

amino scope[®]



KYOWA HAKKO BIO'S NEWS FROM AROUND THE GLOBE • SUMMER 2017



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Science Update

Research on Glutathione for Skin Health

by Yuki Nakamura

A randomized, double-blind, placebo-controlled study was recently published in *Clinical, Cosmetic and Investigational Dermatology* investigating the effects of oral glutathione supplementation on skin health in healthy females¹. The results showed that both reduced (GSH) and oxidized (GSSG) forms of glutathione at a lower dose of 250 mg/day for 12 weeks were effective at influencing skin properties in dark-skinned individuals. They were well tolerated with no serious side effects throughout the study. Both forms of glutathione should be promising ingredients for skin health.

Glutathione is the most abundant antioxidant in the body and plays an important role in protection of our skin. UV radiation enhances reactive oxygen species (ROS) production in the skin and antioxidants such as glutathione detoxify them. When the skin is exposed to excess UV radiation, glutathione levels in the skin decrease and melanin production in melanocytes increases to protect skin from UV irradiation (*Figure 1*). Therefore, glutathione supplementation would be an effective way to improve skin health and brightness against UV irradiation.

In 2012, Dr. Asawanonda at Chulalongkorn University in Thailand reported that oral GSH

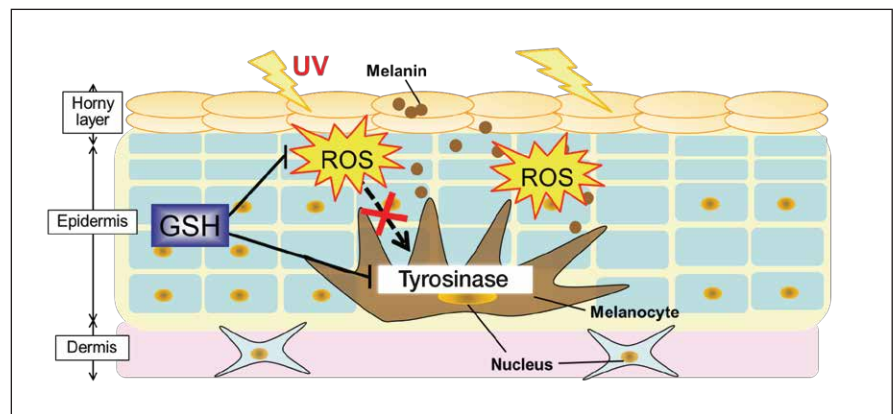


supplementation at 500 mg/day for 4 weeks decreased melanin index of the face and arm in healthy individuals². In the current study, we showed that oral GSH (Setria®) supplementation at a lower dose of 250 mg/day for 12 weeks lowered melanin index in all subjects (*Figure 2*) and reduced wrinkle of arms, especially in middle aged subjects over 40 years old. GSH should be a promising ingredient for dietary supplements for skin health from the study

results. However, there are some limitations of its applications due to its instability in aqueous solutions.

Glutathione exists in two forms in the body, GSH and GSSG, and GSSG is known to be stable in aqueous solutions. We previously reported that topically-applied GSSG significantly reduced melanin indices of the face in healthy individuals³, however, it was not clear if oral GSSG supplementation

Figure 1: Glutathione reduces melanin production by suppressing the activity of tyrosinase and switching the eumelanin synthesis to pheomelanin.



brightens skin and improves other skin properties. In this study, we showed that oral GSSG (Aqua-Gluta®) supplementation at 250 mg/day also lowered melanin index (Figure 3) and improved skin elasticity. GSSG is applicable to cosmetics and drink formulations for skin health.

In a recent report from Global Industry Analysis, Inc (GIA), the global market for skin lighteners is expected to reach \$23 billion by 2020. Especially in Thailand and Philippines, glutathione is already a popular ingredient for dietary supplements and functional drinks for skin health. We hope the results of this study promotes the development of new products all over the world.

1) Weschawalit S., et al., *Clin Cosmet Investig Dermatol.*, 10:147-153, 2017.

2) Arjinpathana N and Asawanonda P. *J Dermatolog Treat.*, 23(2):97-102., 2012

3) Watanabe F. et al., *Clin Cosmet Investig Dermatol.*, 7:267-274, 2014.

