

How Fruitflow[®] achieved health claims approval

31st March 2011, Natural Antioxidants Conference, Amsterdam



Steve Morrison, Chief Operating Officer

Fruitflow[®] - Water Soluble Tomato Concentrate

- A natural tomato extract which benefits blood flow & cardiovascular health
- The first ingredient to receive scientific substantiation for a health claim from the European Food Safety Agency in 2009 under Article 13(5) of European Regulation (No: 1924/2006) which covers emerging areas of science
- Approval of pan-European claim wording agreed with the European Commission
 - “Fruitflow (water-soluble tomato concentrate) helps maintain normal platelet aggregation, which contributes to healthy blood flow”
- Approved for use in beverages, dairy drinks and dietary supplements



Fruitflow - Background

- Original research conducted by Professor Asim Duttaroy (Rowett Research Institute, Aberdeen, UK)*
 - cardioprotective properties of “mediterranean diet” high in fruit & vegetables
 - screened 17 fruit extracts to evaluate effects on platelet aggregation and found tomato was most effective inhibitor of aggregation
- Fruitflow[®] - Water Soluble Tomato Concentrate (WSTC)
 - a lycopene & fat free extract from ripe tomatoes containing >30 bioactive (anti-platelet) compounds including a number of known anti-oxidants e.g. polyphenols
 - established health benefit - reduces platelet aggregation (improves blood flow)
 - target population: healthy adults aged 35-70 years who commonly display biomarkers of increased cardiovascular risk and are interested in maintenance of cardiovascular health

* Published in Platelets (2001) 12, 218-227

Health Claims – The need to prove your claim

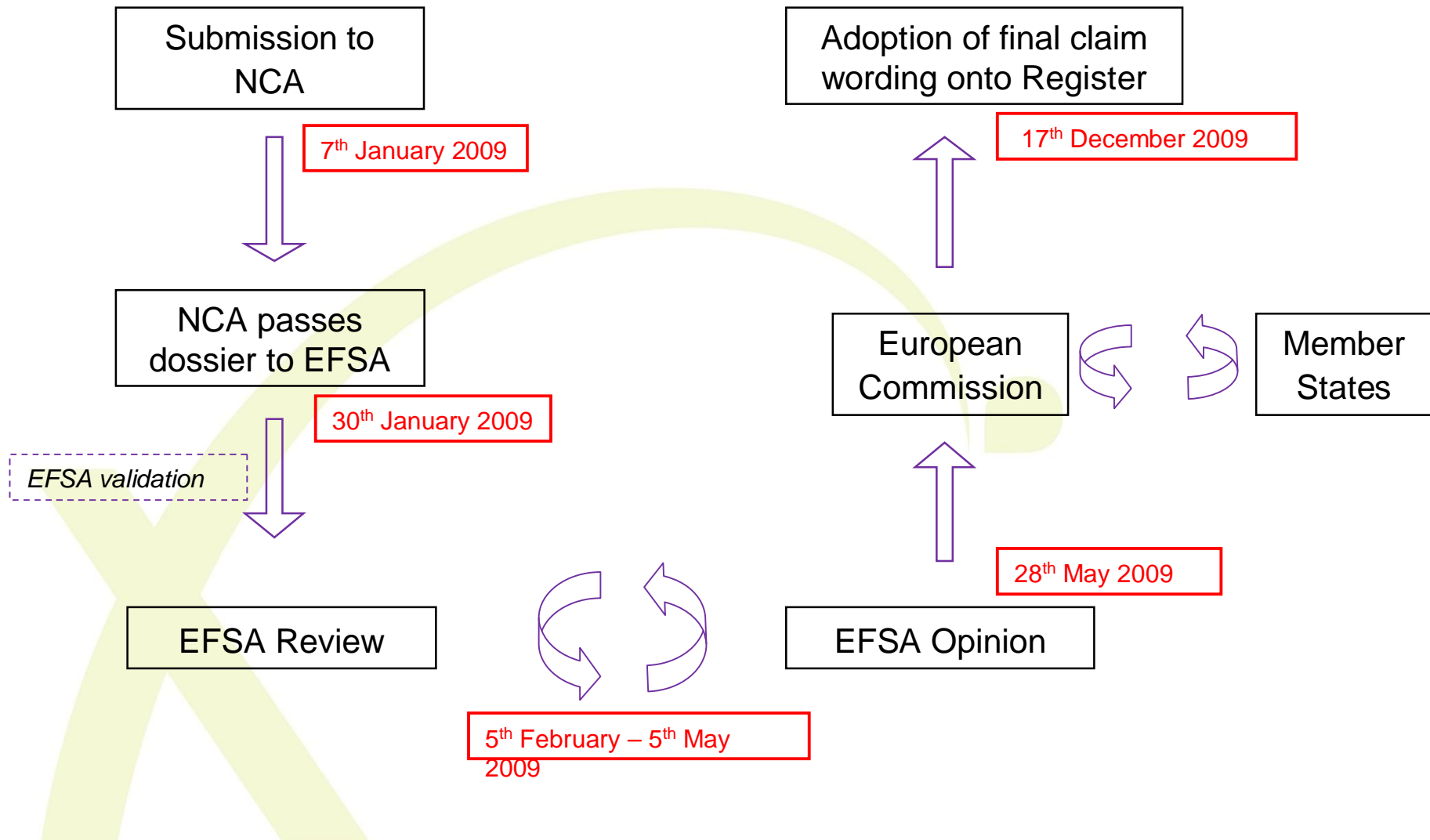
- 16th February 2011 - EFSA published a negative opinion on a health claim related to water and reduced risk of development of dehydration”.
- Does anybody really doubt that consumption of water reduces the risk of dehydration?
- This case highlights the importance of understanding the legislation and the process for obtaining a health claim through EFSA.
 - dehydration was identified as the disease by the applicant
 - “water loss in tissues” or “reduced water content in tissues” were identified as risk factors by applicant but seen as measures of disease by EFSA
 - Article 14 - “significantly reduces a risk factor in the development of a human disease”.

