOPE THIS HELPS YOU
TO KNOW THE PRODUCT
IS VERY GOOD. THANKS
FOR MAKING REGENOURT
YOUR SINCERELY
JILL BARKER

Cefin Brown BSc (Hons) CSci CChem MRSC
Director of Research & Quality Development
The Mentholatum Company Limited

