



**Australian Government**

**Department of Health and Aged Care**  
Office of the Gene Technology Regulator

# **Licence for dealings involving an intentional release of a GMO into the environment**

**Licence No.: DIR 200**

**Licence Holder: Cauldron Molecules Pty Ltd**

**Fermentation and processing of recombinant proteins using genetically modified *Pichia pastoris***

Issued: 07 February 2024

**Office of the Gene Technology Regulator**

### **Gene Technology Regulation in Australia**

Australia's gene technology regulatory system operates as part of an integrated legislative framework. The *Gene Technology Act 2000* (Cth) and corresponding State and Territory legislation form a substantial part of a nationally consistent regulatory system controlling the development and use of genetically modified organisms.

This licence is issued by the Gene Technology Regulator (the Regulator) in accordance with the *Gene Technology Act 2000* and, as applicable, corresponding State law.

In assessing applications for dealings involving the intentional release of genetically modified organisms into the Australian environment, the Regulator is required to consult with, and take into account advice from, a range of key stakeholders, including other regulatory authorities, on risks to human health and safety and to the environment in assessing applications for dealings involving the intentional release of genetically modified organisms into the Australian environment.

Other agencies that also regulate genetically modified organisms or GM products include Food Standards Australia New Zealand, Australian Pesticides and Veterinary Medicines Authority, Therapeutic Goods Administration, Australian Industrial Chemicals Introduction Scheme and the Department of Agriculture, Fisheries and Forestry. Dealings conducted under any licence issued by the Regulator may also be subject to regulation by one or more of these agencies. It is recommended that the licence holder consult the relevant agency (or agencies) about their regulatory requirements.

The licence authorises the licence holder and persons covered by the licence to conduct specified dealings with the genetically modified organism(s) listed in **Attachment A** of this licence.

### **Further information on licence DIR 200**

More information about the decision to issue this licence is contained in the Risk Assessment and Risk Management Plan prepared in connection with the assessment of the application for the licence. This document can be obtained from the [Office of the Gene Technology Regulator \(OGTR\) website](#) or by telephoning the Office on 1800 181 030.

## CONDITIONS OF THIS LICENCE

### Section 1 Interpretations and definitions

1. In this licence:

- (a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;
- (b) words importing a gender include every other gender;
- (c) words in the singular number include the plural and words in the plural number include the singular;
- (d) expressions used to denote persons generally (such as “person”, “party”, “someone”, “anyone”, “no one”, “one”, “another” and “whoever”), include a body politic or corporate as well as an individual;
- (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;
- (f) where a word or phrase is given a particular meaning, other grammatical forms of that word or phrase have corresponding meanings;
- (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

**‘Act’** means the *Gene Technology Act 2000* (Commonwealth) or the corresponding State law under which this licence is issued.

**‘Contingency Plan’** means a written plan detailing Decontamination measures to be taken in the event of the unintentional release of the GMOs.

**‘Closed system’** means a system for growth, processing and/or storage of large scale cultures of GMOs consisting of an enclosed vessel or vessels and transfer lines.

**‘Culture Vessel’** means any of the outdoor Closed system located in the Production facility which is used for the culture of the GMOs pursuant to this licence.

**‘Decontaminate’** (or **‘Decontamination’**) means, as the case requires, a physical and/or chemical process which removes, kills or renders non-viable the GMOs used in the facility but does not necessarily result in sterility by one or more of the following methods:

- (a) chemical treatment;
- (b) heat;
- (c) autoclaving;
- (d) high-temperature incineration; or
- (e) a method approved in writing by the Regulator.

*Note: ‘As the case requires’ has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.*

**‘Denature’** means a physical and/or chemical process which renders DNA and its proteins non-functional.

**‘Equipment’** includes, but is not limited to, Culture Vessels, pipes, pumps, centrifuges, filtration equipment, storage equipment, transport equipment (e.g. transfer vessel), clothing, footwear and tools.

**'GM'** means genetically modified.

**'GMO'** means the genetically modified organisms that are the subject of the dealings authorised by this licence.

**'NLRD'** is a notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

**'Personal information'** has the same meaning as in the *Privacy Act 1988*. Personal information means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

- (a) whether the information or opinion is true or not; and
- (b) whether the information or opinion is recorded in a material form or not.