Fruitflow Background (Health Claim)

- Article 13(5) health claim substantiated - EC Regulation 1924/2006
 - “....newly developed scientific evidence and/or which include a request for the protection of proprietary data....”
 - May 2009 – first product to obtain a positive EFSA opinion under Article 13(5)
 - Dec 2009 – European Commission authorised claim wording “helps maintain normal platelet aggregation which contributes to healthy blood flow”
- Article 13(5) outcomes to date

Article 13(5) – Health Claims	
Number of applications submitted to EFSA	47
Number of applications withdrawn	12
Number of scientific opinions issued by EFSA	27
Number of positive opinions	2

Fruitflow - Health Claim Review Timelines



Article 13(5) – Opinions to date

- The words becoming far too familiar to all applicants.....
 - “The Panel concludes that a cause and effect relationship has not been established between the consumption of.....”
- The clues to what we believe we did correctly with Fruitflow can be seen in the reasons for negative opinions
 - insufficient human clinical data
 - inconsistent trial results or unreliable outcome measures
 - insufficient characterisation of final product
 - studies not conducted using final product form/conditions of use
 - EFSA did not agree beneficial to human health

Adequacy of human trial data

- Fruitflow dossier - 8 pertinent human studies (7 proprietary)
 - no pre-established formula as to how many and what type of studies are needed to substantiate a claim”. – EFSA 2009 FAQ’s
 - studies should be organised according to hierarchy: randomised controlled (RC), randomised non-controlled (RN), controlled non-randomised, other studies
 - “The Panel considers that both the selection of subjects and the method used to assess platelet aggregation were appropriate for such studies”.
 - “These human studies consistently show a reduction in platelet aggregation following consumption of WSTC under the conditions of use proposed by the applicant”

Trial	Primary Purpose	N=	Control	Target Population	Proposed conditions of use
#1	Acute effect	27	RCT	Yes	Yes
#2	Acute effect	93	RCT	Yes	Yes
#3	Chronic effect	22	RCT	Yes	Yes
#4	2 Formats	45	RCT	Yes	Yes
#5	Over-consumption	22	RCT	Yes	No
#6	Acute effect	15	RN	Yes	Yes
#7	2 Formats	9	RCT	Yes	Yes
#8	Chronic effect	20	RCT	No	No

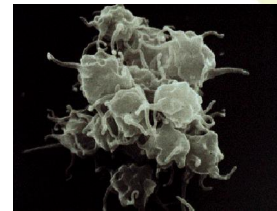
Consistent results with reliable outcome measures

- Mechanisms of platelet activation and aggregation
- Platelet aggregation involves a reversible activation phase followed by an irreversible aggregation stage
- Multiple primary and secondary mediators must be targeted to keep platelets in a resting or 'smooth' state



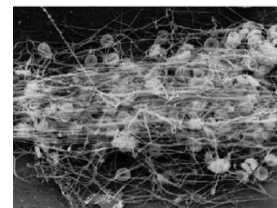
Primary aggregation mediators

Calcium
Fibrinogen
Adenosine diphosphate (ADP)



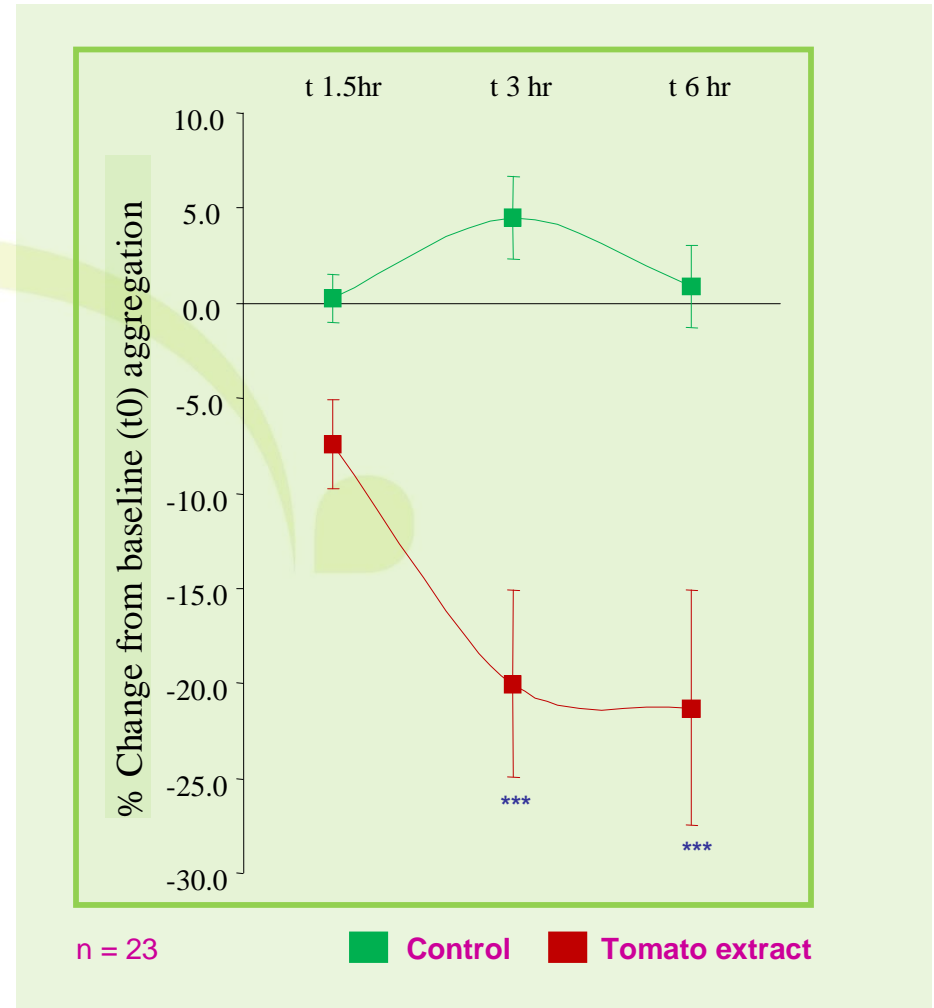
Secondary aggregation mediators

Epinephrine
Factor X cascade products
Eicosanoids e.g. thromboxane A2
Thrombin
Collagen
Serotonin
Platelet activating factor (PAF)



