MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Proposed changes to paracetamol warning and advisory statements

18 March 2020

Consultation outcome

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Executive Summary

This consultation ran from 4 November 2019 until 31 Jan 2020. The aim of the consultation was to gather views on the appropriateness of the Label Statements for non-prescription products containing paracetamol. The need for the consultation came from a recommendation of the Medicines Adverse Reactions Committee to improve the safety of paracetamol use in New Zealand following a report of acute liver failure in a young child.

We received 72 responses to the consultation. Some of the responses contained some very detailed information and in order to ensure that we fully understood all the comments provided it has taken some time to complete our analysis. We would like to thank everyone for their contribution to this consultation.

In general, most respondents agreed with the proposals. There were however, many suggestions for improving the proposals and we have tried to incorporate these into the final statements where possible. Our response and the changes made are detailed below in the main part of this document.

In addition, there were many comments outside the context of this consultation we have provided an overview of these in this document. Comments on activities outside the remit of Medsafe have been passed on to the appropriate agencies. For example, a summary of comments received during this consultation which related to the classification of paracetamol were submitted to the 65th Medicines Classification Committee meeting. Comments on Medsafe related functions are under consideration for further action.

About the consultation

At the December 2018 Medicines Adverse Reactions Committee (MARC) meeting, the Committee discussed a serious case report of acute liver failure in a young patient due to a suspected overdose of paracetamol. The Committee noted that they had discussed similar case reports in the past, indicating an ongoing issue (December 2018 Medicines Adverse Reactions Committee Meeting Minutes).

During this consultation the poisons centre confirmed that they receive calls reporting errors such as:

- Measuring the wrong dose - due to inappropriate measuring device or difficulties figuring out the right dose to give.
- Giving the next dose too soon - usually in paediatrics when multiple carers do not communicate when they have given doses, or in adults taking another dose too soon for the purported therapeutic benefit.
- Giving the wrong strength of the liquid formulation.
- Wrong duration - taking paracetamol for longer than recommended often due to ongoing pain.
- Taking multiple paracetamol products such as taking paracetamol tablets and a paracetamol-containing cold and flu product without realising.

In response to this ongoing problem a working group was set up and a number of recommendations were made with the aim of improving the safe use of paracetamol. One of the recommendations was to check the labelling for non-prescription paracetamol products.

The Label Statements Database (LSD) lists the warning and advisory statements that are required on medicine and related product labels under the Medicines Regulations 1984. Currently, the Label Statements Database has different required statements for paracetamol legacy labelling not changed since 2013. The current statements are grouped under the following conditions:

- new product applications from 1 December 2013 AND new labels for existing products from 1 December 2013
- existing products for which no changes to labels are made.

Medsafe proposed removing the current paracetamol conditions and grouping the required warning statements in dose form groups, under the following conditions:

- when sold in a liquid oral dose form
- all other dosage forms, excluding modified release
- modified release.

Medsafe asked for views on the proposed paracetamol conditions, warning statements and dosing table for liquid paracetamol.

Medsafe sought comments on:

- whether the required paracetamol warning statements should be specific to the proposed dose form groups (conditions)
- whether the proposed paracetamol dosing table for liquid paracetamol products is appropriate and whether a measuring device should be provided

- whether the proposed warning statements include all relevant paracetamol warning statements for each dose form group (conditions)
- whether any of the proposed paracetamol warning statements are unnecessary for the relevant dose form group, and if yes, why.

Medsafe proposed that the new label statements should be implemented within 18 months from the publication of the consultation outcome on the Medsafe website.

The consultation opened on 4 November 2019 and closed on 31 January 2020.

Consultation results

Thank you to everyone who responded to the survey.

We have analysed and summarised the survey results. All the specific comments made by respondents are not included in this document, but themes identified by Medsafe have been highlighted and responses provided. The results section is divided as follows:

- Overview of respondents
- Consultation clarification
- General comments from respondents and Medsafe responses
- Summary of responses to questions on liquid oral dose form
- Summary of responses to questions on all other dosage forms excluding modified release
- Summary of responses to questions on modified release
- Implementation date.

The final statements, as they will appear in the Label Statements Database, are also provided in Appendix 1.

