Practical Considerations in the scale up and manufacture of Antioxidant UHMWPE made by blending the α-tocopherol version of Vitamin E

Lou Matrisciano, P.E. 14/09/2007
MediTECH Medical Polymers
Division of Quadrant EPP
Fort Wayne, Indiana USA

MediTECH MEDICAL POLYMERS

Key points for the conversion of UHMWPE with Alpha Tocopherol

- Relatively small doses required to be effective as an anti-oxidant.
- Higher doses, above approximately 1500ppm, have effects on color, properties and the cross-linking receptivity of UHMWPE.
- Vitamin E appears to offer new streamlined concepts for cross-linking material.
- An Alpha-Tocopherol Supplier specified by the implant manufacturer as not all suppliers are willing to support this application for their product.

MediTECH
MEDICAL POLYMERS

Key points for the conversion of UHMWPE with Alpha Tocopherol

- A lot of work has yet to be done to take this process from the laboratory to the manufacturing floor. The path may be able to be shortened by the application of perspectives to be highlighted in this presentation.
- While the focus of this presentation is on Vitamin E, the concepts and suggested paths can be applied with appropriate modification to other potential antioxidants.

MediTECH MEDICAL POLYMERS

Creating the Specification: Key Elements

- Resin Type, Fabricated Form, and properties thereof as standardized by both ASTM and ISO standards.
- Vitamin E brand, specification, dose, measurement method and tolerance
- Blending protocol, whether pre-blended, left to MediTECH or customer specified.
- Standard (same as conventional) certification requirements.
- Other testing parameters and results expected as validated in preliminary characterization relating to the blend and any subsequent processing.

MediTECH
MEDICAL POLYMERS

Creating the Specification; continued

- Any non-standard annealing specification.
- Cross-linking specification, dose, and tolerance.
- Post-radiation Annealing parameters
  - While it is understood that with the benefits of Alpha-tocopherol this may not be a requirement for free radical protection, it may still be desired to achieve other mechanical properties depending upon the overall specification.
- Final Fabrication
  - Material Removal on all surfaces, final shape
  - Yield Optimization will be done by MediTECH
- Final Storage, Packaging, and Shipping

MediTECH®
MEDICAL POLYMERS

Selection of base resin, fabrication method, and α-tocopherol dose

- Typical Characterization Protocol:
- Compression Molded or Ram Extruded
- Affects the certification and QA control plans because of batch size and logistics of production.
- Potential complexities of multiple doses, brands, types of anti-oxidant and fabrication type.

Example Protocol for Alpha Tocopherol Characterization

Trial Piece	Resin	E-dose	Purpose	Post-Consolidation Anneal	Gamma Dose, kGy	Post-radiation anneal	Testing Requirements					
1	1020	Virgin	Conventional Control	MediTECH Standard	0	customer spec	Visual	Phys / Mech	XL Density	ESR	Oxidation Index	Aging
2	1020	Virgin	Control	MediTECH Standard	A	customer spec	Visual	Phys / Mech	XL Density	ESR	Oxidation Index	Aging
3	1020	Virgin	Control	MediTECH Standard	B	customer spec	Visual	Phys / Mech	D			

MediTECH®
MEDICAL POLYMERS

Batch size considerations:

Affect of batch Size on tolerancing						
E' Dose	kg resin	kg 'E'	gm 'E'	ppt 'E'	Resin accuracy requirement +/-Kg	E' accuracy +/-gm
500 ppm	1000	0.500250	500.25	500.00	52.00	25.0
500 ppm	900	0.450225	450.23	500.00	47.00	22.5
500 ppm	800	0.400200	400.20	500.00	42.00	20.0
500 ppm	700	0.350175	350.18	500.00	36.00	17.5
500 ppm	600	0.300150	300.15	500.00	31.00	15.0
500 ppm	500	0.250125	250.13	500.00	26.00	12.5
500 ppm	400	0.200100	200.10	500.00	21.00	10.0
500 ppm	300	0.150075	150.08	500.00	15.00	7.5
500 ppm	200	0.100050	100.05	500.00	10.00	5.0
500 ppm	100	0.050025	50.03	500.00	5.00	2.5
500ppm	75	0.037519	37.52	500.00	3.75	1.9
500ppm	1003.75	0.498370	498.37	496.26	3.75	1.9
500ppm	996.25	0.502130	502.13	503.77	3.75	1.9

•Comments: Large batch sizes are conducive to tighter tolerances, assuming the inherent as yet unmeasured process repeatability is +/-5%, a good starting point for a dose range specification would be 450ppm to 550ppm,
which equates to +/- 10%, until we have more confidence in the measurement techniques.

MediTECH®
MEDICAL POLYMERS

Selection and Storage of the α Tocopherol

- Selection of the α-Tocopherol 'Brand.'
  - Availability letter from the supplier for its intended use.
  - Shelf life and storage recommendations from the supplier
  - What we've found:
    - Minimize exposure to Oxygen: Sealed containment
    - Minimize exposure to Heat: Ambient storage except during processing.
    - Minimize exposure to Light: Stored in Light-proof containment
    - Compliance with these measures insures a shelf life of 1 year
    - Purchasing logistics and volumes will determine actual scenarios and affect price.

