

## CHAPTER 6

### QUALITY STANDARDS OF MEDICAL GRADE MANUKA HONEY

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The concept of ‘medical grade honey’ started in August 2000 following global demand for high quality medical grade honey and honey-based health products. Our company, Comvita, specifically its medical division, has ongoing activities in honey research and intellectual property development together with the University of Waikato, Hamilton, New Zealand. The company currently holds a range of honey product patents and also participates and funds numerous research and clinical trials for further product development and extension. The research interest of the company extends from wound care to oral/dental hygiene, throat care, internal health, skin care, eye care and immune support.

A unique accredited honey supply programme has been developed as company intellectual property to meet the quality requirements of Medical Device manufacturing internationally. The programme includes an accredited supplier network with the development of quality standards and systems for honey resourcing, harvesting and extraction. Quality management standards and systems have also been developed for honey processing. Strict product testing regimes were also set for ensuring the integrity of ‘medical grade honey’ supply.

Whilst some of the more exact components of the medical grade honey processing and measuring techniques, as well as the supply programme, are held confidentially within intellectual property management, this chapter gives an overview of the exacting efforts put in to ensure that the honey used in the medical arena is of true ‘medical grade’.

The systems developed for the programme were done in consideration of preventing any possible microbiological, physical and chemical contamination that cannot be removed afterwards, and also for the

prevention of natural quality deterioration/loss during storage. Traceability of the honey from hive to finished product is also an essential part of the system developed. A series of workshops with landowners, beekeepers and honey extractors have been carried out to introduce the concept of 'medical grade honey', and to develop standards and systems. At the end of the supply programme an assessment is undertaken of the suppliers, and only the suppliers that pass the assessment are able to supply medical grade honey. The accredited suppliers are also regularly audited and monitored by Comvita, throughout each honey season, to ensure compliance with the standards and systems developed.

We are committed to improving continually the quality of medical grade honey by conducting full breakdown analysis on resource sites, harvesting/beekeeper practices and extraction processes, including a full analysis of all inward raw medical grade honey received each season. Supplier management manuals are updated annually as improvements are required. Feedback and improvement meetings with suppliers are held regularly to ensure that all supplier practices are kept up-to-date and current.

## Introduction

The use of honey as a topical antibacterial agent has been emphasised by New Zealand's University of Waikato Professor, Dr Peter Molan, since 1989, and is gaining acceptance for the treatment of surface infections such as ulcers, burns, injuries, pressure ulcers, and surgical wounds (Cooper *et al*, 2001; Cooper and Molan, 1999; Molan, 1998; Molan, 2001). A feature of the usage of active Manuka honey is the rapid clearance of infection, in many cases from wounds that had not responded to various forms of conventional treatment (Cooper *et al*, 1999; Molan and Allen, 1996).

The supply programme is a unique framework of partnership in land use and honey supply, working together with landowners and beekeepers, to ensure continuing and expanding economic benefit from premium quality medical grade Manuka honey. It was developed from an unwavering commitment to sustainable resource management and robustness of medical grade honey supply into the Medical Device market. The concept started in August 2000 following global interest in, and demand for, high quality medical grade honey and honey-

based health products. Through the consumer and specialty product activities, the company seeks to introduce therapeutic and beneficial effects of honey to all those with a concern for natural health.

We are continuing to develop close business relationships with international companies involved in relevant clinical, therapeutic and health-related products for development, distribution and manufacturing of Medical Device/therapeutic honey products.

## **Microbiological quality control for medical grade honey**

There is a risk of introducing micro-organisms into wounds, especially botulism, if honey is used as a dressing (Molan and Allen, 1996). The risk can be avoided by sterilisation. Gamma irradiation is one of the more common sterilisation methods in the wound dressing industry and it was found that gamma irradiation does not affect the antibacterial activity of honey (Molan and Allen, 1996). An international Medical Device ingredient microbiological requirement for manufacturing is a total plate count (TPC) of less than 500 colony forming units (cfu) per gram (g). The microbiological specification is required to meet a pre-sterilisation (gamma irradiation) requirement, ensuring the sterilisation process is always successful; thereby eliminating the risk of introducing micro-organisms into wounds from honey dressings.