One late submission was received via email. This submission has not been included in the summary tables however the comments have been considered as part of the analysis. Several respondents provided additional supplementary information separately, this information has been considered in this response document.

For each consultation question we have included a table detailing the agreement or disagreement with the proposal organised by category of respondent. A summary of the themes identified from the comments made to each proposal from each category of respondent follows. In some cases, the category 'other' did not have any comments or the comments were the same as those from healthcare professionals. For brevity, comments from 'other' may not be included for every question or may be condensed with the healthcare professional comments. Finally, a response from Medsafe to the comments and the final outcome of the question is included at the end of the discussion on each proposal.

Overview of respondents

You can view the submissions that we have permission to publish.

We received 72 responses via the consultation tool. The majority of respondents submitted as an individual (68%). 32% submitted on behalf of an organisation or group. Most respondents were based in New Zealand (88%) (Table 1).

Table 1 Respondent location

Location	Number	Percentage
New Zealand	63	88
Australia	3	4
Other	3	4
Not Answered	3	4
Total	**72**	**100**

For the analysis, respondents have been categorised into one of three categories (see Table 2):

- Healthcare professional (HCP), n=59
- Industry, n=10
- Other, n=3.

Table 2 Respondent category and numbers

Respondent	Categorised as	Number	Percentage
Healthcare professional[a]	HCP	56	77.8
Professional body	HCP	3	4.2
Industry organisation	Industry	4	5.6
Sponsor	Industry	5	7.0
Manufacturer	Industry	1	1.3
Other	Other	1	1.3
Institution (eg university, hospital)	Other	2	2.8
Total		**72**	**100**

Notes

a. One respondent selected Member of the public and another selected Other. These were changed to 'Healthcare professional' according to other individual information provided and therefore included in the Healthcare professional category.

Consultation Clarification

A number of comments were made throughout the consultation responses about the scope of the consultation. The scope is clarified here.

Many comments were made regarding problems with dispensed paracetamol. This consultation was for labels for paracetamol purchased without a prescription (over-the-counter). The LSD only applies to non-prescription products unless specifically stated in the LSD entry.

There were requests for slight changes to the statements, the ability to combine statements and to change the order of the statements. The LSD allows words of similar meaning, the combination of statements if the meaning is not changed and the order to be rearranged. This flexibility is built in to allow companies to design packaging that can deliver safety messages to consumers in the most effective way for that packaging.

There were comments that the dosing table for liquid paracetamol was too complicated for consumers. The dosing table is not intended to be reproduced in full on the label. Companies should select the part of the table that is relevant for their product and measuring device. In order to avoid any misunderstanding this instruction will be included in the LSD.

General comments from respondents and Medsafe responses

This section is a summary of general comments or questions received from respondents by theme, and Medsafe's response to each of them. Some of these comments apply to some or all conditions; we have included them here rather than repeating them throughout the document. Some of these comments relate to issues outside the scope of this consultation.

Implementation and harmonisation

Concern was raised that the consultation was focused only on labelling. It was noted that the following questions were not raised 'What can be done to improve patient safety, reduce the incidence of over-dose or misuse and what current behaviours are detrimental to these goals'.

Comments were made that there was a lack of scientific justification for the proposals.

Response: This consultation is one of a number of actions being taken by Medsafe in conjunction with other government agencies. For example a recent *Prescriber Update* article reminded prescribers about safe prescribing of paracetamol. The MARC reviewed whether a dose reduction was needed for obese children. HQSC and PHARMAC are working to provide measuring devices when paracetamol is prescribed and the Ministry of Health, ACC and HRC are looking to fund research in this area. The aim of this consultation was to seek views from experts in industry and among healthcare professionals regarding whether changes needed to be made and consumer acceptability.

A campaign that encourages parents or caregivers and health professionals who may be prescribing liquid paracetamol, in particular, to weigh the patient was recommended. They could then be encouraged to calculate the dose according to the recommended 15mg/kg dose with a maximum of 60mg/kg per day. This dosage is evidenced based and consistent with overseas practices and much published medical literature.

Response: Medsafe has published recommendations on safe prescribing which included using weight-based dosing.