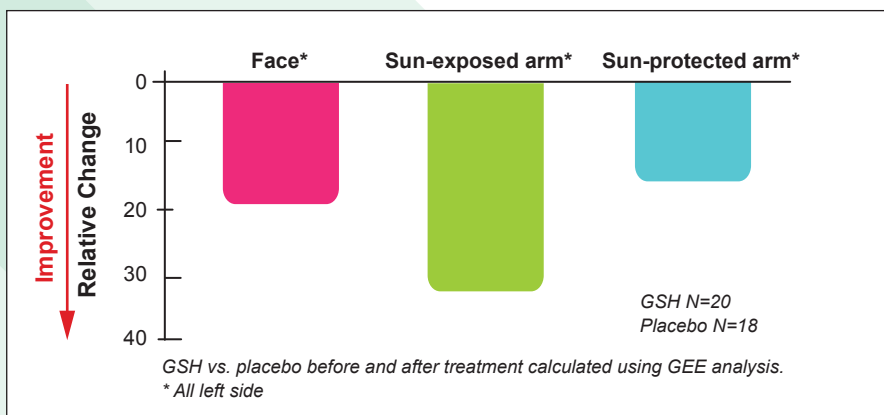


Figure 2: Melanin Index (250 mg/day GSH Group)

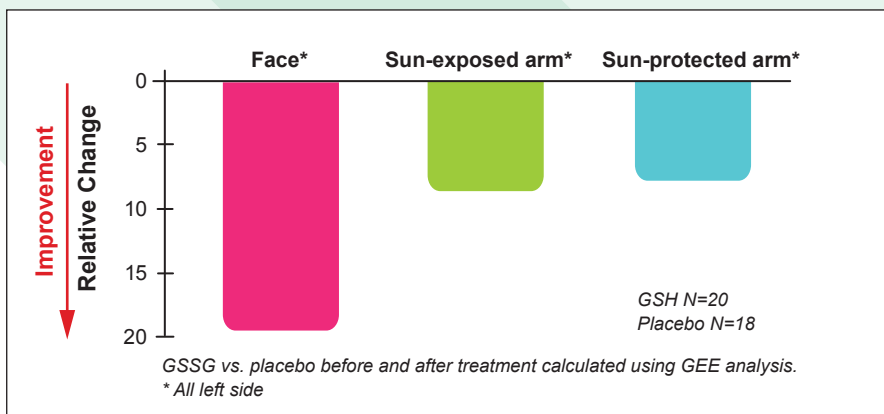


Figure 3: Melanin Index (250 mg/day GSSG Group)

Glutathione Seminar Held in Bangkok

Throughout SE Asia, glutathione continues to grow popularity and is widely used in a broad array of supplements designed to support skin health and beauty. In Thailand and Philippines, where the functional drink markets are expanding rapidly, oxidized glutathione is being used in beauty drinks because of its stability in aqueous solution. Due to the increasing interest in glutathione, Kyowa Hakko Singapore decided to hold an educational seminar on April 21st in Bangkok. Attending the event were 60 delegates from 37 leading dietary supplement and functional beverage brands such as F.C.P., JSP Pharmaceutical, NBD Healthcare, Osotspa,

and T C Union. Yuki Nakamura from Kyowa's Healthcare Product Development Center, presented the newly published clinical data about the skin brightening effectiveness of both Setria® Glutathione reduced and AquaGluta® Glutathione oxidized.



The study was conducted at Chulalongkorn University, Thailand. It is the first clinical study with an oral dose of 250 mg for both reduced and oxidized glutathione which matches the daily intake limit established by

the Food and Drug Administration of Thailand.

Karen Todd, Senior Director of Kyowa's Global Brand Marketing Center, also spoke to the group about current glutathione trends in health-care, and introduced new marketing support for Setria® branded customers. Ryusuke Nakagiri, Kyowa's Glutathione Marketing Manager, presented information on Kyowa's patented production technology and global R&D activities.

The response to the seminar from the Thai delegates was very positive. With consumers concerns about the quality of dietary supplements, manufacturers are looking for high quality ingredients supported by science.

Science Update

by Takeshi Ikeda

Glutathione for Brain Health

An animal study was recently published in *Brain Research* investigating the neuroprotective effects of combined Setria® Glutathione and L-citrulline administration on brain injury in ischemic mice. Oral administration of the combination, but not each ingredient alone, significantly improved memory deficit following cerebral ischemia (Figure 1). The authors suggest that the improvement of endothelial nitric oxide synthase (eNOS) function accounts for the synergistic effects observed in the study.