MediTECH MEDICAL POLYMERS

Blending the α-Tocopherol

- Among the basic options which exist:
  - Pre-blend by Ticona by proprietary method.
  - Blend at MediTECH by proprietary method.
  - Blend at MediTECH by proprietary customer specified and jointly developed method.
- What we've done so far:

MediTECH
MEDICAL POLYMERS

Blending the α-Tocopherol in production scale sheets:

- In multiple presses (Vreden Germany and Fort Wayne, Indiana) by standard processing methods.
- Using pre-blended resin from Ticona at 500ppm
- Blended at 500ppm from direct blending the α-tocopherol and GUR 1020.
- Blended at 500ppm and 750ppm utilizing a 1% α-tocopherol master batch produced by Ticona.

MediTECH®
MEDICAL POLYMERS

Examples: Sheet from resin blended by Ticona at 500ppm α-tocopherol.

MediTECH®
MEDICAL POLYMERS

Examples: Sheet pressed from resin direct blended by MediTECH with α-tocopherol @ 500ppm

MediTECH
MEDICAL POLYMERS

Blending the α Tocopherol

- Consolidate full sheets by direct blending α-tocopherol with GUR 1020 by means of 3 styles of blending equipment and varying processes within each.

- Consolidate material 150mm x 75mm x 45mm blended at 500, 750, 1000, 1500, 2000, 2500, 3000ppm utilizing a 1% master batch produced by Ticona.

- Consolidate material 150mm x 75mm x 45mm blended at 500, 750, 1000, 1500, 2000, 2500, 3000ppm from direct blending α tocopherol and GUR 1020.

MediTECH®
MEDICAL POLYMERS

Examples:

MediTECH
MEDICAL POLYMERS

Examples:

MediTECH
MEDICAL POLYMERS

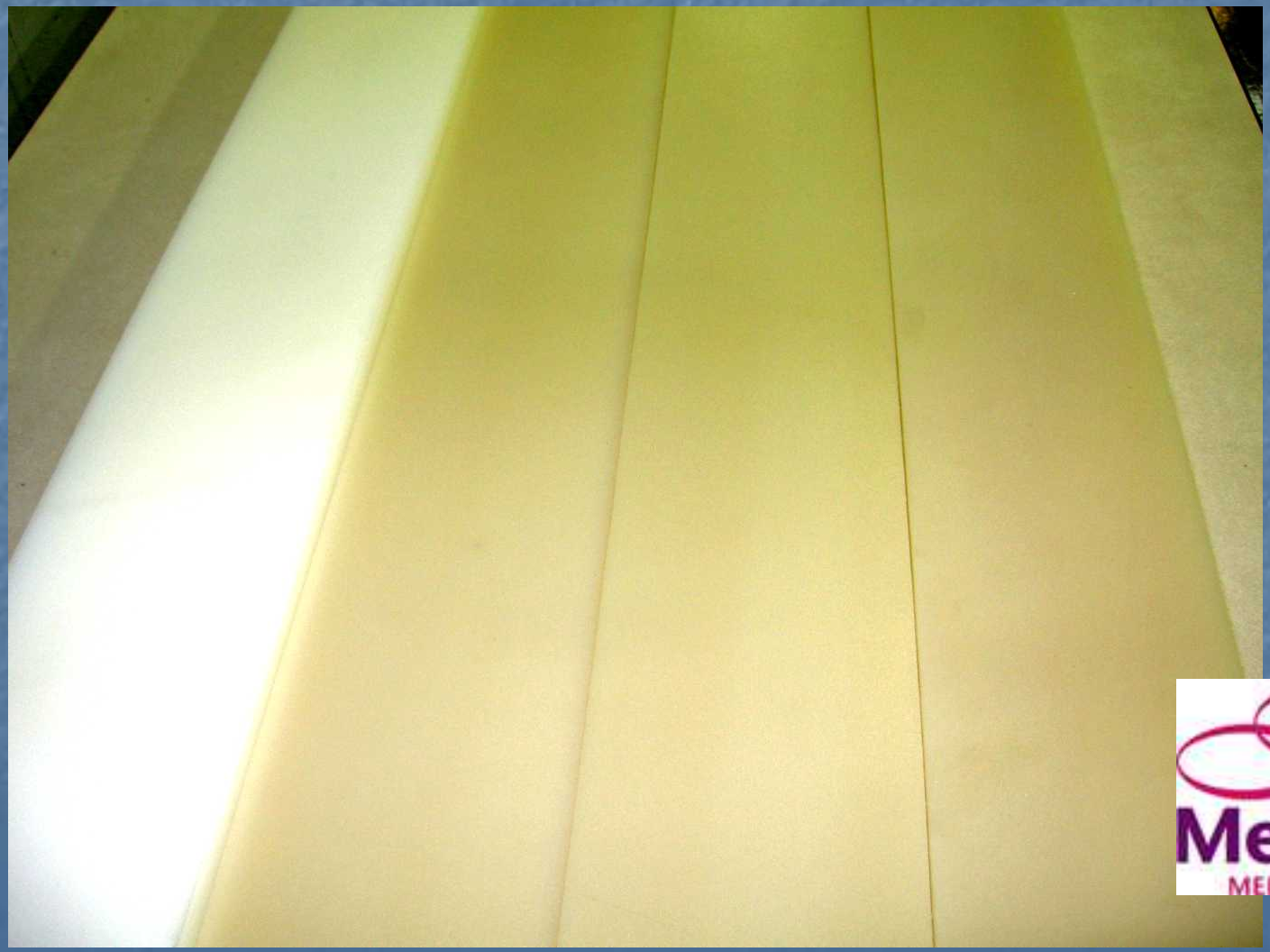
Examples:

Virgin

500ppm From Master batch

750ppm From Master batch

500ppm direct blend



MediTECH
MEDICAL POLYMERS

Current position on Blending methods:

- There are multiple methods by which α-tocopherol can be adequately dispersed within UHMWPE resin. Some are superior to others, and all that we have attempted can work providing adequate trialing is done in the name of process optimization.

- Ongoing work: What effect does the storage of α-tocopherol blended UHMWPE resin have on the outcomes of color, dispersion uniformity, and oxidation resistance?

MediTECH®
MEDICAL POLYMERS

Transporting / Storing Blended Resin

- Pharmaceutical Grade Equipment
- Dedicated lines to minimize cleaning requirements
- Virtually closed system
- Nitrogen Blanket
- Storage for Blended Resin before use
- Final pre-consolidation homogenization

MediTECH®
MEDICAL POLYMERS

Consolidating the Blended Resin

- MediTECH has tried multiple consolidation recipes for the material containing α-tocopherol.
  - As is the case with virgin material, properties can be manipulated
  - All validated processes worked acceptably
  - The α-tocopherol is more sensitive to higher heats and residence times in the press and the evidence is color.
  - There are inherent differences in residence times due to material thickness.
  - No major difficulties are foreseen here, only optimization opportunities before and during validation efforts.

MediTECH®
MEDICAL POLYMERS

Annealing of the consolidated material

- Standard annealing methods have worked well for this material

- Annealing the material reduces the color intensity.

- Annealed and extensively cross-linked material in the 500ppm to 1000ppm range has color that is not so different from virgin cross-linked material. Is this a sign of α-tocopherol interaction with free-radicals,
or otherwise consumption of the α-tocopherol?

MediTECH®
MEDICAL POLYMERS

Cross-Linking of consolidated material

- Can be done in exactly the same way as is currently practiced for non-blended UHMWPE, with a potential factor applied if the α-tocopherol dose is high.

- Material removal of materials for all stock shapes has historically been in the range of a minimum 3mm per surface. This practice could be re-evaluated with respect to Oxidation Protection.

MediTECH®
MEDICAL POLYMERS

Post-radiation annealing of consolidated material

- Up to the device manufacturer to determine IF and WHAT
- While free radicals may not be the issue, there is still a further increase in crystallinity and increased uniformity of tensile and impact properties that may be beneficial.
- With nitrogen annealing in conventional material before, we still removed material afterward.
- Is it still of value now with α-tocopherol blended material?

