



## IMPROVAC® A Food Safety Perspective

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### Introduction

Global population growth will place strong pressure on the world's ability to supply food. To meet demand the pig industry must become more efficient. There are also increasing demands that food producing animals should be raised under conditions that respect environmental sustainability and animal welfare.

The release of the first commercial vaccine to control boar taint, IMPROVAC, gives pig producers a powerful new tool to both improve efficiency and to raise pigs in a more humane and environmentally responsible manner.

However, as with most new technologies introduced to food production, consumers and those representing them are likely to have questions about any potential impact on food safety.

This technical bulletin will review some key studies that confirm the inherent safety of IMPROVAC for use in pigs intended for human consumption.

### What is IMPROVAC?

IMPROVAC is a unique immunological product, or vaccine, for the control of boar taint in intact male pigs. IMPROVAC provides an immunological, non-surgical, non-hormonal solution for this universal problem in pig production.

As a result of how IMPROVAC works and when it is applied its use:

Allows the concentrations of boar taint compounds to fall to the sub-sensory levels typically present in female and physically castrated pigs. <sup>1, 2, 3,</sup>

### KEY POINTS

- IMPROVAC is a novel immunological product for the control of boar taint. It works solely through the immune system of the pig.
- IMPROVAC is a safe and effective alternative to physical castration for the control of boar taint.
- IMPROVAC is not a hormone and has no hormonal or pharmacological activity.
- IMPROVAC is not a genetically engineered product and contains no microbiological agents.
- IMPROVAC has no activity if orally consumed.  
  
IMPROVAC is as effective as physical castration in the successful elimination of boar taint.
- IMPROVAC has been used successfully for almost 10 years in Australia and New Zealand and more recently in many other countries.
- IMPROVAC produces the same high-quality meat that consumers demand in a more humane and efficient manner.

Allows male pigs to show the natural growth pattern of intact boars during the fattening period. In other words, it prevents the losses in growth performance and carcass conformation that occur as a direct consequence of physical castration very early in life.<sup>1, 2, 3, 4, 5</sup>

Eliminates the mortality and morbidity associated with physical castration.

IMPROVAC's only direct effect is to stimulate a specific antibody response that blocks testicular function, which then results in the elimination of boar taint.

IMPROVAC does not add hormones to the animal nor does it stimulate hormone production.<sup>6</sup> To the contrary, it is simply an immunological way to obtain the same effects currently produced by physical castration.

## How does IMPROVAC work?

Vaccination with IMPROVAC stimulates the immune system to produce specific antibodies that neutralise its own gonadotropin releasing factor (GnRF) thus blocking testes function and the accumulation of taint.

GnRF is the key hypothalamic regulator of testicular function. When released from the hypothalamus it binds to specific receptors in the pituitary gland where it stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). These hormones then control the growth and activity of the testicles leading to sexual maturity, behavioural changes and increased levels of boar taint.

Like many vaccines, a full immunization course of IMPROVAC consists of a priming dose followed by a second dose (at least 4 weeks later). The initial dose primes the pig's immune memory cells but does not stimulate effective levels of anti-GnRF antibodies. Thus, there is no suppression of testes function, the pig continues to grow and behave as a fully functioning boar, benefiting from its natural growth factors.

The second dose, administered close to slaughter, stimulates high levels of specific anti-GnRF antibodies. These antibodies bind to and neutralize endogenous GnRF. This temporarily stops stimulation of the pituitary and thus inhibits testicular function. As a consequence, the accumulation of the boar taint compounds (androstenone and skatole), dependent on testicular function, is suppressed and any taint already present at the time of immunization is eliminated.

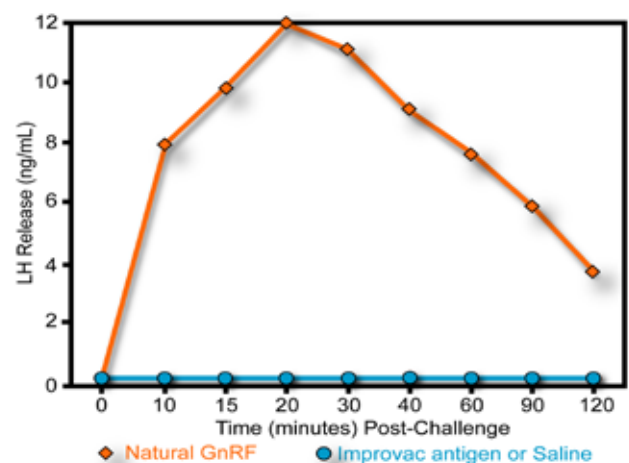
Refer to the Pfizer Technical Bulletin – Mode of Action for further details on mode of action.

## No Hormone Activity

One of the common misunderstandings with the immunological approach to boar taint control is the issue of perceived hormone activity. Frequently it is thought that products, like IMPROVAC, must have hormone activity or that because they affect hormones they must be hormones. **This is simply not the case.**

Because natural GnRF is not immunogenic, IMPROVAC's GnRF analogue is conjugated to a large carrier protein in order to be recognised by the immune system. This process would be expected to abolish direct hormone activity and with IMPROVAC this expected absence has been confirmed. When the IMPROVAC antigen is injected it has zero activity in stimulating LH release from the pituitary.<sup>6</sup>

In an study to test an extreme challenge by direct injection into the bloodstream, sheep were given either 1 µg of natural GnRF, 50 µg of the IMPROVAC antigen or saline. Blood samples were collected at varying intervals following injection and assayed for LH concentration. The results are shown in Figure 1.