Primary microbiological contamination sources for honey include pollen, the digestive tracts of honey bees, dust, air, earth and nectar. The secondary contamination sources (processing, after harvest) include air, water, human/honey handlers, honey extraction and processing equipment and buildings (Snowdon, 1999; Snowdon and Cliver, 1996). Due to the natural physical properties of honey that serve to inhibit microbial growth — ie. low moisture (less than 21%), low water activity ( $A_w$  0.5–0.6) and acidic environment (pH 3.4–6.1), the microbes of concern are from contamination; especially from post-harvest handling (Snowdon and Cliver, 1996).

Commonly found microbes in honey are osmophilic or sugar tolerant yeasts, moulds and spore-forming bacteria. Our medical grade honey processing system has been validated to ensure any existing yeast and mould cells, if present, are destroyed effectively, without damaging any honey quality aspects. However, removal of contaminated spore-forming

bacteria (eg. from the genus *Bacillus*) in honey is not easy; the bacterial load does not reduce during storage, unlike other certain vegetative cells that have been known to decrease after time in honey, due to its antimicrobial properties that discourage the growth or persistence of many micro-organisms (Snowdon and Cliver, 1996). The honey supply programme, which is being managed very successfully, focuses on the prevention of possible spore-forming bacterial contamination.

Due to strict hygiene control from honey collection to honey extracting and processing, possible contamination of micro-organisms (eg. coliform bacteria and pathogenic bacteria such as *Staphylococcus*, *Salmonella* and *Clostridium* species) that indicate poor sanitary quality of honey has not been an issue for the medical grade honey supply programme. Strict packaging standards and storage conditions for extracted honey have also helped in the prevention of possible microbial increases during storage.

## **Development and management of a honey supply programme**

Historically, the microbiological total plate count level of honey could vary from less than 100 cfu/g to greater than 50000 cfu/g. From this historical information on the variance of microbiological levels in honey, the need was recognised to develop a supplier programme to control possible microbiological contamination during the harvesting, extraction and processing stages of honey collection. Adding to the international Medical Device ingredient requirements are specifications for physical and chemical contamination, as well as accurate and reliable traceability of the honey from hive to finished product. These additional factors only reconfirmed the need for a robust mechanism for sustainable medical grade honey supply into the international Medical Device market.

To meet the Medical Device ingredient requirements, a supplier network was developed, with suppliers accredited to our organisation ensuring compliance of quality standards and systems. These standards and systems have been developed with the suppliers, to ensure adequacy and practicability of implementation from the Manuka resources to honey harvesting and extraction, and also for honey processing. The strict raw material and finished product specifications for Medical Device ingredients are adhered to rigorously to ensure that honey supplied to the international market is of appropriate quality.

## Overview

Operating at the heart of the supply and production chain, we have established quality management policies and procedures, setting and ensuring maximum achievable standards to cover the total resource management, product sourcing, harvest, extraction and production cycle. Throughout, we operate to and demand stringent and comprehensive risk management and conformance policies.

Figure 6.1 shows the integrated supply chain management for the extended honey supply programme, which was implemented in 2002, and has been operating effectively ever since.

The honey supply programme involved a series of workshops and education days with landowners, beekeepers and honey extractors. The purpose was to introduce the concept of 'medical grade honey' and develop standards and systems that would enable stringent quality specifications to be met. Once the concept of medical grade honey was introduced to the suppliers, draft protocols for quality management standards were developed and reviewed for each stage of the raw material honey supply chain. Once reviewed, a final set of standards were developed and issued for implementation. Prior to final implementation in the field, one of the last parts of the programme included an assessment of the quality standards. Only those suppliers that pass the assessment are able to supply raw medical grade honey for analysis.

We now have a considerable number of contracted accredited medical grade honey suppliers and extractors, as well as a large pool of contracted general honey suppliers with the potential to become accredited medical grade honey suppliers, as and when honey dressing product growth is seen in the market. We are committed to ensuring large stock piles of medical grade honey are kept available to respond to any market growth for honey dressing products.

Medical grade Manuka honey is grown from a specific resource and harvested and processed purely for that purpose. The Manuka plant is a rapid growing, hardy plant and is native to New Zealand. The Manuka resource of New Zealand is in plentiful supply, which has by no means been exhausted; again allowing for potential future growth of medical grade honey supplies.

Overall, the objective of the supply programme is to assess and manage every stage in the production of the honey, and ensure full traceability back to the hive (Figure 6.2) and collection environment. The quality systems and standards developed ensure that the final product requirements for minimal levels of microbiological, chemical and physical contamination

of the honey are met. We have conducted full audits on each accredited supplier against the standards at the implementation stages, and we will continue an audit monitoring programme to ensure continual compliance throughout each honey production season (*Figure 6.3*).