MediTECH®
MEDICAL POLYMERS

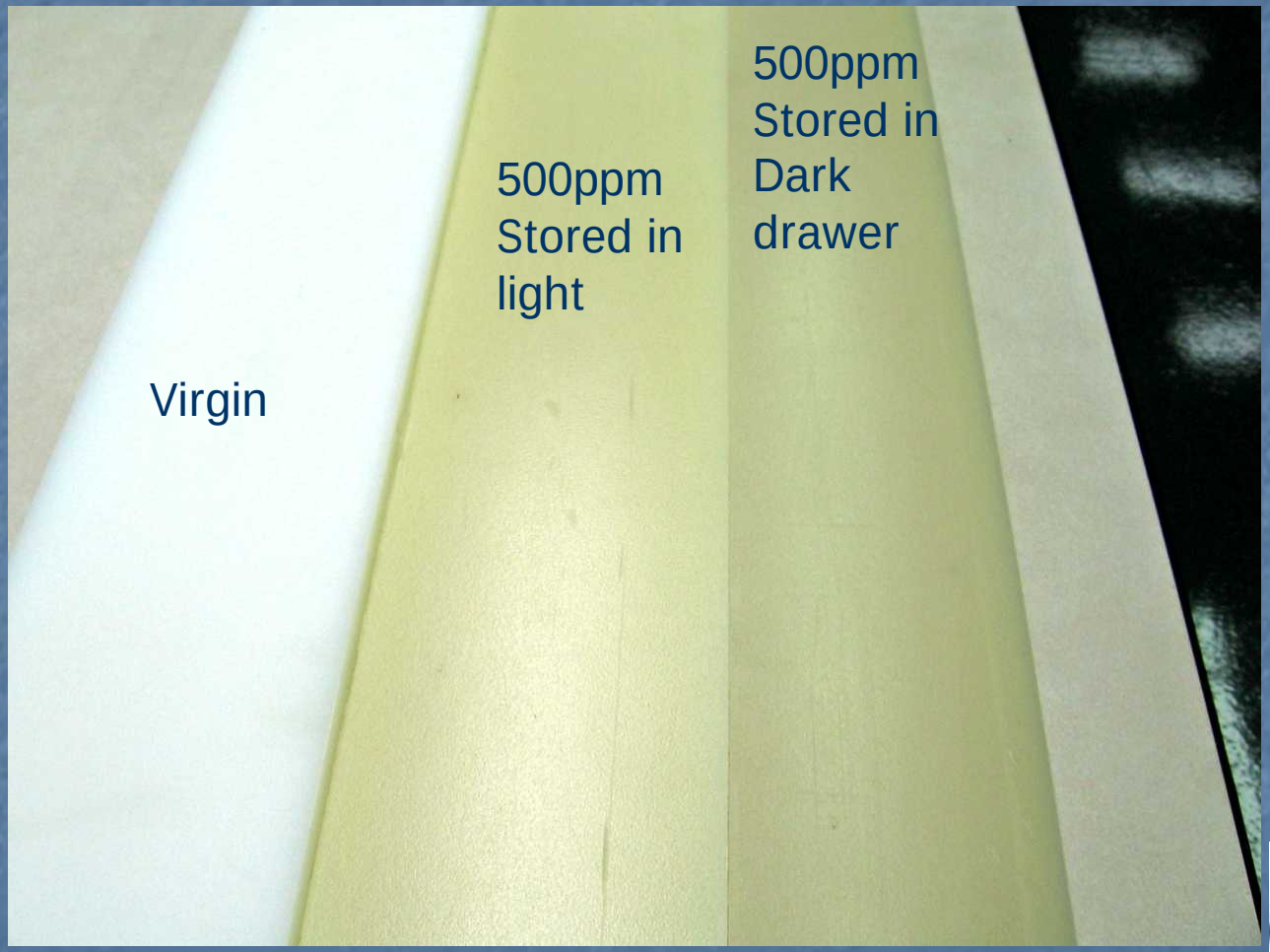
Handling, long term storage and packaging of the consolidated material

- Internal work in process handling will not have to change, as material is typically stored in collapsible crates with covers, protecting the material from light.

- Light barrier packaging for individual bar stocks may be one consideration for preventing light effects in bulk storage, in transit, or at the device manufacturer's cells.