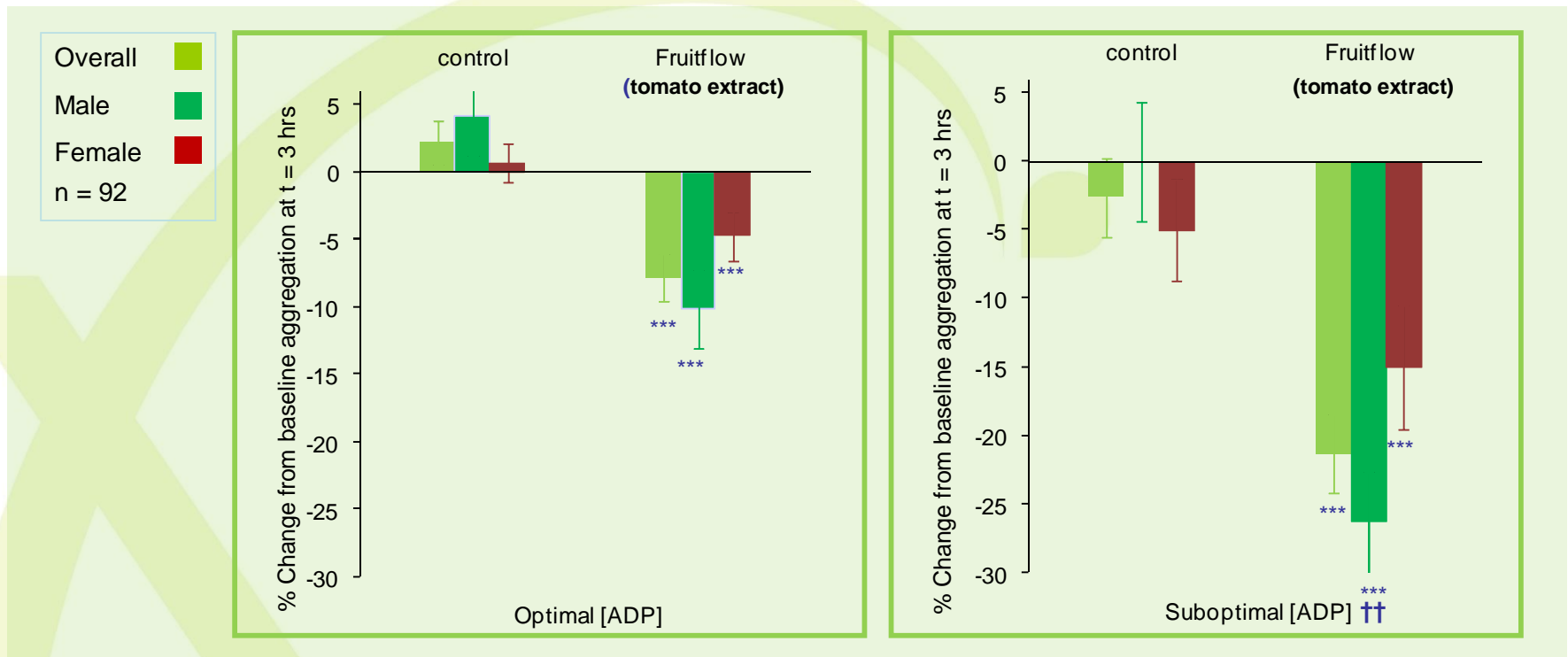
Onset and duration of *in vivo* antiplatelet effect

- Onset of antiplatelet effect seen within 3 hours after ingestion – measured as a significant difference from baseline platelet function
- Duration of effect variable: after 18 hours platelet function returned to baseline in all subjects



In vitro anti-platelet activity translates to ex vivo anti-platelet efficacy

- At suboptimal ADP levels, Fruitflow produced an average 21% decrease in platelet aggregation (men responded more than women)
- At optimal levels of ADP, the effects of Fruitflow can be overcome – for example when a physiological response to injury is needed