Industry were very concerned that 'due to the small size of the New Zealand market and a perceived lack of understanding by the Regulator of the needs for harmonisation, [the proposal] means we could be faced with serious lack of options for New Zealand consumers. Access to well-manufactured, well presented, well labelled self-care medications improves primary healthcare and reduces pressure on the public healthcare system'.

The approved liquid paracetamol products in New Zealand are listed in Table 3 (those with a status of either 'consent given' or 'not available' in New Zealand). Products with lapsed approval are not shown in the table.

The two products that are registered in both Australia and New Zealand do not appear to have harmonised labels, as there are no AUSTR numbers on the New Zealand registered labels.

Table 3 Liquid paracetamol products with consent in New Zealand

Product name	TGA-registered?	AUSTR number on NZ label?
Pamol 250 mg/5 mL (Colour free)	No	-
Pamol (Strawberry Flavour) 250 mg/5 mL	Yes	No
Pamol Infant Drops 50 mg/mL	No	-
Panadol Children 3 months - 12 years 120 mg/5 mL	No	-
Paracare For Babies & Young Children 3 months to 6 years 120 mg/5 mL	No	-
Paracare For Children 6+ years & Adults 250 mg/5 mL	No	-
Paracetamol (Ethics) 120 mg/5 mL	No	-
Paracetamol (Ethics Cherry Flavour) 120 mg/5 mL	No	
Paracetamol (Ethics Strawberry Flavour) 120 mg/5 mL	No	
Paracetamol 250mg/5 mL (Ethics)	No	-
Paracetamol Children 3 Months-6 Years (Ethics) 120 mg/5 mL	No	-
Paracetamol Children 6-12 years (Ethics) 250 mg/5 mL	No	-
Junior Parapaed 120 mg/5 mL	No	-
Parapaed Under 6 120 mg/5 mL	No	-
Six Plus Parapaed 250 mg/5 mL	Yes	No
Your Pharmacy Double Strength Paracetamol Suspension 250 mg/5 mL	No	-
Your Pharmacy Paediatric Paracetamol Suspension 120 mg/5 mL	No	-

Response: None of the consented products for liquid paracetamol in New Zealand are currently harmonised with Australia.

There were concerns that there is a risk of confusion during the transition phase should the changes be implemented. This is not in the best interests of primary healthcare or improving the safety profile of the country's most prescribed medicine.

Response: Medsafe will communicate should this situation arise and work with professional bodies to reduce confusion.

Comments were made regarding the need for consumer testing of the statements to ensure they are better than the current labelling.

Response: These statements have not been tested by Medsafe, however we note that responses from healthcare professionals indicated they had performed consumer testing and provided feedback on improvements. One of the aims of the consultation was to gain this expert insight into the best way of communicating this information on the labels.

Prescribing/dispensing

Industry commented that analysis of available sales data for 2019 demonstrate that 91% of sales of liquid paracetamol products were via prescription. This was further highlighted in a recent industry-conducted consumer survey, in which 69% (345/500) of respondents indicated that when purchasing liquid paracetamol products they generally do so with a prescription from a doctor or a nurse.

Consumer research also supports that in 30% of instances these products have been supplied without a measuring device.

Other comments were made about paracetamol available on prescription.

- Providing doses for all children in the family to avoid the caregiver guessing or using a dose calculator.
- Measuring devices should be provided every time paracetamol is dispensed.
- Child resistant caps should always be used on dispensed bottles.
- Parents and caregivers need better instructions on storage, for example NOT to put it in the fridge and information on when it expires and how to safely dispose of it.

In particular with liquid formulations, parents are often confused between dosing information on different brands, the information they have been given by a doctor/pharmacist and what is on the bottle. Having consistent dosing information on bottles (both store-bought and prescribed) should help correct some of the current confusion.

Response: These comments have been noted and passed to appropriate agencies.

Quantity, strength and flavour

A number of comments referred to the quantity, flavour and strength of liquid paracetamol.

In general, where comments were made it was felt that too much paracetamol was prescribed at one time. It was suggested that 200 mL should be the maximum amount of liquid paracetamol and 50 tablets the maximum number of tablets provided on prescription. Another suggestion was that the amount of liquid paracetamol able to be dispensed at one time should be the same as an OTC branded product.