**'Production facility'** means the non-OGTR certified area of the Cauldron Molecules Pty Ltd's purpose-built protein production facility in Borenore, New South Wales.

**'Regulations'** means the Gene Technology Regulations 2001.

**'Regulator'** means the Gene Technology Regulator.

**'Sample'** means any culture volume collected from Culture Vessels for analysis as part of the protein production process.

## **Section 2      General conditions and obligations**

### **Holder of licence**

3.      The licence holder is Cauldron Molecules Pty Ltd.

### **Remaining an Accredited Organisation**

4.      The licence holder must, at all times, remain an accredited organisation.

### **Validity of licence**

5.      This licence remains in force until it is suspended, cancelled, or surrendered. No dealings with the GMOs are authorised during any period of suspension, or after the licence has been cancelled or surrendered.

*Note: Although this licence has no expiry date, the duration of culture of the GMO is restricted in accordance with Condition 21.*

### **Persons covered by this licence**

6.      The persons covered by this licence are:

- (a) the licence holder, and any employees or agents engaged by the licence holder; and
- (b) the project supervisor(s); and
- (c) other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.

7.      The licence holder must keep a record of:

- (a) all persons covered by this licence; and
- (b) the contact details of the project supervisor(s) for the licence.

8.      The licence holder must provide information related to the persons covered by the licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

## Description of GMOs covered

9. The licence authorises specified dealings in respect of the GMOs identified and described in **Attachment A**.

## Dealings authorised by this licence

10. The licence holder and persons covered by this licence may conduct the following dealings with the GMOs:

- (a) grow, raise or culture the GMO;
- (b) use the GMO in the course of manufacture of a thing that is not the GMO:
  - i) to produce recombinant proteins for analyses;
- (c) conduct the following experiments with the GMOs:
  - i) to optimise the scale-up fermentation process; and
  - ii) to characterise genetically modified (GM) *P. pastoris*
- (d) transport the GMOs;
- (e) dispose of the GMOs;

and may possess, supply, use or store the GMO for the purposes of, or in the course of, any of these dealings.

11. Supply of the GMOs for the purposes of dealings by a person or organisation not covered by this licence is only authorised by this licence if the Regulator provides prior written approval to the licence holder.

*Note: For approval to be granted, the receiving person or organisation must have an appropriate authorisation to conduct dealings with the GMOs. This is likely to be an NLRD or a licence issued by the Regulator.*

12. This licence does not apply to dealings with the GMOs conducted as an NLRD or pursuant to another authorisation under the Act.

## Conditions imposed by the Act

*Note: The Act mandates the following 3 conditions.*

### Informing people of licence conditions (section 63)

13. The licence holder must inform any person covered by the licence, to whom a particular condition of the licence applies, of the following:

- (a) the particular condition, including any variations of it; and
- (b) the cancellation or suspension of the licence; and
- (c) the surrender of the licence.

### Monitoring and audits (section 64)

14. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

### Additional information to be given to the Regulator (section 65)

15. The licence holder must immediately inform the Regulator if they become aware of:

- (a) additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or
- (b) any contraventions of the licence by a person covered by the licence; or
- (c) any unintended effects of the dealings authorised by the licence.

*Note 1: For the purposes of this condition:*

- (a) *The licence holder is taken to have become aware of additional information if they were reckless as to whether such information existed; and*
- (b) *The licence holder is taken to have become aware of contraventions, or unintended effects, if they were reckless as to whether such contraventions had occurred, or such unintended effects existed.*

*Note 2: Contraventions of the licence may occur through the action or inaction of a person.*

*Note 3: Additional information includes any changes to the production facility, which might increase the likelihood of unintentional exposure of people or release of the GMO into the environment.*

*Note 4: An example of informing immediately is contact made at the time of the incident via the OGTR free call phone number 1800 181 030.*

### **Informing the Regulator of any material changes of circumstance**

16. The licence holder must immediately, by notice in writing, inform the Regulator of:

- (a) any relevant conviction of the licence holder occurring after the commencement of this licence;
- (b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State, or a foreign country, being a law relating to the health and safety of people or the environment;
- (c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

17. The licence holder must provide information related to the licence holder's ongoing suitability to hold a licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

### **Further conditions with respect to informing persons covered by the licence**

18. If a particular condition, including any variation of it, applies to a person with respect to any dealing, the licence holder must not permit a person covered by this licence to conduct that dealing unless:

- (a) the licence holder has obtained from the person a signed and dated statement that the person:
  - i) has been informed by the licence holder of the condition and, when applicable, its variation; and
  - ii) has understood and agreed to be bound by the condition, or its variation; and
  - iii) has been trained in accordance with sub-condition 18(b) below; and
- (b) the licence holder has trained that person in a manner which enables them to conduct the dealings in accordance with the conditions of this licence.

19. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

20. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence who are conducting dealings with the GMO.

*Note: The licence may be made available electronically.*

### Section 3 Limits and control measures

#### Limits on the release

*The following licence conditions maintain the risk assessment context within which the application was assessed, by imposing limits on where and when the GMOs may be cultured, and on other activities that can be undertaken.*

21. Culture of the GMOs may only occur at the Production facility listed below and must be completed within five years from the date of issue of the licence.

#### Production Facility

Location	Local government area
Cauldron Molecules Pty Ltd 36 Underwood Road Borenore, New South Wales 2800 Australia	Cabonne Shire Council

#### Control measures

*The following licence conditions restrict the spread or persistence of the GMOs and their genetic material in the environment.*

#### **Viable GMOs must not enter food or feed, or be released into the environment**

22. The viable GMOs must not be used, sold or otherwise disposed of for any purpose, which would involve or result in their use as food for humans.

23. Only Decontaminated and, where antibiotic resistance genes are present, Denatured GMOs may be used for the purpose of preparation of animal feed, as a soil conditioner or disposed of as waste.

*Note: The Decontamination and Denaturation method must be tested and validated to be effective against killing and Denaturing the GMOs in accordance with Condition 37.*

#### **Control measures related to exposure of the GMOs**

24. Staff conducting dealings with the GMOs must wear appropriate personal protective equipment (PPE) including coveralls, P2 mask and gloves.

#### **Control measures related to dispersal of the GMOs**

25. Culture of GMOs may only be undertaken in:

- (a) closed Culture vessels; or
- (b) vessels approved in writing by the Regulator.

26. Transfer of fluids must be either through stainless steel pipes or a closed transfer vessel.

27. During culture of the GMOs, and until all Culture vessels and Equipment in contact with GMOs have been Decontaminated, any person that may come into contact with the culture solution must:

- (a) ensure that containers are clearly labelled;
- (b) employ work practices that minimise the production of aerosols;
- (c) use appropriate protective clothing as specified in Condition 24; and
- (d) Decontaminate hands before leaving the Production facility.

28. While the GMOs are growing in a Culture vessel, the Production facility must be inspected by people trained to recognise spills/leaks of culture medium, and actions taken as follow:

Area	Period of inspection	Inspection frequency	Inspect for	Action
Production facility	<b>From</b> the commencement of culture of any GMOs in a Culture Vessel <b>until</b> culture of any GMOs in a Culture Vessel has ceased, and the Culture Vessel and all Equipment in contact with GMOs has been Decontaminated.	At least once every two days. Inspection records must be kept and provided to the Regulator, if requested.	Spilled Culture solution containing GMOs.	Implement contingency plan in accordance with Condition 38
			Failures of reticulation system or Equipment	Repair. Failure incidents and repairs must be notified to the Regulator as soon as reasonably possible.

29. Equipment used for separating the supernatant and GMO must be operated in a manner that avoids generation of aerosols and dispersal of GMOs.

30. The final purified proteins must be tested for absence of the GMOs using a documented and validated procedure. If GMOs are found to be present, they must be destroyed before further use. Records of the validation procedure must be kept and provided to the Regulator on request.

### Transport and storage of the GMOs

31. Unless covered under another authorisation under the Act, the licence holder must ensure that transport of the GMOs is conducted only for the purposes of, or in the course of, another dealing permitted by this licence, or for supply in accordance with Condition 11.

32. Unless covered under another authorisation under the Act, the licence holder must ensure that transport and storage of the GMOs or samples containing GMOs within the Production facility or between the Production facility and the clients follows these sub-conditions:

- (a) GMOs must be contained within a sealed, unbreakable primary container, with the outer packaging labelled to indicate at least:
  - i) that it contains GMOs; and
  - ii) the contact details for the licence holder; and
  - iii) instructions to notify the licence holder in case of loss or spill of the GMOs; and
- (b) procedures must be in place to ensure that GMOs can be accounted for and that a loss of GMOs during transport or storage or failure of delivery can be detected; and
- (c) access to the GMOs is restricted to authorised persons for whom Condition 18 has been met; and
- (d) a consolidated record of all GMOs being stored under this condition is maintained and made available to the Regulator upon request.