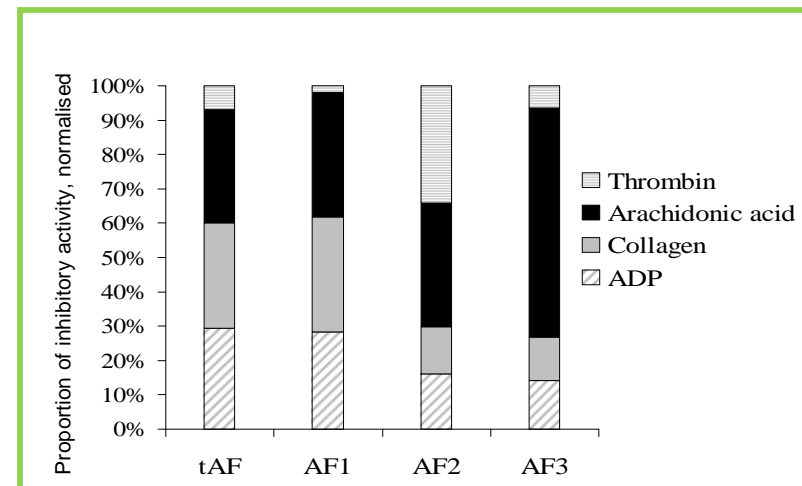
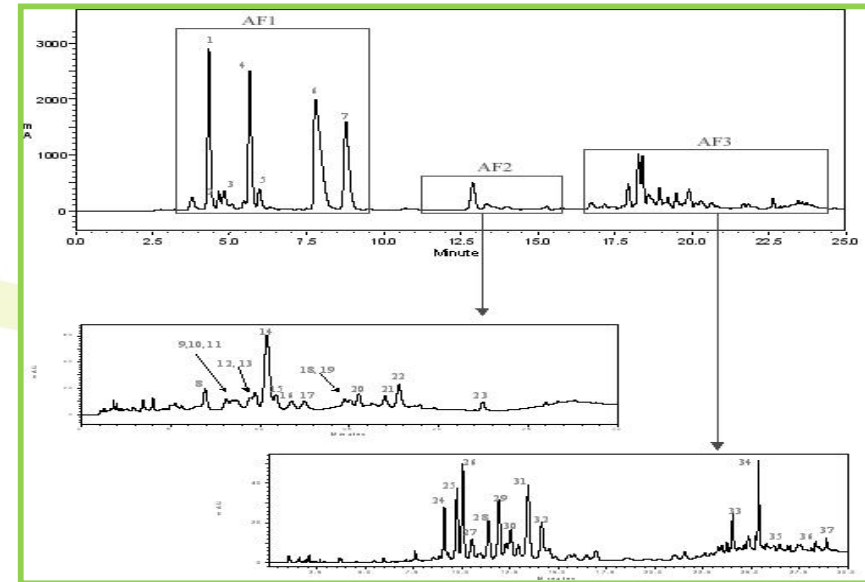


Tomato antiplatelet compounds

Tomato antiplatelet components (total active fraction, tAF) have been isolated and characterised

tAF components can be separated into distinct bioactive subfractions, AF1, AF2 and AF3

The three subfractions contain different types of compound and exhibit different modes of action in vitro



Steps 1 & 2 – Submission to National Competent Authority & EFSA validation

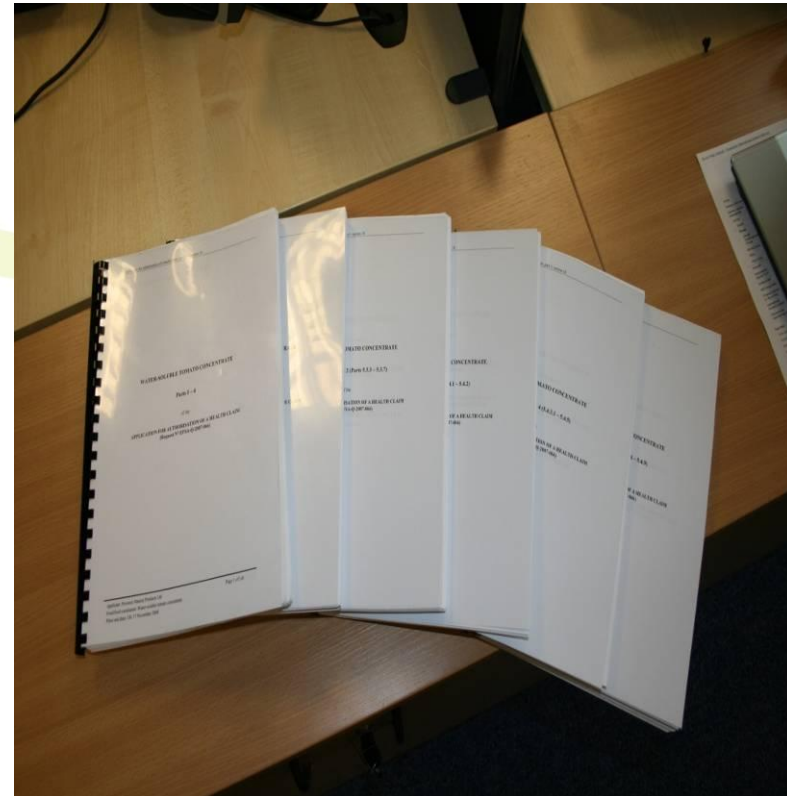
- NCA's primary role at this stage is a simple one
 - conduct an “admissibility check” – EFSA FAQ's
- Advice on structure & formatting received within 2 weeks of receipt
 - claim wording (single health benefit or single health claim?)
 - making changes doesn't mean need to re-submit full dossier !
- Fundamental issue related to proprietary/confidential information.
 - published studies cannot be considered confidential but scientific data presented by applicant should be treated as confidential.
 - EFSA discloses only what is absolutely necessary about the composition of the product for the opinion to be understood.
 - EFSA may have to disclose details on the research studies submitted as confidential if pertinent to the claim.

Step 3/4 – EFSA review & European Commission validation

- Questions within 2 months and were a good early indicator of whether dossier is sufficiently detailed & appropriately formatted
 - EFSA communication by e-mail (followed up by letter) and responses requested in both electronic & hard copy
 - Questions on individual clinical trials, correlation of in-vitro/ex-vivo results to in vivo situation, magnitude of observed effect versus health benefit
- Publication EFSA Opinion
 - Following a positive EFSA opinion, the Commission takes a decision with regard to inclusion of Article 13(5) claims on permitted list.
 - Commission decision should take into consideration EFSA's opinion, relevant provisions community law and other legitimate factors relevant to the matter. Decision should be taken within 2 months !
- 2 key issues in following discussions
 - Need for consumer understanding in final claim wording
 - 5 year proprietary data protection

Fruitflow Experience - Summary

- Follow all the available guidance documents closely
- Understand the process & roles of NCA, EFSA, European Commission and the applicant
- Critically review all the available literature & your own data
 - Make the process you follow transparent in your application
- Make sure your clinical data package is adequate
 - Health benefit & claim must be driven from this data
- Communicate actively with NCA, EFSA & Commission