MediTECH
MEDICAL POLYMERS

Examples: 11 month comparison



MediTECH
MEDICAL POLYMERS

Examples: 11 month comparison

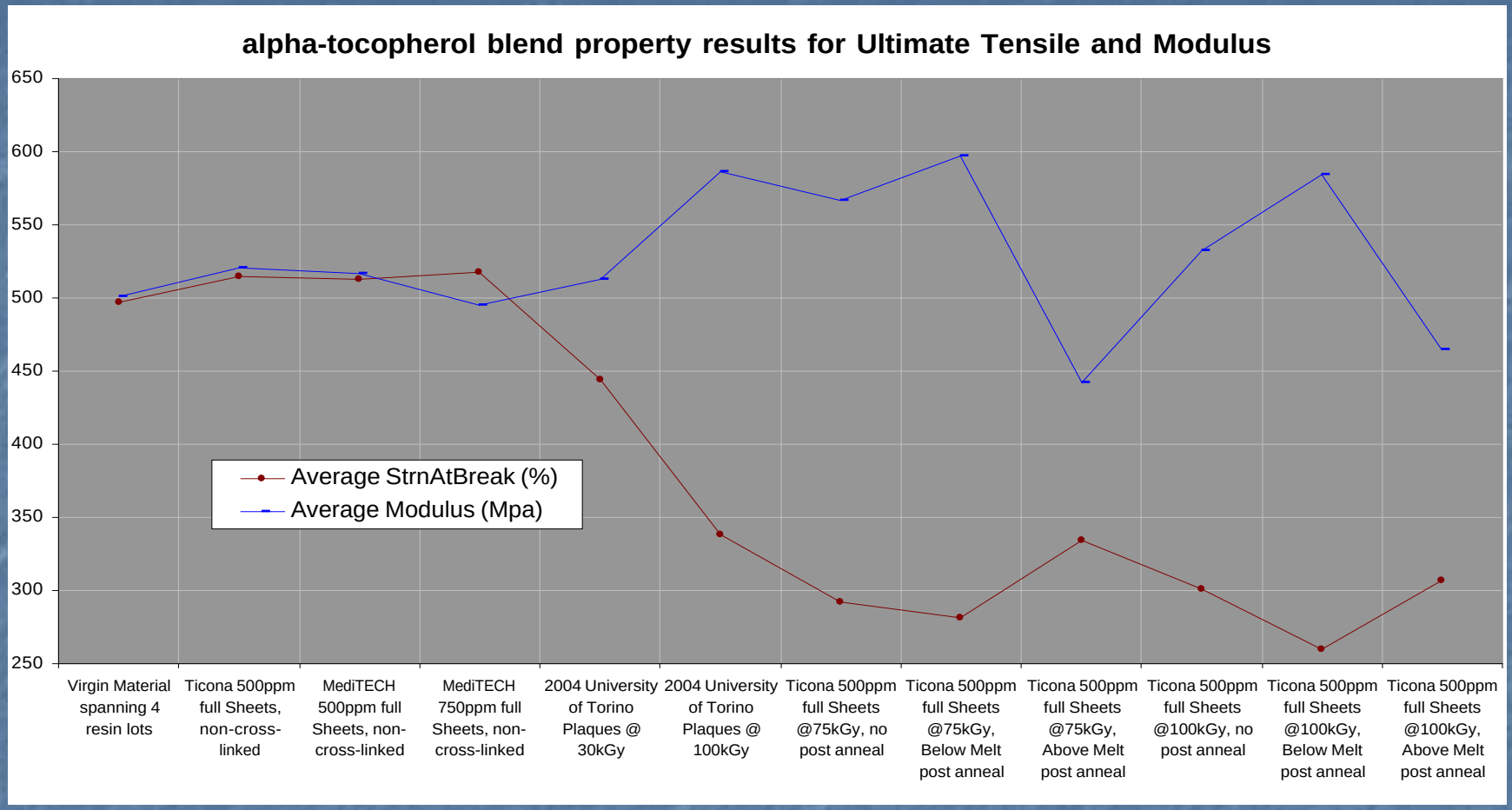
Virgin GUR 1020

500ppm Blend Pressed In November 2006, Shelved in fluorescent light

500ppm Blend Pressed In November 2006, Stored in a dark drawer

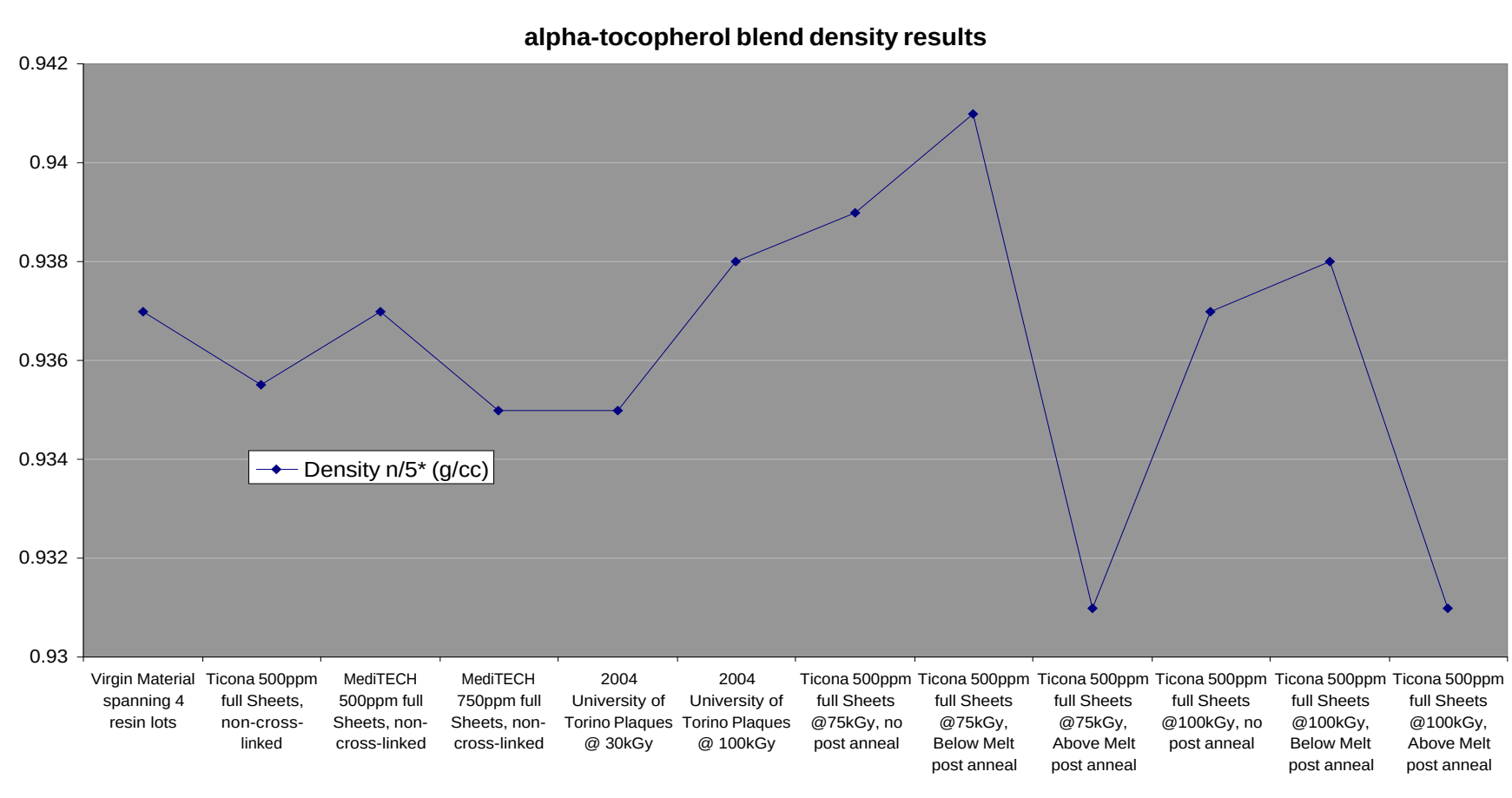
MediTECH
MEDICAL POLYMERS

Testing of the consolidated material:



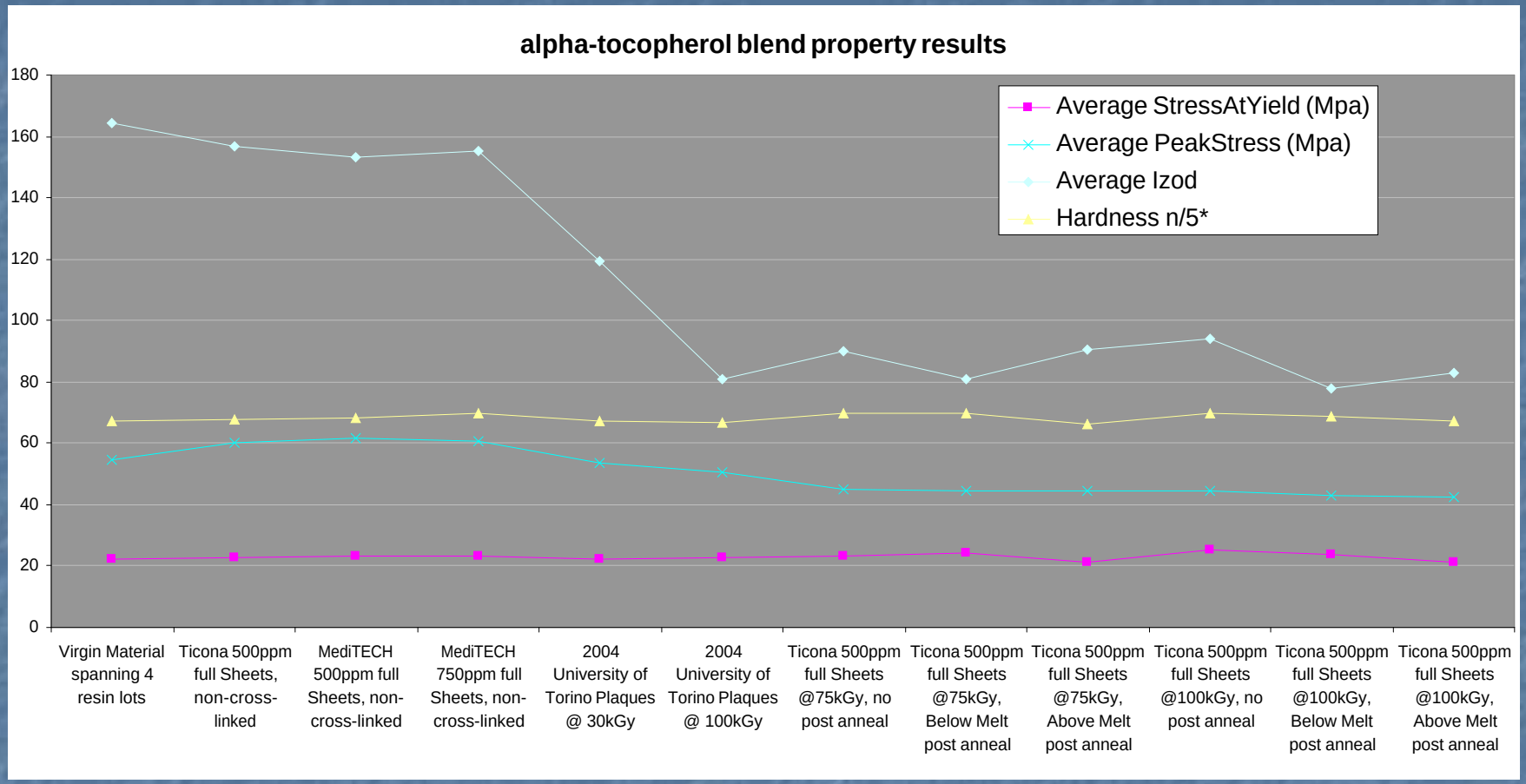
MediTECH®
MEDICAL POLYMERS

Testing of the consolidated material:



MediTECH
MEDICAL POLYMERS

Testing of the consolidated material:



MediTECH®
MEDICAL POLYMERS

New Quality Assurance Challenges with Blended UHMWPE:

- Dispersion Uniformity Test Methods Under Consideration:
  - Infrared Spectroscopy
  - FTIR and spectral subtractions
  - DSC
  - UV Visibility Spectroscopy
  - Colorimetery
- Other Testing for efficacy:
  - Oxidation Index
  - Cross-Link Density
  - ESR
- Scale up concerns:
  - Practicality on a production basis
  - Testing of Resin form to reduce risk