*Note: All stored GMOs remain the responsibility of the licence holder.*

33. The licence holder must ensure that a record is kept documenting, at a minimum, each individual GMO covered by this licence and the details of its genetic modification. Records must be kept and made available to the Regulator, if requested.

### Decontamination



34. Unless covered under another authorisation under the Act, the licence holder must ensure that all GMOs and all waste reasonably expected to contain GMOs are Decontaminated:

- (a) prior to disposal, unless the method of disposal is also a method of Decontamination; and
- (b) before or upon suspension, cancellation or surrender of the licence, unless covered by another authorisation under the Act, or exported; and
- (c) by autoclaving, heat or chemical treatment, or any other method approved in writing by the Regulator.

35. The GM yeast slurry and Equipment that comes into contact with GMOs must be Decontaminated by a heat treatment or chemical inactivation that have been tested and validated for effectiveness in killing the GMOs. Records of validation methods must be kept and provided to the Regulator on request.

36. The Decontamination method and test results from the first run must be documented and provided to the Regulator before proceeding with the next run.

37. Where antibiotic genes are present in the GMOs, in addition to Condition 35 and 36, the GMOs must be Denatured with a method or methods that have been tested and validated for effectiveness at Denaturing the GMOs. The validation results from the first run must be documented and provided to the Regulator before proceeding with the next run.

#### **Contingency plans**

38. If there is a spill or an unintentional release of GMO at the Production facility, the following measures must be implemented:

- (a) the GMOs must be contained to prevent further dispersal;
- (b) persons cleaning up the GMO must wear appropriate PPE;
- (c) the exposed area must be Decontaminated with an appropriate chemical disinfectant effective against the GMOs or in case of a large spill, the effluent that goes to a holding tank must be Decontaminated;
- (d) any material used to clean up the spill or PPE worn during clean-up of the spill must be Decontaminated; and
- (e) the licence holder must be notified as soon as reasonably possible;

39. The licence holder must inform the Regulator as soon as reasonably possible:

- (a) In the event of a loss or spill of the GMO; and
- (b) In the event of the exposure of a person to the GMO.

## **Section 4 Reporting and Documentation**

*Note: The following licence conditions are imposed to demonstrate compliance with other conditions and facilitate monitoring of compliance by staff of the OGTR. Notices and reports may be emailed to [OGTR.M&C@health.gov.au](mailto:OGTR.M&C@health.gov.au).*

#### **Notifications to the Regulator**

40. At least 14 days prior to commencing culture, or a timeframe agreed to in writing by the Regulator, the licence holder must provide the Regulator with a Compliance Management Plan, specifying:

- (a) the role and contact details for key persons responsible for the management of the protein production process at the site;
- (b) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the protein production process and have been consulted regarding site specific procedures;

- (c) the proposed reporting structure for the protein production process at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16 and 28;
- (d) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;
- (e) the person(s) or class of persons working with the GMO;
- (f) the expected date of first culture of the GMO; and
- (g) method of analysis of detecting the GMO in the environment. The detection method must be capable of identifying each GM yeast under this licence.

41. Upon request from the Regulator, the licence holder must provide any records, signed statements, written agreements or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.

## Attachment A

**DIR No: 200**

**Full Title:** Fermentation and processing of recombinant proteins using genetically modified *Pichia pastoris*

### Organisation Details

Postal address: Cauldron Molecules Pty Ltd  
36 Underwood Road  
Borenore, New South Wales 2800

Phone No: +61 263652266

### GMO Description

#### **GMOs covered by this licence:**

*Pichia pastoris* genetically modified only by the genetic modifications listed in Table 1 below.

Common Name: *Pichia pastoris*

Scientific Name: *Komagataella phaffii*

#### **Modified traits:**

Categories: Animal proteins

Description: The GMOs secrete several animal food and fibre proteins via a non-animal source.

