To:

Office of the Gene Technology Regulator

Subject: Review of Gene Technology Regulations

DSM Food Specialties Australia Pty Ltd.

9, Moorebank Avenue
NSW 2170, Moorebank
P.O. Box 83
Moorebank NSW 1875
Australia
Phone: 02 87789800
ABN 60 003 994 198

December 2, 2016

Dear Sir/Madam,

We very much appreciate the opportunity to provide input for the Review of the Gene Technology Regulations, in particular regarding genome editing technologies.

For the four options outlined in the Discussion Paper, the Pros and Cons are outlined very well and in a balanced manner. In revising the Gene Technology Regulations, to reflect and incorporate technological advancements made since the last review, appropriate consideration must be given to keep the amendments appropriate, fair and enforceable, as clearly stated in the Discussion Paper.

As shown convincingly in a schematic manner in Figure 2 of the Discussion Paper, **option 4** comes closest to these ambitions, and **is** therefore **to be favoured**. Still, we would like to provide some additional thoughts that, to us, seem worthwhile considering:

- The genome editing technologies not only blur the distinction between classical mutagenesis on one hand, and genetic engineering on the other hand, but they also question a process-centric approval process altogether. Europe is currently facing the same dilemma. A working group has come up with recommendations in 2012 whether and which technologies to exempt from GMO legislation, but the European Commission is still struggling to come up with a decision on the matter.
- A decision based on the technology alone (whether something is in scope or not) does not seem feasible, since:
  - CRISPR/Cas9 can be used to introduce a single base substitution, but can also be used to introduce an entire heterologous gene; and
  - High-throughput technologies will allow to repeat base substitutions through genome editing one after the other, so that at the end, the same result may be obtained as directly introducing a heterologous gene.
- Random mutagenesis (i.e., chemical and radiation mutagenesis) is represented in the Discussion Paper in an “idealistic” way, implying that it only affords minor modifications, such as single base substitutions. This is not fully true:
  - Random mutagenesis is known to cause, next to single base substitutions, also more complex modifications, up to complex genome rearrangements, the effects of which are, likely, only poorly understood in their entirety;

  - Next to the 'beneficial' mutations, also a considerable number of 'background' mutations are introduced, the effect of which, again, is only poorly understood.
- In line with the above, genome editing technologies, under some circumstances (assuming that they have limited off-target effects, and if only used for single-base substitutions), may actually be even more subtle and more controlled than classical mutagenesis. In such case, also the risk assessment would seem more straightforward for such a genome editing approach than for classical mutagenesis.
- Let us address also a fairly detailed, but very relevant case: if we aimed at deleting the activity of an extracellular protease, because of its negative effect on the expression level of an enzyme of interest, we could do this in at least two different ways: (a) by a single-base substitution that inactivates the gene; or (b) by a partial or complete knock-out/deletion of the gene. According to the reasoning provided in the Discussion Paper, the single-base substitution might be exempted from GMO legislation, while the partial or full gene deletion might not (based on the technology applied; and/or based on the extent of modification introduced). However, the gene deletion might eventually also occur through random mutagenesis. On top of that, the single-base substitution bears the risk of reverting back to the wild-type (which may cause inconsistent product quality), whereas the partial or full gene deletion would not. From a scientific and safety perspective, it would again not be justifiable to exclude one, but not the other, from GMO legislation.

To conclude, the technological possibilities offered by genome editing technologies make it almost inevitable to abandon a process-centric regulatory approval system, and to move to a product-centric approach. Eventually, all methods of genome modification (from random mutagenesis to synthetic biology) may need to undergo a risk assessment process, the depth of which may depend on the number and 'severity' of genome modifications introduced. We fully appreciate the fact that this is the solution that is most difficult to realize politically, but we sincerely hope that Australia has the courage to walk this path and set an example.

Dr Neil Hendy
Quality Manager
DSM Food Specialties Australia