It was noted that some parents use flavour as a shorthand for strength but different flavours are available for the same strength and the same flavour for different strengths. Neither is there consistency between over the counter liquid paracetamol and prescription paracetamol. It was also noted that households may have both strengths of paracetamol because they have different aged children and the wrong strength bottle is selected (often when given at night). Having only one strength would be a solution to this problem. However, there was no overall agreement on which strength was appropriate, although most respondents nominated the 250mg/5ml strength. An analysis provided by Industry of sales data demonstrated that, for example, Paracare Orange 250 mg/5 mL in a 1 L bottle accounted for almost all of the Paracare range of paracetamol products purchased by pharmacies for dispensing in New Zealand.

It was noted that there is no limit on the quantity of paracetamol prescribed or purchased. There is no limit on the size of Pharmacy Only liquid paracetamol packs. In general, it is sold over-the-counter in sizes of 50 mL, 100 mL, 200 mL.

Response: The quantity of paracetamol available for purchase is in part an issue of the classification statements. Medsafe provided this feedback in a comment to the Medicines Classification Committee (see also below). Medsafe has provided feedback to College of GPs and Pharmaceutical Society on the amount of prescribed paracetamol.

Classification and availability

Several respondents made comments about reducing the availability or changing the classification of paracetamol to reduce its availability. Healthcare professionals considered that the widespread availability of paracetamol and bargain bins of paracetamol found in supermarkets and pharmacies encourages a misperception that paracetamol is safe. Having paracetamol available for sale in garages and dollar shops was perceived negatively. Another problem noted was that paracetamol is often on shelves at child height making it easy for children to access without parents or caregivers being aware.

It was suggested that all paracetamol products be returned to pharmacy medicine status as a minimum, although a change to restricted or prescription status was also suggested. Other suggestions to control availability and reduce harm were to restrict sales to one pack at a time, reduce maximum pack sizes, limit sales to one transaction per day and not to allow discounted sales of paracetamol.

Comments on modified release paracetamol were that it should be made prescription only or withdrawn completely.

Response: Medsafe has provided this feedback in a comment to the Medicines Classification Committee.

Literacy and Consistency of dose and safety information

There were comments that all liquid paracetamol products should be required to have the same comprehensive label information including those dispensed on prescription. As prescribed liquid paracetamol will not have any cost to the patient, it is likely that those in the highest deprivation areas will be more likely to have their liquid paracetamol dispensed in this way. Thus, there is an inequity in having the most vulnerable of society with less access to the safety tools and instructions they need to enable their safe use of these medicines.

Some examples of patients misunderstanding paracetamol dosing instructions because English was a second language were provided. It was suggested that a visual card could be developed and provided. The ability to print the dosing table and supply with a dispensed bottle was suggested to be helpful particularly for families with more than one child.

There is a need for all sources of information on dosing to be consistent to avoid confusion amongst patients and caregivers.

There are also leaflets and videos that have been produced to educate consumers in dosing and use of liquid paracetamol in children which will need to stay consistent with any labelling information. Some examples were provided:

https://www.healthnavigator.org.nz/medicines/p/paracetamol-children/, https://www.healthnavigator.org.nz/media/5078/paracetamol-safe-use-of-paracetamol-for-children-july-2018.pdf

http://www.saferx.co.nz/assets/Documents/2cd5f854df/paracetamol-for-children_leaflet.pdf https://www.kidshealth.org.nz/safe-use-paracetamol-children https://eastmed.co.nz/paracetamol-dose-calculator/

Response: Medsafe in conjunction with Ministry of Health, ACC and HRC is funding research into how caregivers give paracetamol and their understanding of how to use paracetamol and its safety. Medsafe has also communicated with the Pharmaceutical Society regarding these suggestions. The relevant bodies will be notified of any changes so that educational materials can be updated accordingly.

Issues with the consultation tool

The following limitations to the consultation tool were noted:

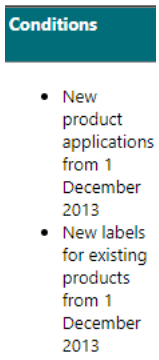
- can't include graphics
- can't include tables
- formatting including bolding and colour not allowed
- can't add citations or footnotes
- can only see 5 lines of text at a time.