Glutathione is the most abundant antioxidant in the body and plays an essential role in maintaining normal brain function¹. The brain is particularly susceptible to oxidative stress because 1) reactive oxygen species (ROS) are generated in high rates within the brain, and 2) it is rich in lipids with unsaturated fatty acids which are targets for lipid peroxidation. Glutathione is a major antioxidant involved in the detoxification of ROS in brain, so its deficiency promotes lipid peroxidation in cell membranes,

leading to brain cell damage. It has been reported that glutathione levels in the brain decrease with age and glutathione deficiency in the brain is associated with many neurodegenerative diseases including cerebral ischemia².

Recently, Dr. Fukunaga at Tohoku University reported that oral Setria® Glutathione administration improved memory deficit following transient cerebral ischemia in mice by restoring reduced glutathione levels and reducing oxidative stress in the brain³. Furthermore, they showed in the current animal study that the combination of Setria® Glutathione and L-citrulline improved memory deficit synergistically (Figure 1). It has been reported that L-citrulline alone has a neuroprotective effect by promoting nitric oxide (NO) production in brain endothelial cells⁴. NO is inactivated rapidly in the presence of ROS, however, Setria® Glutathione would maximize its neuroprotective effect by prolonging biological half-life of NO and reacting with NO to form S-Nitroso-L-Glutathione (GSNO), which acts as a slow releaser of NO (Figure 2).

Kyowa has developed “Setria® Performance Blend” for sports performance by taking advantage of this unique mechanism of the combination, and sales have been growing in the sports nutrition segment.

From the latest animal studies of glutathione on brain function, supplementation of Setria® Glutathione or its combination with L-citrulline, shows that it also has the potential to support brain health by helping prevent neurodegenerative diseases or age-related cognitive decline. Kyowa filed an international patent application for the combination of glutathione and L-citrulline on brain function (WO2014069667). Clinical studies are expected in the near future.

References

- 1) Dringen R. Metabolism and functions of glutathione in brain. *Prog Neurobiol.* 62(6): 649-71, 2000
- 2) Rae CD, Williams SR. Glutathione in the human brain: Review of its roles and measurement by magnetic resonance spectroscopy. *Anal Biochem.* 2016 Dec 26. pii: S0003-2697(16)30434-1.
- 3) Yabuki Y, Fukunaga K. Oral administration of glutathione improves memory deficits following transient brain ischemia by reducing brain oxidative stress. *Neuroscience.* 250: 394-407, 2013
- 4) Yabuki Y, Shioda N, Yamamoto Y, Shigano M, Kumagai K, Morita M, Fukunaga K. Oral L-citrulline administration improves memory deficits following transient brain ischemia through cerebrovascular protection. *Brain Res.* 1520: 157-67, 2013

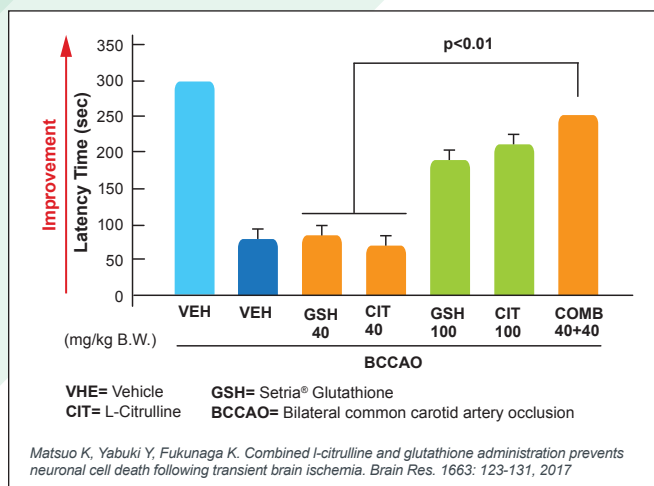


Figure 1: Combined Setria® Glutathione and L-citrulline administration synergistically decreases memory impairment following cerebral ischemia in the passive avoidance test. (BCCAO mice, n = 5-7 per group)