#### **Genetic modifications responsible for conferring the modified traits**

GM *Pichia pastoris* will have an insertion of expression cassette for producing either bovine milk, chicken egg or spider silk fibre protein (Table 1). The expression cassette may also contain:

- antibiotic selectable marker genes that confer resistance to a specific antibiotics limited to zeocin, hygromycin, ampicillin or kanamycin to enable selection for the GMO
- secretion signal peptide to facilitate secretion of proteins
- constitutive or inducible promoter to facilitate expression of introduced sequences
- tags such as epitope or polyhistidine to detect and purify the recombinant proteins

Table 1: Expressed proteins

<b>Class of proteins</b>	<b>List of Proteins</b>
Bovine proteins from <i>Bos taurus</i> :	<ul style="list-style-type: none"><li>• <math>\beta</math>-lactoglobulin</li><li>• <math>\alpha</math>-lactalbumin</li><li>• Bovine lactoferrin (bLf)</li><li>• <math>\beta</math>-Casein A1 and A2</li><li>• <math>\alpha</math> casein <math>\alpha_{S1}</math> and <math>\alpha_{S2}</math></li><li>• <math>\kappa</math> casein</li></ul>
Chicken Egg Proteins from <i>Gallus gallus domesticus</i>	<ul style="list-style-type: none"><li>• Ovalbumin (Gal d 2)</li><li>• Ovomuroid (Gal d 1)</li><li>• Ovotransferrin (Gal d 3)</li></ul>

	<ul style="list-style-type: none"> <li>• Type 1 Egg collagen protein Col1A1 and Col1A2; collagen X (<i>COL10A1</i>)</li> <li>• fibrillin-1 (<i>FBN1</i>)</li> <li>• Cysteine rich eggshell membrane protein (<i>CREMP</i>)</li> </ul>
Orb weaver spider proteins from <i>Nephila calvipes</i>	<ul style="list-style-type: none"> <li>• Major ampullate spidroin 1 (MaSp1 or MaSp2)</li> <li>• Minor ampullate spidroin1 and 2 (MiSp1 and 2)</li> <li>• Flagelliform protein (Flag)</li> </ul>

**Purpose of the dealings with the GMOs:**

The purpose of the protein production process is:

- (a) To optimise the fermentation process, and
- (b) To characterise the GM *P. pastoris* during production of animal proteins.

## Attachment B – Summary of reporting requirement

Prior to the commencement of the protein production process	Condition	Timeframe for reporting
<p>A written Compliance Management Plan for the production facility:</p> <ul style="list-style-type: none"> <li>(a) the role and contact details for key persons responsible for the management of the protein production process at the site;</li> <li>(b) that the IBC associated with the site (if any) has been notified of the protein production process and have been consulted regarding site specific procedures;</li> <li>(c) the proposed reporting structure for the protein production process at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16 and 28;</li> <li>(d) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;</li> <li>(e) the person(s) or class of persons working the GMO;</li> <li>(f) the expected date of first culture of the GMO</li> <li>(g) method of analysis of detecting the GMO in the environment.</li> </ul>	40	At least 14 days prior to commencing work with the GMO, or a timeframe agreed to in writing by the Regulator
Information to be provided at any time during the protein production process	Condition	Timeframe for reporting
Any additional information related to the health and safety of people and the environment associated with the dealing covered by the licence, or any unintended effect of the dealing authorised by the licence	15(a),(c)	Immediately
Information related to any contravention of the licence by a person covered by the licence	15(b)	Immediately
Any relevant conviction of the licence holder	16(a)	Immediately
Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country, being a law relating to the health and safety of people or the environment	16(b)	Immediately

Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately
Spill or failure identified during inspections	28	As soon as reasonably possible
<b>Information to be provided on request by the Regulator</b>	<b>Condition</b>	<b>Timeframe for reporting</b>
Information related to the persons covered by the licence	8	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
Information related to the genetic modifications to each of the GMOs covered by this licence	33	Made available to the Regulator upon request
The Decontamination method and test results must be documented and provided to the Regulator.	36	Test results from the first run must be documented and provided to the Regulator before proceeding with the next run
The Denaturation method and test results must be documented and provided to the Regulator.	37	Test results from the first run must be documented and provided to the Regulator before proceeding with the next run
Any records or documentation collected under a condition of this licence	41	Within a timeframe stipulated by the Regulator