Fruitflow[®]

a new hero in DSM's ingredient portfolio

Dr Theodor Graser, VP Marketing HNH EMEA

March 2011



Double Gold for Fruitflow® at HIE 2010: Heart Health AND Most Innovative Ingredient



“Chosen by the judges for the overall excellence of its entry, which encompassed in-depth consumer insights, ground breaking science, clear positioning and the potential for manufacturers to address a significant and real global health issue”

Henry Dixon,
Chairman of the Judges





Fruitflow®

- The first natural, scientifically substantiated solution for healthy blood flow - globally marketed by DSM
- The first ingredient with an EFSA Art. 13(5) health claim
- Effective in 97% of people; works within 1.5 hours and keeps working for up to 18 hours





Composition

- Fruitflow® is a water-soluble tomato concentrate available in two forms:
 - Fruitflow® I (water soluble syrup; 3g per dose; available now)
 - Fruitflow® II (powder format; 150mg per dose; available late 2011)
- Produced from tomato using a patented process, which is fully compliant with Food technology processes
- Chemical specifications of the constituents are provided and batch to batch reproducibility has been demonstrated.
- Fruitflow® contains 37 bioactive constituents, all of which have been shown to contribute to the platelet activity



Fruitflow® Applications

- FF1 (syrup): 3g per serving.
 - Fruit juices and fruit shots
 - Yoghurts and other dairy applications
 - Non-clear water based beverages
 - Certain food applications
- FF2 (powder): 150mg. Available in end 2011
 - Supplements (tablets, capsules etc)
- Minimal taste and colour impact - maskable in application





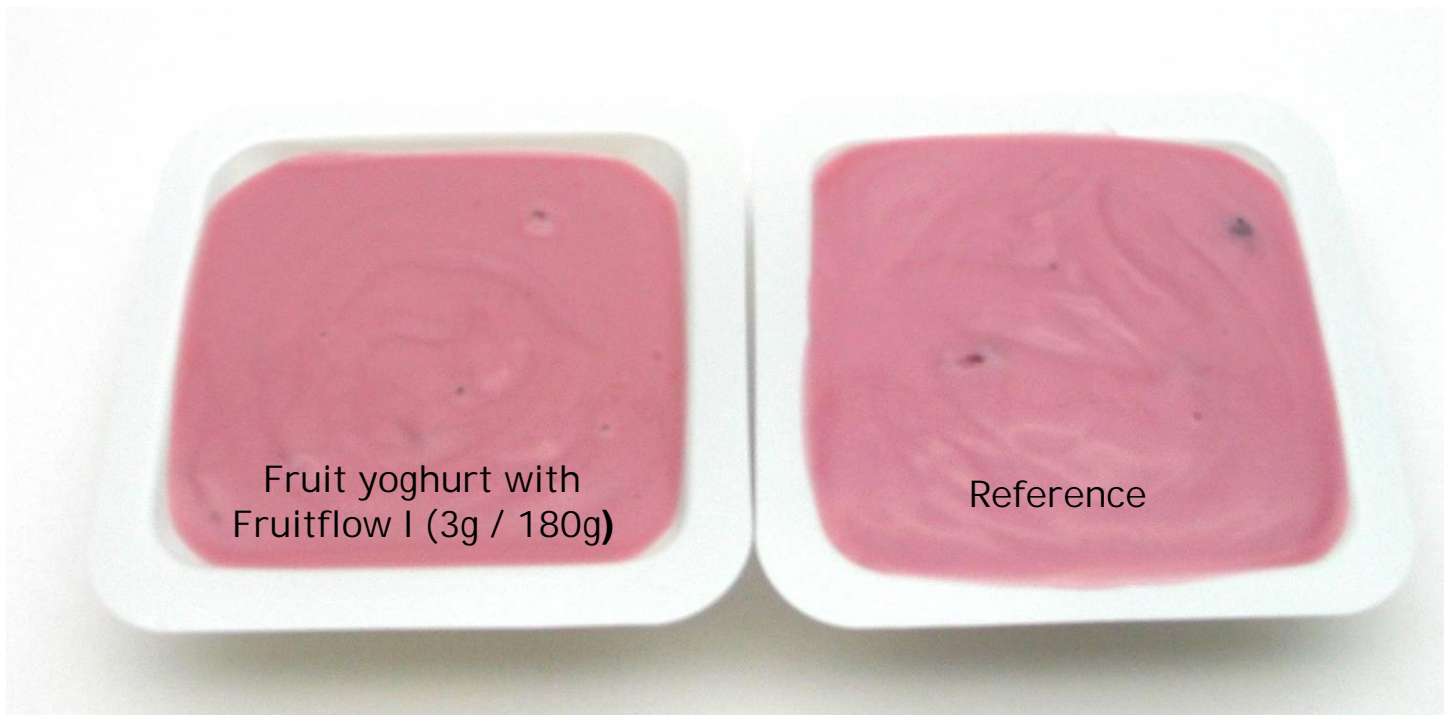
Fruitflow Application Testing

- Sensory evaluation by a trained taste panel of Fruitflow prototype compared to a reference using an interval scale
- Interval scale with 7 intervals (1 = not detectable to 7 = extremely intense)
- Attributes:
 - Odor: musty / earthy, tomato / vegetable, fruity, off-odor
 - Taste: tomato / vegetable, musty / earthy, condimental, sweet, fruity, off-taste
- Stability test:

Application	Stability test
Yoghurt	Initial, 2 weeks
Fruit Smoothie	Initial, 2, 4, 8 weeks
Juice Beverage	Initial, 1, 2, 3, 6 months