MediTECH®
MEDICAL POLYMERS

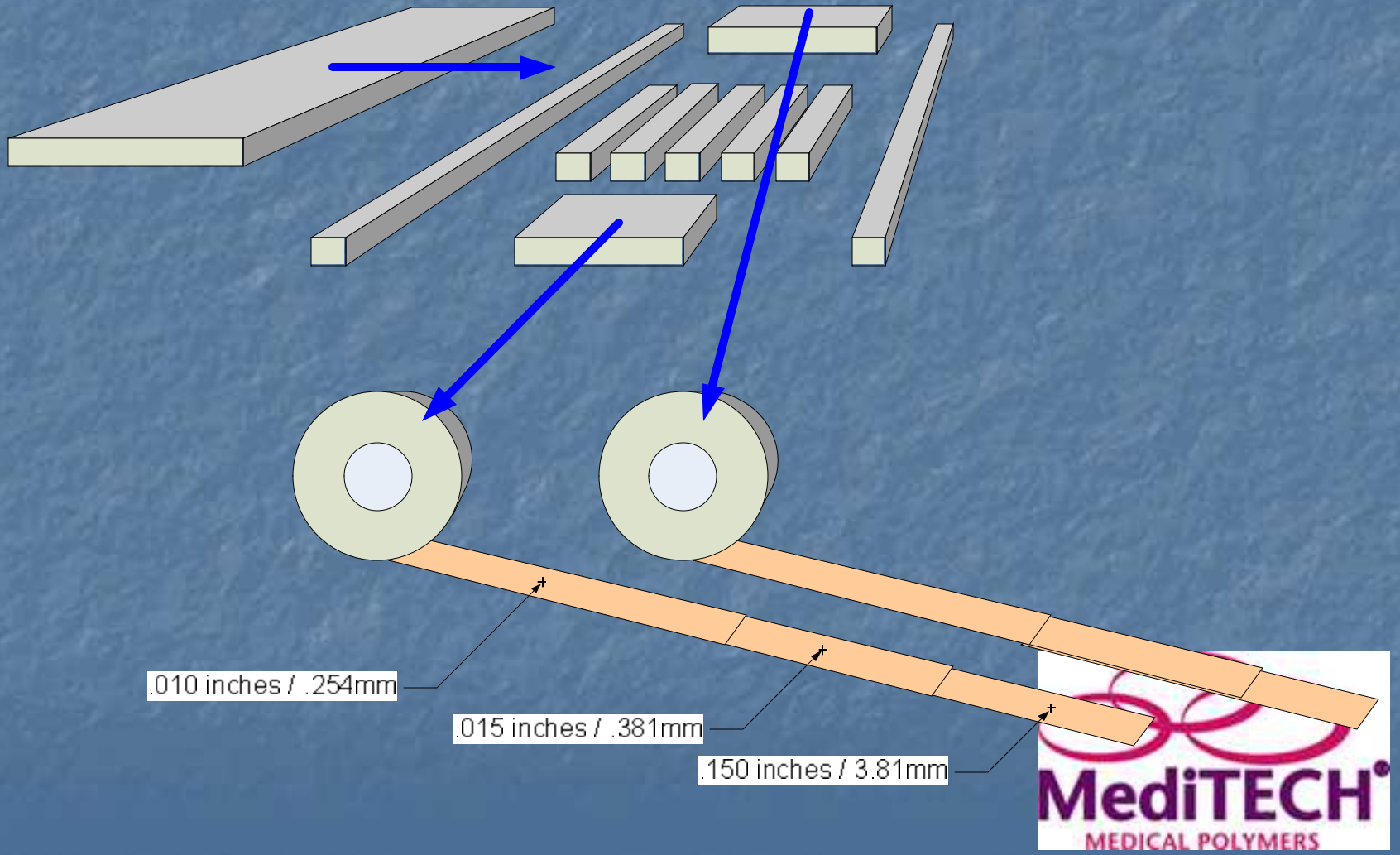
New Quality Assurance Issues with Blended UHMWPE:

- Certifications:
  - Irresponsible logistics can make for significant work load increases for QA, and increases the risk for failed material.
  - Table shows how the number of discrete certificates could vary from ~400 to over 2600.