## **Systems and standards**

We have set the systems and standards for production of honey, based on international criteria for raw material supply for medical device manufacturing. The systems are also designed for preventing contamination that cannot be removed afterwards, and for the prevention of natural quality deterioration/loss during storage. The honey quality aspects that need to be considered to meet the standards are contamination issues (physical, chemical and microbiological), sensory quality (smell, taste, and colour) and other quality issues such as moisture content, honey fermentation, sugar crystals and Manuka honey gelling character.

## **Resource management**

The honey supply programme has been designed with landowners who are actively engaged with our organisation and our honey suppliers in the production of medical grade honey. The Manuka resource land management standards are based on 'organic' land use programmes and require that landowners work closely with beekeepers in all aspects of land management and honey harvesting. In return, accredited landowners who meet the specific requirements of the honey supply programme can expect to see land-usage benefits, and financial reward, from a percentage of the volume of medical grade honey produced off their land.

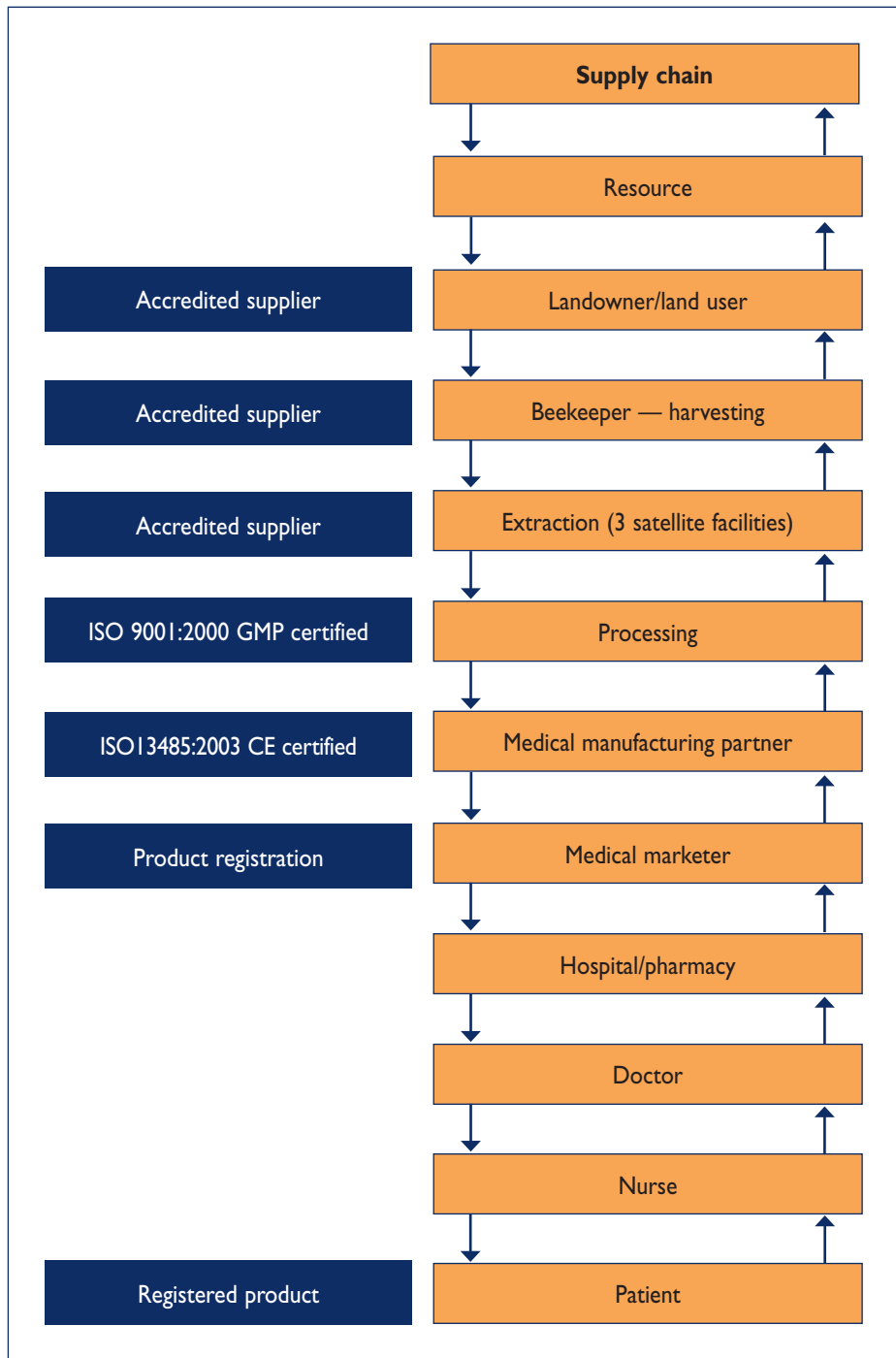


Figure 6.1: Integrated supply chain management





Figure 6.2: Site identification — ensuring product traceability



Figure 6.3: Auditing 'medical honey' harvesting — quality manager (medical)



## **Harvesting management**

For medical grade honey harvesting, we require strict beekeeper conformance with harvest and apiary management standards. The harvest and apiary management standards involve hive site location and hive management. As part of hive management the beekeeper must use appropriate hive materials and have correct maintenance procedures. The components of the hives and their foundations must be considered, along with pest and disease management. During harvesting, smoker fuel is