Response: These comments have been fed back to the Ministry of Health Communications team.

Summary of comments – when sold in a liquid oral dose form

Question 1: Do you agree that the two current paracetamol conditions in the Label Statements Database should be replaced by three new conditions for different dosage forms?

Current



Proposed

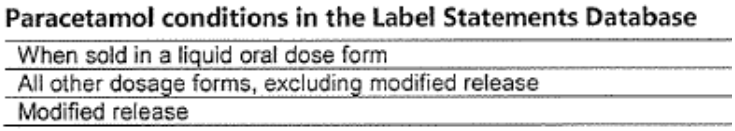


Table 4 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	62	86.1	50	84.7	9	90	3	100
	No	8	11.1	7	11.9	1	10	0	0
	Not answered	2	2.8	2	3.4	0	0	0	0

* See Table 2 for details of respondent categories.

Comments from Industry

A different set of conditions were proposed.

- When sold in liquid oral dose forms.
- When sold in immediate release solid oral paracetamol dose forms.
- When sold in modified release solid dose oral paracetamol forms.

Medsafe Response

The suggestion to change the conditions was appreciated but does not capture labelling for other dose forms such as suppositories.

Outcome

The current conditions in the LSD will be changed to:

- When sold in liquid oral dose forms.
- All other dosage forms, excluding modified release.
- Modified release.

Question 2: Do you agree that the current paracetamol dosing table should be revised?

Table 5: Current dosing table

Age	Average body weight (kg)	Single dose (mg)
1 - 3 months	4 - 6	60 - 90
3 - 6 months	6 - 8	90 - 120
6 - 12 months	8 - 10	120 - 150
1 - 2 years	10 - 12	150 - 180
2 - 3 years	12 - 14	180 - 210
3 - 4 years	14 - 16	210 - 240
4 - 5 years	16 - 18	240 - 270
5 - 6 years	18 - 20	270 - 300
6 - 7 years	20 - 22	300 - 330
7 - 8 years	22 - 25	330 - 375
8 - 9 years	25 - 28	375 - 420
9 - 10 years	28 - 32	420 - 480
10 - 11 years	32 - 36	480 - 540
11 - 12 years	36 - 41	540 - 615
> 12 years	500 to 1000mg. Dosage should not exceed 4g in 24 hours.	

(Wider age ranges (e.g. 1-3 years) may be used on product labelling where appropriate. A medicine label may include only a subset of the age groups - for example, dosing for ages 6-12 years only. Doses must still be consistent with the above table.)

Table 6 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	62	86.1	55	93.2	4	40	3	100
	No	7	9.7	2	3.4	5	50	0	0
	Not answered	3	4.2	2	3.4	1	10	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments were made about the complexity of the new table; having two strengths of liquid paracetamol increases the potential for confusion. It was noted that if there is a variation in dose people will choose the higher dose even if the child weighs less. One dose per age/weight bracket is much less confusing for consumers.

Comments from Industry

Supportive comments in favour of removing ambiguity and confusion were made. Comments warning about the effect of no longer harmonising labelling with Australia were also made. Further it was pointed out that no evidence had been provided that the current table requires revision or that the proposed table improves consumer usability and ultimately child safety. Published literature highlights that the use of a

single dose of paracetamol within specified age for weight bands poses a significant limitation. Removing the dose range and replacing it with a single dose per age/weight band sends a message to the consumer that dosing accuracy is unimportant.

Medsafe Response

Industry concerns regarding harmonisation were discussed above.

Medsafe proposed an update to the dosing table due to concerns that the current table has potential for misinterpretation by parents and caregivers. The following potential problems were identified.

- Where a dose range is given for an age and weight range, the parent may select the higher dose believing that this is suitable for all children within the age and weight range. For example, a parent with a 3 month-old, 6 kg child experiencing significant discomfort might select a dose of 120 mg, when the correct dose based on body weight is 90 mg.
- Dosing should be based on weight, but the table could be interpreted as saying there are two possible dosages for a given weight, where the weight ranges overlap. For example, for a 20kg child the parent can potentially decide the dose is 270 mg to 330mg.
- The table requires parents to make a choice of dose from a range, when they might not understand what to consider when selecting a dose (eg, weight and not severity of pain). The dose range could be interpreted as the lower end being for mild pain and the top end being for severe pain.
- The dose for a child of weight within the range is not clear. For example, no dose is given for an 11kg child and either 150 mg or 180 mg could be selected in the current table. The correct dose is 165 mg.
- The sponsor can create wider dosing bands on the label that may not be appropriate, and these differ between brands.
- The dose is stated only in milligrams in current table, with no requirement for volume to be given and no advice on rounding doses.