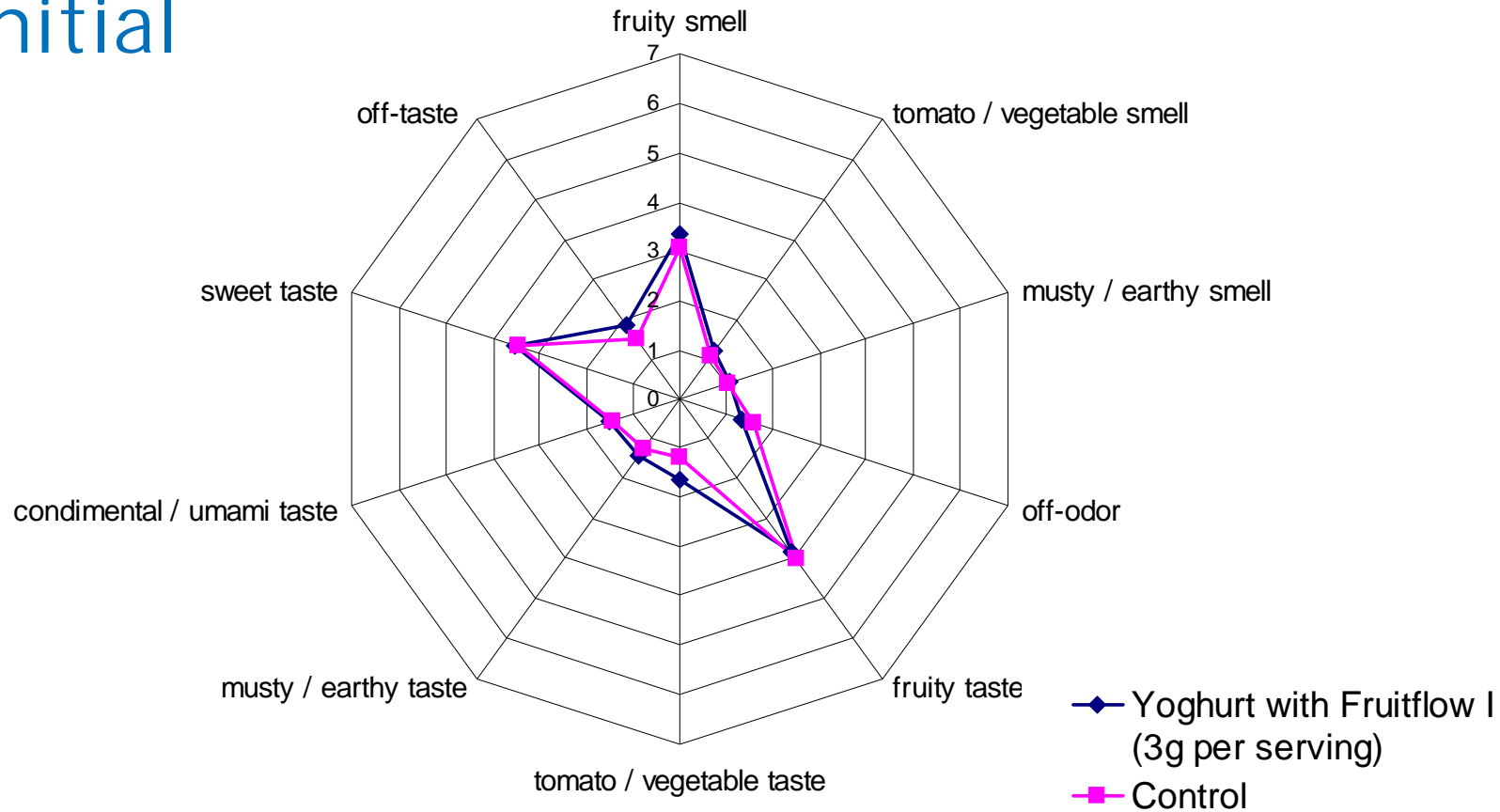


Fruitflow I in Spoonable Fruit Yoghurt



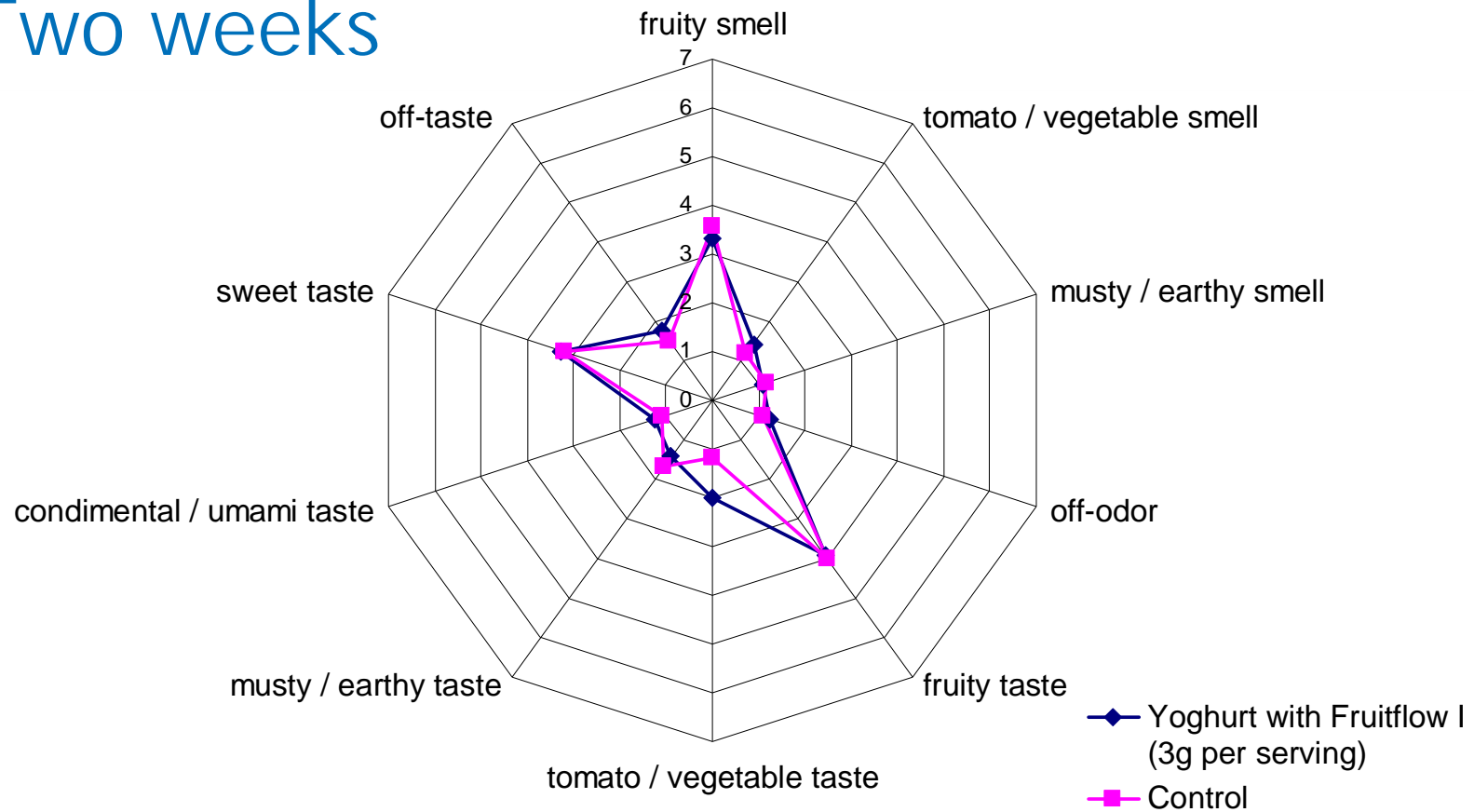


Fruitflow I in Spoonable Fruit Yoghurt - Initial





Fruitflow I in Spoonable Fruit Yoghurt - Two weeks





Communicating the Message to Consumers

- “Helps to maintain normal platelet aggregation, which contributes to healthy blood flow”
- Interpretation and purpose of the regulation is critical to translating the message into consumer language
- Getting the balance right:
 - “Platelet aggregation”: too complex and medical
 - “Healthy heart”: too generic and unconvincing
 - Clear focus on consumers with a genuine *need* for solutions to support healthy blood flow

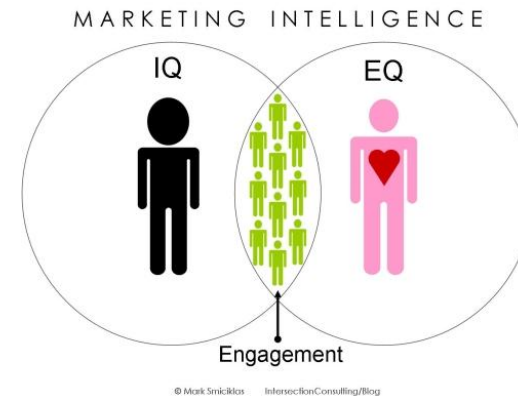


Communication Strategy

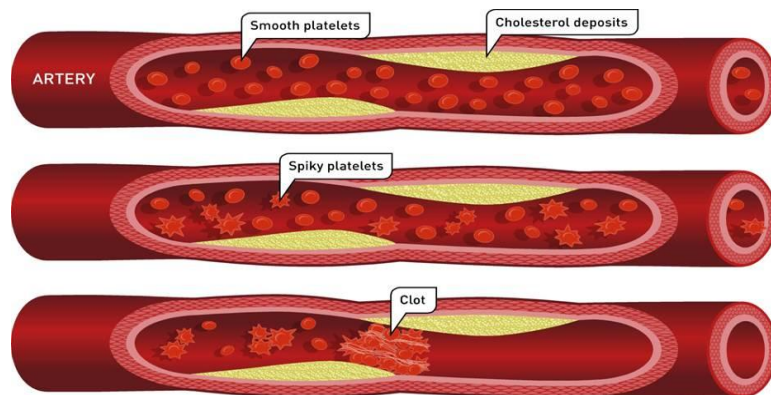
1. Building a Bridge to Existing Awareness



2. The Emotional Connection



3. Show it!



Fruitflow® works by keeping the blood platelets smooth, which allows them to flow more smoothly in the blood vessels.

Platelets can become “spiky” i.e. more prone to clotting due to a variety of factors such as stress, being overweight and high cholesterol.

Fruitflow® can therefore help to maintain healthy blood flow to prevent a critical or life threatening blood clot.



1. Building a Bridge to Existing Awareness

Cholesterol Management - One side of the Coin

- Consumers understand the need to manage their cholesterol levels
- Consumers and health care professionals are aware that sterols and stanols can help manage cholesterol levels