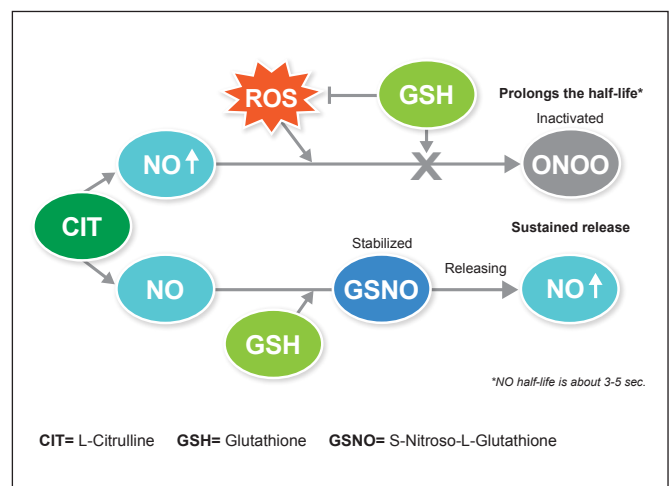


Figure 2: A proposed mechanism of action.

Product News

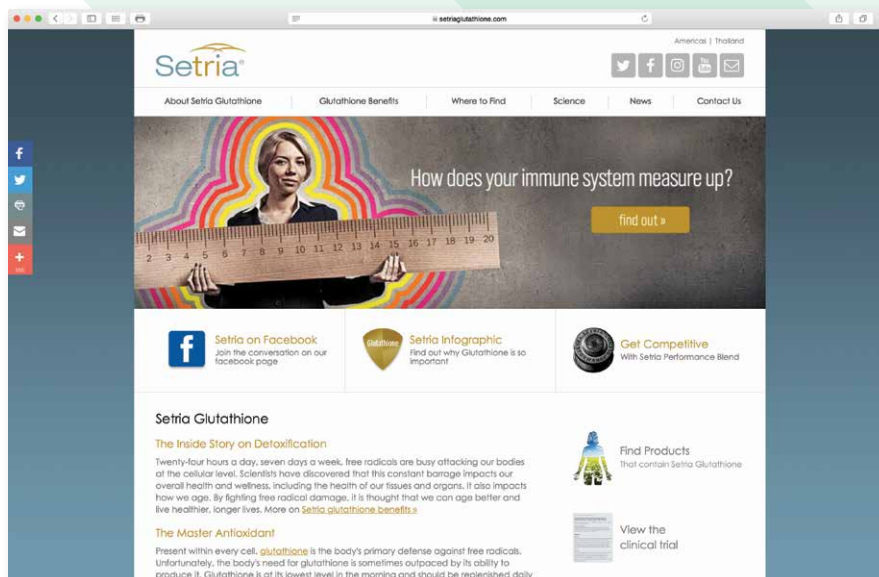
by Oksana Ritchie

Kyowa Hakko expands Setria® Glutathione brand in Europe

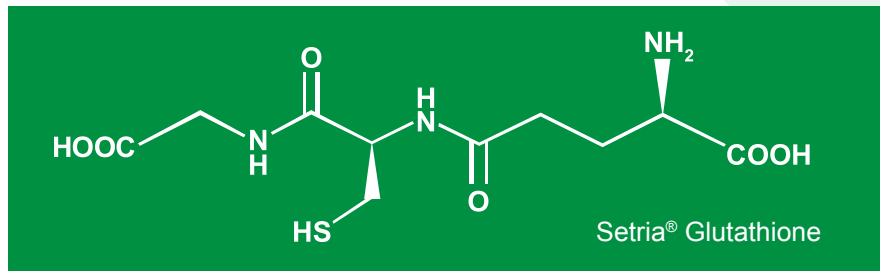
In April 2017 Kyowa launched its premium branded ingredient Setria® Glutathione in the European markets. Setria® Glutathione is already successfully sold and marketed in the USA and Asia as a key antioxidant and detoxifying ingredient. With its expansion into the European dietary supplement market Kyowa Hakko hopes it will present consumers with a wider range of options when it comes to supplementing with glutathione to support their health.

Setria® is a branded form of glutathione—an antioxidant present in almost all cells of the body. Glutathione plays an important role in numerous bodily processes, including antioxidant protection, detoxification and immune system fortification. Glutathione may be depleted as the result of poor lifestyle choices, stress and natural aging. Supplementation is needed when the diet does not include abundant unprocessed fruit and vegetables.

Setria® Glutathione is a unique tripeptide consisting of three important amino acids—glutamic acid, cysteine and glycine. The name SETRIA comes from SET (balance) + TRI (tripeptides). In other words, SETRIA is a tripeptide that helps to set the body's glutathione levels back into balance.