controlled and the bee removal process is designed in such a way that there is minimal contamination from both the equipment used and the bees themselves. Hygiene throughout the honey harvesting and transportation process is a critical factor (*Figures 6.4 and 6.5*). The harvest and apiary management standards even extend to supplemental feeding during the winter time.

## **Extraction standards**

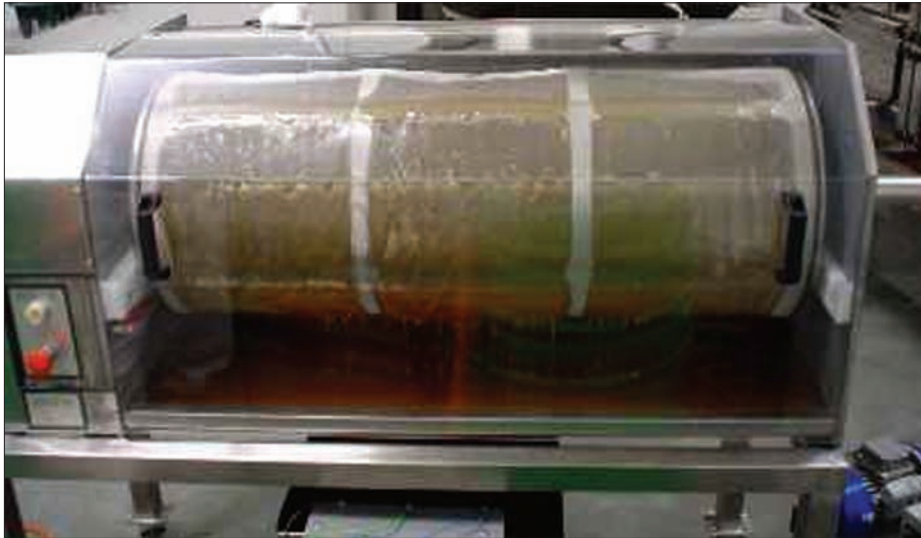
For medical grade honey extraction, we require extractor conformance with its extraction management standards. In summary, the standards cover critical factors of the extraction process, such as the implementation of stringent cleaning programmes to ensure hygienic extraction and the control of cross-contamination of products via appropriate extraction methods with effective wax removal procedures. Extraction facilities are required to have specifically designed and controlled air conditioning and filtration systems, along with an effective pest management programme. Processing temperatures and honey filtering systems are controlled adequately with specific requirements being placed on the filter pore size (*Figure 6.6*). Careful consideration is given to the type of drum used for raw medical grade Manuka honey, as well as the requirements of drum storage. Overall, throughout the extraction process, product traceability is still maintained to a high standard to ensure accurate trace-back if required.



Figure 6.4: Stringent medical grade honey harvesting in practice



Figure 6.5: Special care for harvested honey boxes to be transported to extraction facility



**Figure 6.6: Medical grade honey filtration**

## **Product testing regimes**

We undertake strict testing regimes on the raw medical grade Manuka honey, using well developed in-house laboratory methods, as well as independent external laboratories for specific testing. The testing protocols involve rigorous analysis methods to ensure that products are safe and as pure as possible for inclusion in Medical Device manufacture.