- BUT - cholesterol is only one side of the coin: the Next Generation in Cardiovascular Health is Blood Circulation





Awareness

The Natural Alternative for Healthy Blood Flow

The Daily Telegraph
Daily Mail

Fruitflow® is a “good natural alternative to low dose aspirin”

December 2009

Fruitflow® “works like aspirin”

November 2009

- Millions of people around the world take anticoagulant drugs daily to “thin the blood”
- However, such products have side effects such as stomach ulcers and bleeding
- Fruitflow® is the natural alternative without side effects



1. Building a Bridge to Existing Awareness

Deep Vein Thrombosis

- More consumers are concerned about DVT than stroke
- Substantial consumer education in place
- Perfect platform to highlight the importance of blood flow



Deep Vein Thrombosis

Reading this on the plane?
Get up.

Reading this at your desk?
GET UP.

When restless legs
can save your life.

SMART ADVICE

Don't strain your veins

Trips of more than four hours increase the risk of a deep vein thrombosis – a potentially fatal clot. Here's how to reduce that risk.

Before you fly...
Certain conditions can put you at higher risk of a DVT, so see your doctor if any of the following apply to you:

- You have or have had cancer.
- There's a family history of clotting problems.
- You've had major surgery in the past three months.
- You're pregnant – changes in hormones can make blood clot more easily.

