Validation Strategies for OTC Products

Presented by William E. Hall, Ph.D.
“practical, verifiable and achievable”

- A phrase common to many regulatory and guidance documents
Surprise!

- Validation is **not** a ‘bullet-proof’ guarantee of quality

- i.e. you still must compliant
Old saying

“The road to hell is paved with good intentions”

A more recent version is

“E. coli happens”
Risk Assessment

- A good first step, especially for OTC’s

- Let’s look at a risk continuum for all types of products and see where OTC’s generally fall
## A Risk Continuum*

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate Risk</th>
<th>Lower Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile injectables</td>
<td>Oral non sterile products</td>
<td>OTC’s</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
<td>Class 2 Medical Devices</td>
<td>Dietary Supplements</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td>Cosmetics</td>
</tr>
<tr>
<td>Certain hormones</td>
<td></td>
<td>Some topicals</td>
</tr>
<tr>
<td>Class 1 Medical devices (pacemakers, implantable devices)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly Potent Drugs (New Category)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*List is not all-inclusive and is based on use as intended and could change with misuse situations.
Further evidence that OTC’s are less risky

- The public is allowed/encouraged to purchase without a prescription
- Self-medication, i.e. to determine when more is needed (based on label instructions)
My Basic Assumption

- Based on being ‘less risky’, it should be possible to allocate less resources to validation of OTC products so that more resources could be devoted to more potent products.
Does all this mean that OTC’s are not potentially hazardous

Answer = not necessarily, it depends on the situation
Medicines recall alert

Alarm on herbal, vitamin remedies

The Therapeutic Goods Administration (TGA) ordered the immediate withdrawal of 215 products after finding that their maker, Pan Pharmaceuticals, had been substituting ingredients, manufacturing test results and engaging in substantial misleading practices.

Thousands more health products made by Pan and sold throughout Australia under other brand names could also be recalled, the TGA said. But a complete list of them might not be available for some days.

The announcement came to confusion last night as supermarkets and pharmacies were told to remove the products from their shelves.

The TGA said prescription medicines were not affected, and that people should continue taking essential medicines.

An initial list of recalled products appears in The Age today on page 12.

The pharmacy suppliers, including Blackmores, Heritage and AustraLife and Unicare issued statements last night saying their products were not affected. A list of other companies and brands, not affected for the recall can be found on The Age website.
Lives in danger as contaminated vitamins recalled

Trudy Harris
Andrew Fraser

EVERYONE should stop taking all non-essential vitamin and mineral supplements following the nation's biggest recall of medical products.

Health authorities issued the warning after yesterday recalling 239 vitamin and nutritional supplements, pain relievers and other products adding that thousands more could be recalled in coming days.

The recall a crisis for the billion-dollar over-the-counter natural remedy industry, was sparked by a Therapeutic Goods Administration audit of the nation's largest maker of herbal and nutritional supplements, Pan Pharmaceuticals.

The audit found Pan was taking live by releasing products despite failing to test raw ingredients, or folding the results of tests. Equipment at its headquarters in Sydney was not licensed between batches, potentially contaminating products.

Federal and state health authorities said the problems at Pan appeared to be widespread.

Some of the recalled products

- 3211 21st Century
- Delicia Children's
- Hall's Mints
- Men's Healthy
- Orangeupal
- Tablet-acetaminophen
- Tablets-eferous
- Tablets-750mg
- Women's Multi
- Zinc Oxide

The full list is at www.therickinaus.com.au

Cities charged could be laid and the company's licence had been suspended.

The TGA found a litany of insanitary and unsanitary practices, including manipulation of test results and substandard manufacturing processes. Ms Worth said: "It is possible that there are still other products in many homes in Australia."

Advertisements will appear in newspapers today and tomorrow listing the recalled products and their five-digit identification numbers. The TGA conceded the extent of the problem was unknown because Pan supplied other companies that reformulated the products. It refused to name the companies but warned that a second wave of recalls was expected later this week.

Until then, TGA chief medical advisor John McEwen warned against taking any vitamin or nutritional product.

Only the most reputable brands of painkillers and cold and flu tablets sold over the counter should be taken, he said. But consumers should not stop taking prescription medicines, he stressed. Vitamin giant Atesco and drug company Hennessy said Pan made none of their products.

Pan has 70 per cent of the natural remedy market and recorded a $10.6 million profit last financial year. Founder James Selin said his personal wealth of $10 million collapsed by 80 per cent as shares plunging after the recall.

Ms Worth said Pan's vitamin A and natural remedy testing gels could be very harmful to pregnant women and children.

The audit was sparked after one of Pan's products, Travelcalm, was recalled in January when faulty batches made 78 people sick.