Setria® consumer website



Help shield your immune system.*

Glutathione plays an essential role in supporting immune health and helps protect cells from the damaging effects of oxidative stress and toxins. While our bodies make glutathione, levels can become depleted through poor lifestyle choices—and even the natural aging process. A strong immune system is critical for good health. Support it with good habits like eating right, regular exercise, and by taking Setria®—the first glutathione clinically studied to raise levels in the body.^{1*}



Setria®
Glutathione

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1) Randomized controlled trial of oral glutathione supplementation on body stores of glutathione. J.P. Richie. Published in the European Journal of Nutrition, May 2014

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Look for these fine brands with Setria® Glutathione in their formulations.



BioKyowa

by Joel Melka

BioKyowa's food grade packaging facilities contain numerous features to ensure that customers receive the correct amount of high quality product. As a vital component in our Food Defense Program, entry into each packaging facility is via a tap card system. This system limits access to packaging areas to those who work in or support the area. A muster report is electronically generated to show who entered and left the facility at various times throughout the day.

Before entering a filling room an operator needs to follow a strict gowning procedure to dress out in a Tyvek suit, boot covers, gloves, hair net, beard cover, hard hat which is designated for packaging area use only and goggles, in a dedicated changing area. Once an operator is gowned they use their tap card a second time to enter into the air shower before entering the product filling room. The air shower blows any loose matter off of them before entering the product filling room.



Packaging materials are stored in a clean area that is bathed with UV light when the area is not occupied. All packaging suppliers are audited by our logistics group prior to being approved to sell packaging supplies to BioKyowa. Packaging materials and



product move through the filling rooms in a logical flow that is designed to be simple, efficient and accurate. Small items such as rubber bands, desiccant, labels and drum seals are counted off-line and stored in sealed totes prior to commencing packaging of each batch of product. The small items remaining after packaging are then reconciled with the filled drums to ensure that the correct number of each item remains when the packaging run is complete.

The net filled weight of each container is strictly controlled. First a check weight is placed on the drumming scale to ensure the scale is operating properly. A weigh ticket is electronically generated for this step. The start of drum filling is interlocked with the check weight step so that filling cannot physically commence until the check weight step is completed. Each drum is then filled to a specified amount with a weigh ticket printed for each container filled.

At the end of a packaging run or the end of a work shift, whichever comes first, the check weight step is repeated

to ensure that the filling/weighing system worked properly during the run or shift. Operators use the tap card system to exit the filling room and then again when exiting the packaging facility. All records of packaging and supplies reconciliation are reviewed by the packaging supervisor before they are sent to the Quality Assurance department for final review and approval. No product is shipped until all reviews are complete. BioKyowa takes great pride in supplying customers with high quality product. Our food grade packaging areas, procedures and personnel reflect our high commitment to customer satisfaction.



Marketing News

by Elyse Lovett

Kyowa Hakko Launches Kyowa Quality® Website

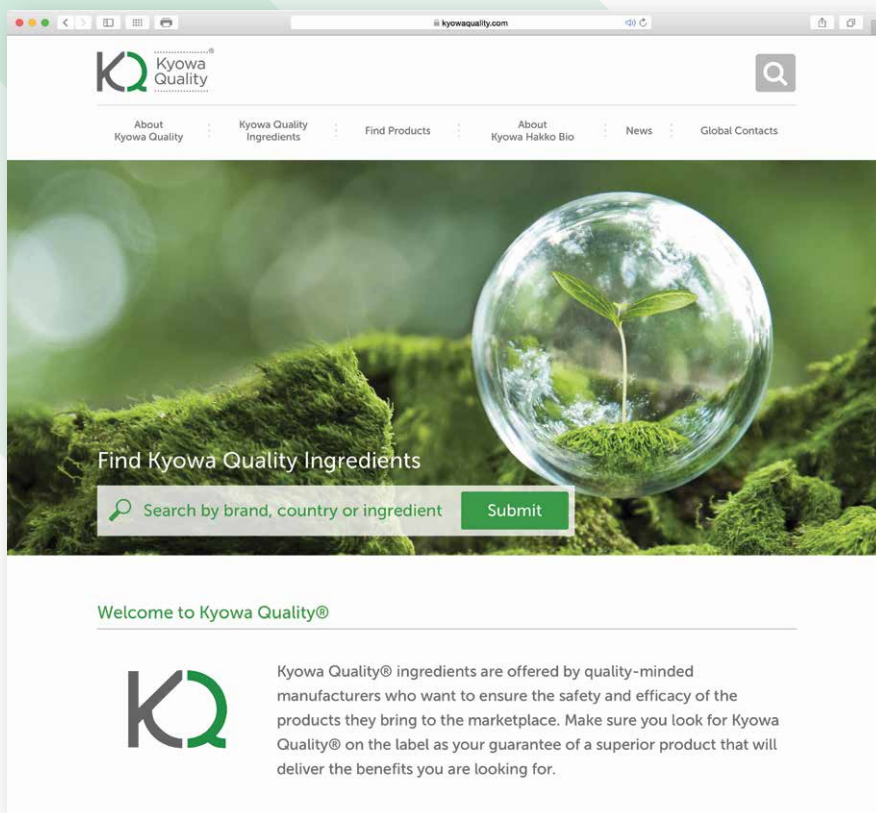
Kyowa Hakko represents a line of well-researched, branded ingredients and an extensive line of quality-assured, ultra-pure amino acids that are guaranteed with the Kyowa Quality® name or seal.