## **Raw medical grade honey**

The raw medical grade Manuka honey arrives from accredited suppliers in new, unused food approved drums with tamper evident seals. Each consignment is documented and recorded upon receipt with a batch number; a further number is issued individually to each drum, allowing individual traceability of the drums. Once documented and receipted into the system, the laboratory begins the sampling, testing and grading process.

The honey is sampled representatively by the in-house laboratory ready for analysis. Honey samples are then tested for the following;

moisture content, total activity, non peroxide antibacterial activity (UMF® rating), foreign matter, sensory attributes such as Manuka typical taste and colour, and microbiological criteria, including the total plate count, and yeasts and moulds. Once test results are collaborated, each drum is individually graded against the raw medical grade Manuka honey specifications. Any drums that do not pass the raw medical grade Manuka honey specifications are reassessed for suitability within the therapeutic or food grade; if unsuitable for these grades the drums will be rejected (*Table 6.1*).

**Table 6.1: Examples of some of the differences between the raw medical grade honey standard compared with food and therapeutic honey grades**

	Food grade	Therapeutic grade	Medical grade*
Microbiological	<100,000 cfu/g	<10,000 cfu/g	<500 cfu/g
Chemical	No chemical residues, includes plant toxins and antibiotics	No chemical residues, includes plant toxins and antibiotics	No chemical residues, includes plant toxins and antibiotics
Physical	Insoluble matter content <1.0%	Insoluble matter content <0.5%	Insoluble matter content <0.2%
Drums	New/ remanufactured with food grade linings	New with food grade linings and tamper evident	New with food grade linings and tamper evident

\* Medical grade honey must be sourced from accredited suppliers who have participated and passed the accredited honey supply programme.

## Processed medical grade honey

Processed medical grade honey is raw medical grade Manuka honey formulated into a batch of product for use as an ingredient in medical devices. We operate a quality management system which complies with the requirements of AS/NZS ISO9001:2000 and is also Good Manufacturing Practice certified by the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE).

The raw honey is loaded in the factory and undergoes a minimal heat treatment process to ensure product quality. This heat treatment step has been carefully designed, implemented and validated, specific to the characteristics of honey, to ensure that the active Manuka content of the medical grade honey is unaffected.

The honey then passes through a fine filtration system and finally begins a homogenisation and pre-determined crystallisation process. Medical grade honey requires the best possible filtration techniques. We use very fine filters for the filtration of medical grade honey. Once the final stage of the process is completed the honey is pumped into new, unused drums which are fitted with a medical grade quality internal liner. This bag liner acts as the primary packaging and the honey is completely sealed within the liner to minimise or eliminate the risk of the processed medical grade honey coming into contact with the secondary packaging, the drum, and, more importantly, the external environment. At this stage the honey is tested for moisture content, pH level, heavy metal content, microbiological content, multi-pesticide residues (nil tolerance), 5-(Hydroxy methyl)-2-furfural (HMF) level, total activity and non-peroxide activity.

Once the honey has been cleared by quality personnel it is shipped to the Medical Device manufacturer where the honey is used as an ingredient for honey-impregnated Medical Devices. The Medical Device manufacturer operates a quality management system which complies with the requirements of BS EN ISO 13485 for the design and manufacture of medical products. The Medical Device Manufacturing Company also complies with the European Directives for medical devices in order to affix 'Certification European' (CE) marking on its products. Both our company and the accredited honey supply programme have been audited by the Medical Device Manufacturing Company, providing a double guarantee that the honey received as a Medical Device ingredient meets the Medical Device system requirements and specifications.

## **Achievements of the programme**

The required quality level demanded of medical grade honey does not come without cost implications. It is this high level of quality (achieved through specific standards and systems defined by Comvita) that sets medical grade honey above all other grades of honey, and warrants the exclusive use in premium medical applications for the medical market.

Until the year 2002, it was difficult to find honey that met the stringent international Medical Device manufacturing requirements. Through workshops, education programmes, assessment and auditing processes, the accredited honey supply programme was able to produce sufficient medical grade honey in 2003 to see the first honey-impregnated Medical Devices launched onto the medical market. With the ongoing support and supply of the honey suppliers within the accredited honey supply programme, we are able to sustain the supply of raw medical grade honey, as well as to begin to extend the range of honey-impregnated Medical Devices.

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