First, put a pair of elasticated compression stockings on, a couple of hours beforehand. You can get these from pharmacies and they help prevent blood 'pooling' in the legs.

During the flight...
Keep legs uncrossed and bend legs, feet and toes every half-an-hour

when seated. Every so often, press the balls of your feet hard against the floor. Finally, walk up and down the aisle every half-an-hour.

Cabin air dehydrates, so drink plenty of water (your urine should be no darker than pale yellow) and keep alcohol to a minimum.

Sleeping pills slow circulation and obviously keep you seat-bound, so avoid.

After you land...
Don't just jump in a cab or a hire car – have a walk around to get your circulation going.

If you develop a swollen, painful calf or breathing difficulties shortly after a long trip, see a doctor. But slight puffiness of the feet and ankles without any pain is common and NOT symptomatic of a DVT.

3 PRODUCTS TO LOWER THE RISK

Activa Unisex Sock, £11, (www.activahealthcare.co.uk)
Wear them the whole day of your flight to prevent a DVT.

Sirco Heart Health Fruit Juice, £1.99, Holland & Barrett
Approved by the European Food Safety Authority, even a glass helps to boost circulation.

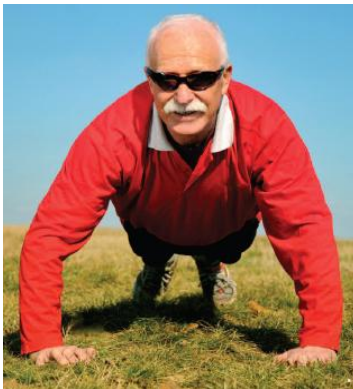
Ginkgo Biloba, 120 tablets, £24.55, Holland & Barrett
These contain antioxidants, which help to improve blood flow.

2. The Emotional Connection

What Does Circulation Mean to Consumers?

- “Physical benefit” is clear: Maintaining healthy circulation to prevent unwanted blood clots, but what are the emotional connotations?

Energy and vitality:
“Keeping the blood flowing to
keep you going”



Less coldness in
hands and feet



Better blood flow
= better health





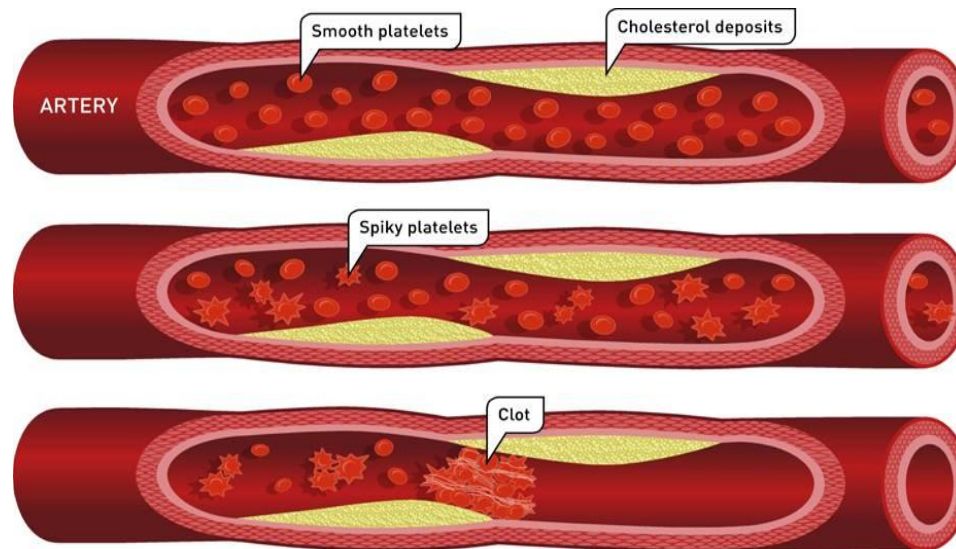
3. Show the Benefits *Visuals and Animations*

Smooth Platelets

'Spiky' Platelets

Blood clot

Platelet aggregation involves a reversible **activation** phase followed by an irreversible **aggregation** stage



Fruitflow® works by keeping the blood platelets smooth, which allows them to flow more smoothly in the blood vessels.

Platelets can become "spiky" i.e. more prone to clotting due to a variety of factors such as stress, being overweight and high cholesterol.

Fruitflow® can therefore help to maintain healthy blood flow to prevent a critical or life threatening blood clot.





Concepts: Travel Shot, Daily Heart Health Drink & Combination with Plant Sterols / Stanol Esters

TRAVEL SHOT

- Great tasting 100ml fruit or dairy shot with 3g Fruitflow®
- "The first natural solution to the health risks of travel related stress and inactivity"
- More people are concerned about DVT than stroke; 71% vs. 58% (2006 Survey)



DAILY HEART HEALTH DRINK

- 250ml fruit or dairy drink with 3g Fruitflow®
- "Daily support for healthy blood flow in a tasty, convenient format"
- Leverages familiarity with shots as a delivery device for functionality & health



COMBINATION WITH PLANT STEROLS / STANOL ESTERS

- Cholesterol is only a part of the story for a healthy cardiovascular system...
- "The next generation in cardiovascular health; reduces cholesterol AND contributes to healthy blood flow"
- Provides differentiation for existing brands and a means of entry for new players



Summary

- Fruitflow is the first natural, scientifically substantiated solution for healthy blood flow
- It is protected by patents, the first and only *proprietary* health claim and various trade secrets
- It offers a new opportunity in the highly consumer-relevant field of heart health; the NEXT GENERATION IN HEART HEALTH
- It is suitable for a number of food, beverage and supplement applications to offer consumers a convenient, appealing solution to maintaining healthy blood flow



BRIGHT SCIENCE. BRIGHTER LIVING.™

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