"Some people were very, very ill. They tried to jump out of places, off ships and things like that because of the hallucinatory effect," Ms Worth said. "We've been reliably informed it was fortunate nobody died."

Business - Page 19
Phone 1800 220 007 for more details or visit:

www.tga.health.gov.au

Medicare: Life imitates art as diva defies despair
THE VICTIMS

SHAE FRAWLEY, 10
Taken to hospital by ambulance after taking travel sickness tablets Travacalm. "I thought there were spiders, elephants and monkeys in front of me. They looked so real and I was pretty scared because I hate spiders."

BELINDA THOMSON, 18
The Lyrupda woman's dream holiday ended in hospital after taking Travacalm. "I was dizzy. It was scary. It was shocking. It was so bad."

MARK TIOHER, 37
The stockbroker suffered terrifying hallucinations from Travacalm. "You get nightmares but you're not actually dreaming at your head to.

MILLIONS OF PILLS DUMPED

MILLIONS of pills have been stripped from shelves across the nation. More than half the country's best-known health products were blacklisted.

Health watchdog Mayne Group yesterday launched its own probe into the failure by Pan Pharmaceuticals, Australia's biggest over-the-counter medicine maker, to recall Travacalm, Nature's Own and Bio-Organic vitamin brands as well as other national brands.

Mayne urged consumers to return products for refunds, among them Sanquil, Prenatal Lecithin and Epsom salt.

Prime Minister John Howard yesterday urged Australians not to panic amidst deepening uncertainty and confusion that was "beyond our control." Mayne chairman Mark Bevan said Travacalm was "the largest medical recall in Australian history and the suspension of Pan Pharmaceuticals' licences."

More than 300,000 Pan products, including the ASA in Epsom salt and Lecithin, were found to contain excessive levels of the active ingredient.

The Pharmaceutical Society of Australia and New Zealand said serious adverse events had been reported for Travacalm.

Recall: some of the products pulled from the shelves of the Ewelyn Faye nutrition store in Melbourne yesterday.

The public is being urged not to take vitamin supplements and other mass-produced pharmaceuticals until further notice.

Prescription medicines are not affected.

In developments yesterday, LEGAL action was set to begin in behalf of a 13-year-old girl and several other victims who suffered severe reactions to Pan-produced Travacalm.

A MELBOURNE woman said Travacalm turned an ordinary holiday into a $1,000 hospital nightmare.

AN INDUSTRY group warned up to 2000 small businesses could fail and $500 million could lose jobs as a result of the Pan Pharmaceuticals suspension.

FINANCIAL watchdogs ASIC began investigating Pan over apparent panic trading of its shares ahead of Monday's
Disease, safety fears hit alternative medicine and wheat industries

Banned drugs still on shelves

Trudy Harris
Robert Gottliebsen

PAN Pharmaceuticals products were still on shelves last night as confusion gripped the country over which alternative medicines were dangerous. Chemists and retailers demanded a list of specific products they should pull from shelves, but the Therapeutic Goods Administration, the industry regulator, said it had yet to finalize such a list.

Instead, companies are selling vitamins. Marine Group recalled hundreds of its complementary and alternative medicines manufactured by Pan, a move expected to cost the plant company up to $20 million.

The TGA has published on its website a list of 1500 export products that had been

Emergency plan to halt crop virus

Sophie Mouns
Richard Sproould

A NATIONAL emergency plan was activated last night after the discovery of a second case of the devastating wheat streak mosaic virus confirmed fears that the virus had jumped quarantine barriers.

Hundreds of grain farms and glass houses across the nation will be tested for the virus under the plan, activated by Federal Agriculture Minister Warren Truss after detection of the disease in Adelaide.

The Adelaide outbreak of the virus, which can reduce yield by up to 90 per cent, is the second in a fortnight to threaten the $15 billion grain industry.

The CSIRO destroyed 40,000 plants in its Canberra site earlier this month after detecting the virus in its glass houses there.

CSIRO experts last night insisted there was no link between the two outbreaks. But the new outbreak could mean the virus was more widespread.

We are talking hundreds of millions of dollars in losses to the industry.
Stonewalling Pan staff shredded files to foil watchdog

Goods Administration revealed attempts to investigate Pan’s operations were stonewalled. On one occasion, a Pan employee told TGA auditors that computer records could not be produced because they did not have the right password. The TGA’s chief auditor later complained to Pan management that staff had been disruptive.

‘A senior person is helping the company with its investigations’

Colin Henson Pan non-executive director

contradicted Pan’s claim of co-operation with the TGA in the hope of being back in the market. Henson was under investigation over problems that led to the recall. “There is one analyst who has been dismissed and there is a senior person who is helping the company with its investigations,” he said.