The brand essence behind Kyowa Quality is Nature, Health, and Science. Nature: Kyowa's products are plant based, produced through a natural fermentation process. Health: contributing to the health and well being of people around the world. Science: scientifically tested and provide world class quality. For over 60 years Kyowa has been at the forefront of research and the development of high quality ingredients.

In recent years the advent of the internet has allowed consumers to become increasingly knowledgeable and they are now looking not just for brand names they know but also for key ingredients from manufacturers they can trust. Kyowa Hakko is well positioned to help consumers find products containing Kyowa ingredients.

The new Kyowa Quality website, www.KyowaQuality.com, is our home for products containing ingredients that are backed by our Kyowa Quality mark around the world.

Kyowa's Quality ingredients include strategically branded ingredients and amino acids, pharmaceutical-grade ingredients, food-grade ingredients and industrial grade ingredients.





Tradeshows & Conferences

by Oksana Ritchie

Kyowa at Vitafoods Europe 2017

Vitafoods Europe was just buzzing this year! The nutraceutical market is expanding in all directions at the moment. There were lots of new things to see and do including a tasting center, a probiotics resource center, a sports nutrition zone, and many new products. The number of innovative products were remarkable.

Despite restrictions regarding permitted health claims in Europe, Vitafoods exhibits indicated a continuous level of interest in positive nutrition and products with added health benefits, such as vitamins, prebiotics, probiotics, Omega-3s and other ingredients. Many exhibitors were focused on offering clean labels free from additives and preservatives, plant derived ingredients, and products designed to address the specific health concerns of demanding consumers.

Healthy aging, in the context of lifestyle and good nutrition, is more and more a focus of an increasing older population

both from a physical and mental perspective. Educated younger consumers are also far more accepting of the use of nutritional supplements for all stages of their lives.

Kyowa presented its branded ingredients Cognizin®, Sustamine® and Setria®— and with Setria® recently launched in Europe, it generated a huge amount of interest with both food and dietary supplement formulators. Setria® Glutathione was also showcased in the New Ingredients zone to increase awareness for this product.

Kyowa's Karen Todd, Sr. Director Global Brand Marketing, presented a seminar on Cognizin® Citicoline's breakthrough benefits for cognition along with a review of the supporting science to a full theatre audience. Her presentation was enthusiastically received and generated a lot of interest.

All in all, Vitafoods was a tremendous event to be part of—and as you can see from the picture, the Kyowa team was very happy!



Upcoming Events



June 22-24, 2017
Phoenix, AZ USA



June 25-28, 2017
Las Vegas, NV USA, Booth 5048



July 17-20, 2017
Verdes, CA USA



Sept 5-6, 2017
Singapore, Stand K22



Sept. 13-15, 2017
Bangkok, Thailand, Stand J29



September 25-29, 2017
Las Vegas, NV USA, Booth PP135



November 9-11, 2017
Mumbai, India, Stand D38



Nov. 20-22, 2017
ExCel, London
(Cognizin & Setria Presentations)



Nov. 28-30, 2017
Messe Frankfurt, Germany
Stand 11.OH78



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