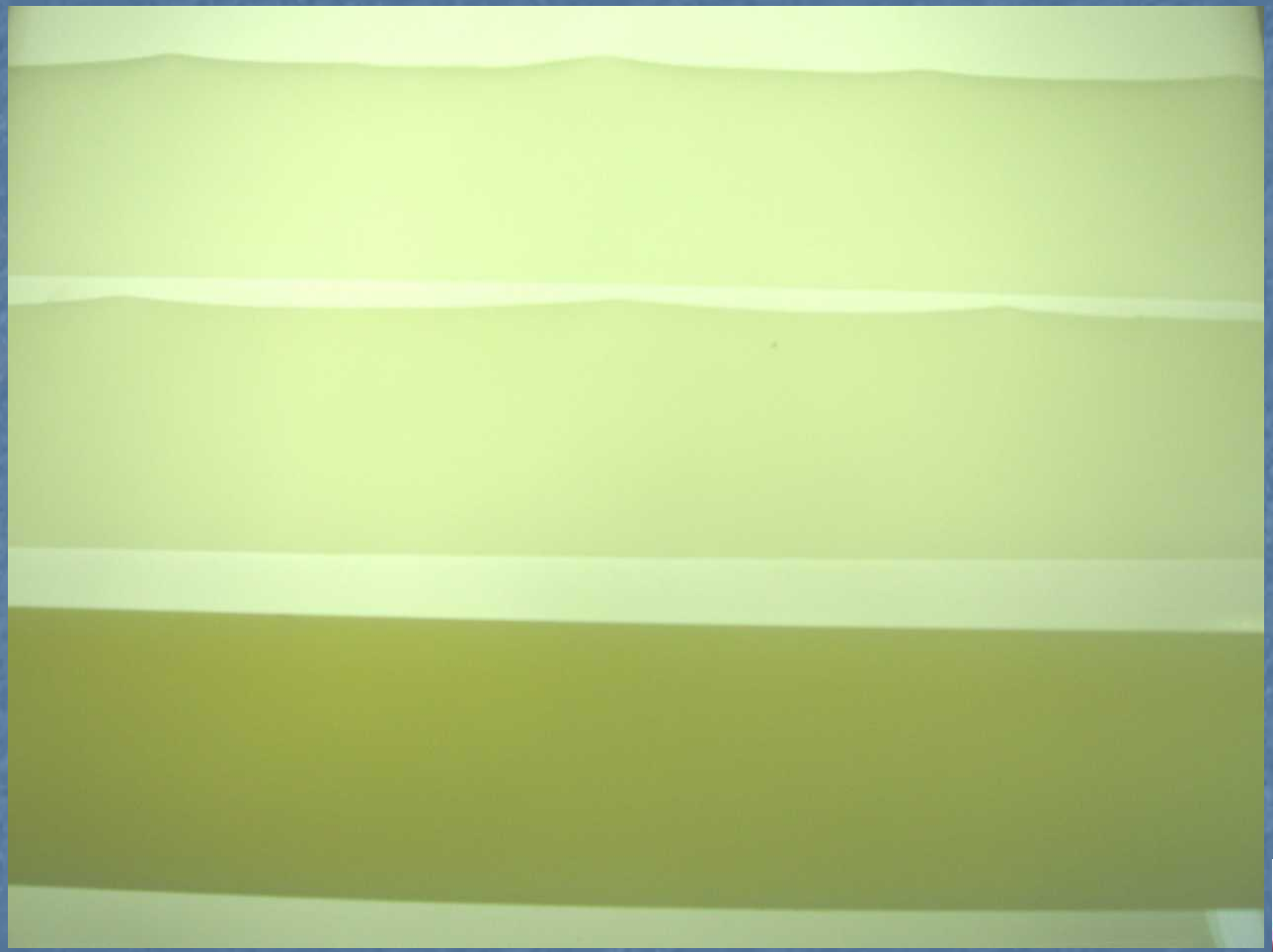
Batch components	Size, kg	Certs per Resin Lot	Smallest Batches Possible, kg	Certs per Resin Lot
Resin Lot	100000	1	1	1
Extrusion Run	1000	100	100	1000
a-tocopherol lot	50	1	5	10
Resin Lots per year:		2		2
Discrete Certificates:		204		2022
Resin Lot	100000	1	1	1
Compression Molding	500	200	75	1334
a-tocopherol lot	50	1	5	10
Resin Lots per year:		2		2
Discrete Certificates:		404		2690

MediTECH® MEDICAL POLYMERS

A novel way to view blended material in a blending method validation, although not practical on a production basis.



Examples:



0.254 mm film

0.381 mm film

3.81 mm film

MediTECH
MEDICAL POLYMERS

Examples:

8x picture of small section of 3.81mm film

MediTECH
MEDICAL POLYMERS

Examples:

8x pictures of .381mm and .254mm films, respectively

MediTECH
MEDICAL POLYMERS

Continuing Efforts Summary:

- The Orthopaedic Community is already beginning to voice individual and collective opinions as to the benefits and opportunities of making UHMWPE oxidation resistant.

- There are significant steps to be taken in working with the enhanced material by the blender and converter:
  - Specification, Specification, Specification.
  - How to quantify and verify dispersion uniformity (Resin & Sheet)
  - Assessing effectiveness of ά tocopherol for consolidated material
  - Post-Radiation Annealing considerations

- Explore Oxidative Performance of Production Processed UHMWPE and processing effects on α-tocopherol consumption.

MediTECH®
MEDICAL POLYMERS

Acknowledgements:

- Ticona, for their provision of virgin and blended resin to support these efforts
- Orthopaedic Device Manufacturers for partnering with us in development rather than working exclusively, which benefits us both.
- Dr. Luigi Costa, who for years has been spiriting this activity.
- The Universidad Autonoma de Madrid for hosting the forum to present this information.

- DISCUSSION

MediTECH MEDICAL POLYMERS