**Figure 1.** Effect of the IMPROVAC antigen or saline or natural GnRF on LH release.

The complete lack of hormonal activity of the antigen provides convincing evidence that no direct hormonal effect can possibly occur either in the pig, or in man following hypothetical consumption of the antigen.

## IMPROVAC is not active if orally consumed

A human food safety question which is often raised for products used in animals is that of residues in meat and possible effects on consumers. Such questions are typically directed to drug or pharmaceutical products rather than vaccines as the complex biological molecules found in vaccines are usually quickly degraded, either in the body of the vaccinated animal or, if they should ever get so far, by cooking or in the gastro-intestinal tract of a consumer.

To confirm that the expected intrinsic food safety of a protein-based vaccine also applies to IMPROVAC Pfizer has conducted a number of studies to assess the oral bioavailability of the IMPROVAC antigen.<sup>6</sup> The conclusion from these studies is clear. The IMPROVAC antigen is not bioavailable when given orally.

Repeated oral ingestion of the antigen, even at doses 70 fold higher than the maximum possible exposure if a human ate an entire uncooked injection site immediately after vaccination, has been proven to have no activity on the immune system, testicular function, biochemistry, haematology or the test animals' general health and well-being.

**Study 1** - This study involved the pig as a model for human gastric function. Six male pigs were orally dosed with 2 full doses of IMPROVAC at an interval of 4 weeks. Six non-dosed pigs served as negative controls.<sup>6</sup> Blood samples were assessed for anti-GnRF antibodies and testosterone at intervals before and after dosing.

No antibody response was detected following the two oral doses of IMPROVAC. Testosterone in treated pigs was not different from that in the control pigs (Table 1). All pigs remained well during the study.

**Table 1.** Mean ( $\pm$  SD) serum testosterone concentration (ng/ml) in pigs given 2 oral doses of IMPROVAC.

	Day 14*	Day 28**	Day 42
Control	0.69 ( $\pm$ 0.35)	1.04 ( $\pm$ 0.35)	1.18( $\pm$ 0.49)
Improvac	1.33 ( $\pm$ 0.84)	1.15 ( $\pm$ 0.49)	0.92 ( $\pm$ 0.26)
P value	0.44	0.59	0.57

\* 14 days after first dose \*\* day of second dose

The conclusion is that IMPROVAC has no effect when administered orally to pigs – a good model for human gastric physiology.

**Study 2** – The effects of repeated oral dosing was conducted using laboratory animals at doses up to 70-times the exposure if a 60 kg human directly consumed a full 2  $\mu$ L dose of IMPROVAC.<sup>6</sup>

In brief, IMPROVAC was orally administered twice, 4 weeks apart to Sprague Dawley rats at doses of 11.4  $\mu$ g/kg, 272  $\mu$ g/kg or 462  $\mu$ g/kg. IMPROVAC given by subcutaneous injection was also included as a positive control.

All oral doses failed to elicit any immunological or hormonal effects. Based on these results, an oral no-observed-effect level (NOEL) for the IMPROVAC antigen was considered to be at least 462  $\mu$ g/kg, the highest oral dosage level given. On a weight-for-weight basis, this oral NOEL is at least 70-fold greater than the recommended 2 mL injectable dose for IMPROVAC.

*Or put another way the NOEL for antigen exposure was equivalent to that received if a person were to drink 140 mL of IMPROVAC on two occasions.*

In addition to no oral bioavailability there was no quantifiable antigen detectable in the serum of any rat whether the vaccine was given orally or by SC injection at any of the sampling times (1, 4, 8, 12, and 24 hours and 2, 7, 14, and 21 days after either dose).

As may be expected for a protein based vaccine designed to be given by injection, the results of these 2 studies demonstrate the lack of bioavailability following oral ingestion of IMPROVAC. These data further support the expectation that hypothetical consumption of meat containing vaccine residues would have no biological effect, either immunologically or hormonally.

## 10 years of commercial use

IMPROVAC has been safely used in Australia and New Zealand for almost 10 years with no reported consumer concerns about food safety. In recent years IMPROVAC has been registered in an additional 17 countries and is being increasingly used in many other countries around the world including – Korea, Philippines, South Africa, Mexico and Brazil.

## Consumer acceptance

Consumer market research has been conducted in a range of countries <sup>7, 8, 9, 10</sup> to assess consumers' reactions to the use of vaccines to control boar taint and to gauge their preference for the vaccination approach or physical castration (either with or without anaesthesia). In each study the vast majority of consumers preferred the vaccination approach compared to physical castration.

In addition to these public surveys numerous consumer sensory assessment studies have consistently demonstrated that consumers were unable to distinguish any quality differences between pork from boars given IMPROVAC and pork from female or physically castrated pigs. <sup>11, 12, 13, 14, 15</sup>

## Summary

IMPROVAC is a safe and effective vaccine that works through the pig's immune system to block the compounds that cause boar taint in certain male pigs.

Utilisation of this approach by the international pig industry will allow improvements in the efficiency of pork production, place less pollution pressures on the environment and significantly improve animal welfare.

The studies presented above confirm that pork from boars given IMPROVAC is fully safe for human consumption.

These studies prove that IMPROVAC has no hormone activity, and even at significant overdoses, has no oral activity.

Indeed the national regulatory agencies in 19 countries (as of May 2008) that have licensed IMPROVAC have all applied a zero day withholding time.

Care should be taken not to extrapolate the results in this paper to other experimental immunocastration vaccines reported in the literature or under development. These results are specific for the antigen used in IMPROVAC.

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