Mr Henson

The TGA recalled a product that sparked a TGA investigation – Trasalam. “We felt sorry for him it wasn’t his fault,” one colleague said, adding that Mr John, a father from Sydney’s west, was just following orders. The TGA recalled a product called Trasalam in January when 19 people were hospitalised after taking the tablets. The subsequent TGA investigation another 450 last night. Yet another 300 are set to be banned coming days as the TGA determines which alternative medicine companies are connected to Pan. The recalled products include Woolworths, Homebrand and ephedra.

Australian Pharmaceuticals Industry has recalled seven products under the Soul Pan son, Chemcow, Headi
PILL SAFETY LIST

- The government list of recalled pills
- Your questions answered
<table>
<thead>
<tr>
<th>AUST L or AUST R</th>
<th>PRODUCT NAME</th>
<th>Sponsor/Supplier</th>
<th>Batch Number</th>
<th>Expiry Date</th>
<th>AUST L or AUST R</th>
<th>PRODUCT NAME</th>
<th>Sponsor/Supplier</th>
<th>Batch Number</th>
<th>Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>16774</td>
<td>NPM Skin Cleanser Herbal Tablet</td>
<td>NATURAL PRACTITIONER MARKETING P/L</td>
<td>20074</td>
<td>12/05</td>
<td>27086</td>
<td>NATURAL NUTRITION HIGH Potency, Pineapple Enzymes Bromelain 500mg Tablets</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>16787</td>
<td>NPM Disctal Multivitamin and Mineral Tablet</td>
<td>NATURAL PRACTITIONER MARKETING P/L</td>
<td>11532</td>
<td>06/2004</td>
<td>28155</td>
<td>NATURE S OWN Natural Orange Flavour Super Antiacetic Powder bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>16805</td>
<td>NPM Zinc Balanced Formula Multinutritional and Vitamin Tablet</td>
<td>NATURAL PRACTITIONER MARKETING P/L</td>
<td>20004</td>
<td>05/2004</td>
<td>28137</td>
<td>NATURE S OWN Super Papaya Enzyme Tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>16904</td>
<td>NUTRITIONAL SCIENCES CO-ENZYME Q10 WITH BIOTIN, VITAMIN E CAPSULES (NI25%, NI25%)</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28159</td>
<td>NATURE S OWN 100% Natural Squalene 500mg tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17083</td>
<td>BIO-ORGANICS CO-ENZYME Q10 Capsule - Hard capsule</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28191</td>
<td>NATURE S OWN Extra High Potency Choline Stabilised Refined Multivitamin &amp; Mineral Tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17244</td>
<td>BIO-ORGANICS AMINO HAIR &amp; NAILS Nutritional Formula (with Herb)</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28178</td>
<td>NATURE S OWN Vitamin B Complex Forta, Waterara, Tingt Uitang &amp; Lecitina, 10mg Tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17269</td>
<td>BIO-ORGANICS ANTIOXIDANTS Multi Vitamin &amp; Mineral Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28199</td>
<td>NATURE S OWN Natural Orange Flavour, Tonic &amp; C (Zinc Gluconate 50mg &amp; Ascorbic Acid 25mg) Lorange bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17293</td>
<td>BIO-ORGANICS BIO-CHROMIUM 500MCG PLUS Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28224</td>
<td>NATURAL ALTERNATIVE Glucosamine Mega Garc 100mg Tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17307</td>
<td>BIO-ORGANICS ESSENTIAL ENZYMES Full Spectrum Digestive Activity Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28233</td>
<td>NATURAL ALTERNATIVE NATURAL ENZYMES Tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17312</td>
<td>BIO-ORGANICS HORSE RACING COMPLEX WITH ODOLESS GARLIC Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28273</td>
<td>NATURAL NUTRITION High Quality Siberian Ginseng 1000mg Tablet (195) bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17316</td>
<td>BIO-ORGANICS L-HISTIDINE COMPLEX Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28274</td>
<td>NATURAL NUTRITION L-Glutamine 1000MG Tablets</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17317</td>
<td>BIO-ORGANICS L-lysine COMPLEX Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28292</td>
<td>NATURAL NUTRITION NATURAL A 10000U &amp; D (60IU) Capsule (7) bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17320</td>
<td>BIO-ORGANICS MAGNESIUM &amp; POTASSIUM PLUS Capsule bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28295</td>
<td>NATURAL NUTRITION NATURAL B 5000 U &amp; D (30IU) Capsule (7) bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17332</td>
<td>BIO-ORGANICS SUPER BISO-CALCIUM MICROCRYSTALLINE HYDROXYPATITE - PLUS Capsule TBA</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28305</td>
<td>NATURE S OWN Super B Complex Forta, Waterara, Tingt Uitang &amp; Lecitina, 10mg Tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17335</td>
<td>BIO-ORGANICS DIETARY FAT METABOLISER tablet bottle</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28314</td>
<td>NATURE S OWN Super Lecithin 200mg (3%)</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
<tr>
<td>17337</td>
<td>BIO-ORGANICS SUPERSLIM</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
<td>28348</td>
<td>NATURE S OWN CRANBERRY 400</td>
<td>BULLYNANTS NATURAL HEALTH PRODUCTS P/L</td>
<td>All Batches</td>
<td></td>
</tr>
</tbody>
</table>
WHAT YOU NEED TO KNOW

