Commentary

Performance Enzymes for Food Ingredients at the BIO World Congress—Enabling Biotechnologies and Supporting Capabilities Join in a Model for Successful Commercialization of Food Ingredients

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The educational program at the July 2017 Biotechnology Innovation Organization's World Congress in Montreal included several panels on the rapidly evolving tool box in support of industrial biotechnology. One panel included representatives from many well-established names and early pioneers in synthetic biology (Twist Bioscience, South San Francisco, CA), protein engineering (Arzeda, Seattle, WA), biofoundries (Ginko Bioworks, Boston, MA) and CRISPR Cas9 (Estes Advisors) to discuss the new outsourced value chain that has emerged to assist especially smaller companies in their discovery and development efforts.

Another panel—Performance Enzymes for Food Ingredients—discussed how the same tools are used by the enzyme industry in the discovery and development of enzymes tailored to new food applications and deployment of those enzymes in novel food applications. As members of the enzyme industry vary greatly in size AND in-house resources and capabilities, they rely to differing extents on the so-called outsourced value chain. Larger enzyme companies have established deep understanding and capabilities in protein engineering and the management of fermentation cell factories to develop and scale-up their process, but rely heavily on outsourced DNA sequencing and made-to-order synthetic DNA.

Each of the Performance Enzymes panel speakers gave detailed presentations on their companies' integrated suites of technical capabilities. Marc Struhalla discussed one-pot enzymatic synthesis of biomolecules by c-Lecta (Leipzig, Germany). Andrew Ellis of Biocatalysts (Cardiff, United Kingdom) discussed genome sequencing, protein engineering and high-throughput screening as put into practice by Biocatalysts, as did John Perkins (DSM, Parsippany, NJ) and Vince Sewalt (DuPont Industrial Biosciences, Palo Alto, CA). Chandrakant Rathi of Advanced Enzymes Technologies (Louiswadi, Thane, India) focused on his company's efforts in application development for palm oil extraction, illustrating that biotechnology

is directed toward solving very practical problems, anywhere in the world.

The ensuing discussion led by panel moderator Vince Sewalt of DuPont focused on what panel members perceived to be the next bottlenecks in effective enzyme development and commercialization—including making sense of the abundance of sequence data and gene expression information, which will require Big Data capabilities. Another bottleneck identified for smaller companies was the development and continuous improvement of “cell factories” at full-scale fermentation volumes, a capability that today is limited to only the largest enzyme companies.

In his introduction to the other speakers, Vince Sewalt also emphasized the need for additional commercialization capabilities that include safety assessment, regulatory approvals, and advocacy for science-based and risk-focused regulatory oversight, globally. In the discussion, it became abundantly clear that industry needs to collaborate in demonstrating product safety by using well-established safety evaluation methods. Such procedures focus on the safety of the production organism, in addition to addressing the enzyme, the manufacture process, supporting safety data, and a thorough exposure assessment (*Fig. 1*).

Collectively, we can aid regulatory agencies in their assessment of our products by familiarizing them with the technology and the safety of the resulting food enzymes, which, if done in a consistent manner, results in knowledge-building among regulators. For example, the enzyme industry has produced numerous toxicology studies on enzymes from genetically engineered microbes (Pariza and Johnson),¹ including for protein-engineered enzymes (as summarized by Pariza and Cook),² and introduced the concept of Safe Strain Lineage to regulators. The latter builds on the repeated use of common production organism as our work horses, such as *Bacillus subtilis*, *B. licheniformis*, and *Trichoderma reesei*, and the optimization of these lineages into so-called “cell factories.”

The knowledge built over multiple years and even decades for these production organisms includes a rich database of safety data, which supports Generally Recognized as Safe (GRAS) status of new enzymes when produced by members of a microbial lineage that has already been established as safe by repeated evaluation through standard, publicly recognized

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Fig. 1. Industry needs to collaborate in demonstrating product safety by using well-established safety evaluation methods.

decision trees. The Safe Strain Lineage concept was recently reviewed by Sewalt et al.³ and is finding acceptance by the US Food and Drug Administration.

In fact, food safety experts from the broader food ingredient industry recently highlighted the success rate for enzymes in FDA's Center for Food Safety and Applied Nutrition GRAS Notification program times in a review paper by Hanlon et al. in *Food and Chemical Toxicology*,⁴ as evidenced by near 100% FDA concurrence and relatively short review times. These authors were wondering how the enzyme industry is able to support the common-knowledge element of GRAS for enzymes, given that only one third of the enzyme GRAS Notices used a GRAS expert panel to review the GRAS determination. We have since then reviewed the history of safe use of enzymes, their production organisms, and the generally recognized safety evaluation methodology with these authors and documented our rationale in a Letter to the Editor of *Food Chemical Toxicology*,⁵ and Hanlon et al. acknowledged that the safety experience documented for food enzymes can serve as a model for other

food ingredients. Such an endorsement is illustrative of the impact of successful advocacy in support of societal and regulatory acceptance of biotechnology products. If experts from the broader food industry agree that the enzyme case study can serve as a model for other food ingredients, then the broader industrial biotechnology community should certainly be able to leverage the enzyme industry's efforts to underpin the safety of all well-designed biotechnology products produced with carefully selected microbial expression hosts in a similar manner. Doing so will again aid regulatory agencies in their assessments of microbial biotechnology products by making them more familiar with the technology, allowing for easier bridging to existing safety data to support approval and facilitating GRAS exemption claims. As always, establishing and maintaining a science-based, risk-focused regulatory oversight framework for industrial biotechnology products requires effective dialog with all stakeholders (expert groups, regulators and consumer groups) on the technology, its safety, and its benefits.

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