- What to look for in bathroom and kitchen cabinets
  Any vitamin, mineral or herbal pills or supplements, weight-loss formulas, cholesterol-lowering tablets, pain-relief pills or cold and flu tablets.

- Are my prescription medicines affected?
  No.

- How do I read the labels?
  Look for the products’ AUST L or AUST R number. This five-digit number is on the product label. Also look at the batch number and expiry date. As many product names are similar, it is important to check these against the list of recalled products.

- Do all affected products have a Pan label?
  No. Pan also made medicines for other companies. Brands including Genovis and Nature’s Own are among those affected.

- Which products are not affected?
  Panadol, Nurofen, Codral, Nicorette, Plurovital, Dencorub, Disprin, Dimetapp and Difflam are among a large list of medicines not affected.

- What do I do if I have recalled pills?
  Do not take them. Either dispose of them safely or return them to your pharmacy or retailer.

- Will I get a refund?
  It is up to the individual supplier. Most companies have offered refunds or exchanges. Check with the outlet where you bought the product.

NEED HELP?
OFFICIAL PHONE HOTLINE 1800 220 007
INTERNET: www.TGA.health.gov.au
They're for travel sickness.

I don't get travel sickness.

You do when you take these.
Other factors to consider

- Now have GMPs for dietary supplements
  - However, there is no validation requirement (process and cleaning)

- Cosmetics in Europe (EC) are now treated as drugs and must comply with GMPs
Also, have to consider the type of facility

- i.e. what other types of products might be made in the same facility?
- For example, does the facility manufacture Rx products and cosmetic products in the same facility?
So how can we develop a strategy for validating the manufacturing process for an OTC?

- Clearly FDA feels that there is no difference in the validation required for OTC products and other more potent products.
- This is evident in the increased citations by FDA of OTC facilities.
So what can we do to simplify validation?

Identify and validate only critical manufacturing steps

- not all steps are critical
  - Blending & mixing times are critical
    - Content uniformity testing performed to confirm uniform distribution of active
  - Transfer of a solution from a manufacturing to a holding tank may not be critical
    - Once dissolved, an active will remain uniformly distributed due to Brownian motion

- Don’t overlook packaging
  - Filling – over and underfilling
  - Labeling – including vision systems
  - However, it is usually not necessary to validate steps downstream from filling?
Can bracketing be used for process validation?

- Answer = yes

- For example, consider an ointment manufactured in multiple strengths (e.g. 0.25, 0.5, 1.0, 1.5 % active) – could do process validation for 0.25 and 1.5 % products)

- Would the same consideration be true for multiple strength tablets (e.g. 2, 5, 10, 20 mg active)?
• Grouping – for similar products

• Matricing
  • low dose (e.g. 2-10 mg) – more extensive content uniformity testing
  • High dose (> 100 mg) – less extensive content uniformity

• Validate critical parameters/processes only
Utilities

- Concentrate on intimate i.e. product-contact utilities
  - e.g. sterile steam – yes, full validation
  - But ‘dirty’ steam for nonsterile jacketed tanks – do only abbreviated OQ to verify that required temperatures are achieved

- Potable water
  - Probably meaningless to validate
  - Typically used in early stages of cleaning
Packaging

- Concentrate validation effort on filling, sealing, and labeling and control systems such as vision systems.
- Control but do not validate areas downstream of sealing, i.e. conveyor belts, case packers, shrink wrapping (vision systems).
What about monographed OTC products?

- Monograph speaks to finished product quality, but not to the manufacturing process used to make it.

- Validation speaks to the manufacturing process itself.
Is a ‘grouping’ approach acceptable for cleaning validation of OTC’s

- Yes, it is acceptable to group similar products which are cleaned by the same cleaning procedure, select a ‘worst case’ representative and perform cleaning validation on the worst case representative.

- However, don’t ‘overdo’ it. For example, all of the products in the group should be manufactured in the same equipment and cleaned with the same cleaning procedure.