Comments from Industry indicated that using a single dose for age/weight bands is a significant limitation according to the literature. However, the only literature cited was a study supporting the MHRA paracetamol dosing recommendations which use a single dose per age band[1].

Outcome

There is support to update the dosing table.

1 Eyers S, Fingleton J, Perrin K, Beasley R. Proposed MHRA changes to UK children's paracetamol dosing recommendations: modelling study. Journal of the Royal Society of Medicine. 2012;105:263-9

Question 3: Do you agree that the current paracetamol dosing table should be revised to only include one dose per age/weight bracket?

Table 7 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	59	81.9	52	88.1	4	0.4	3	100
	No	9	12.5	5	8.5	4	0.4	0	0
	Not answered	4	5.6	2	3.4	2	0.2	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

It was noted that calculating doses may be a problem for some people so the dosing table may not be the solution. However, if doses are in mL no calculations are needed. If there are a range of doses it can cause confusion, people will not know which dose to use, or will choose the higher dose even if the child weighs less so a single dose for each age range was considered better. It was noted that the new table is quite complex and may be hard to follow. Other suggestions were to only have one strength of liquid paracetamol available and to reduce the total volume given (per prescription or purchase).

Comments from Industry

Comments in favour included that the proposed revisions will be much clearer for parents and caregivers. Where there is a dose range, this increases the chance of an incorrect dose being provided to a child.

Negative comments included that the current dosage table is preferable as it maintains the 15mg/kg dose and a change does not benefit the patient. It was stated that a dose of 15 mg/kg has a faster onset and longer duration of action than 10 mg/kg. Currently, the table provides an age range and a corresponding dosage range, so consumers can match the upper or lower end of the age range with the dosage range. This was considered to send a message to consumers that the dose must correspond to the appropriate age and weight. When a single dose per age/weight bracket is recommended, it is unavoidable that the younger and lighter children are given a comparatively higher dose than the older/heavier children in that age bracket. The possible consequence of a single dose per age/weight bracket is that for the children in the lowest percentile of weight for a given age, the dose given is comparatively high and there is less margin for dosing error, and for the children who are in the higher percentiles for weight compared to age, the comparatively lower mg/kg dose could compromise effectiveness. Neither of these outcomes are desirable.

Comments from Other

Having the dose in volume is clearer for users and takes away the need for dose volume calculations and risk of error. A single dose per age or weight bracket will reduce the potential for error.

Medsafe Response/Outcome

We were seeking opinion on whether having one dose for a small weight range was easier for consumers to understand. We had noted that this was how the dosing was described in the UK (albeit by age range rather than weight range).

Whilst healthcare professionals agree that this would be easier to understand industry pointed out the potential issues if labels are not harmonised with Australia. However as noted above there are currently no harmonised liquid paracetamol products.

Whilst Medsafe agrees that the consensus for paracetamol dosing is 15mg/kg, there is evidence for the dose range being 10-15mg/kg.

- The Medicines and Healthcare products Regulatory Agency (MHRA) considers 10-15mg/kg to be a standard dose range, and has based their OTC product dose bands on this as a therapeutic range[2].
- Martindale states dose range as 10-15 mg/kg/dose, with a number of supporting references.[3] [4] [5] [6] [7]

A recent review[8] cites a study showing that doses of 10-12.5 mg/kg effectively achieve antipyresis. A cited study[9] within the review found small differences in onset and duration of action that may not be clinically relevant. The paper concludes that a dose range of 10-15mg/kg is effective.

With regards to analgesia, the review states that higher CNS concentrations are required, with oral doses ≥15 mg/kg required for effective analgesia. However, it is unclear how this information was extrapolated from the cited studies.

Outcome

The dosing table will be updated to give a single dose per age/weight bracket.

2 Eyers S, Fingleton J, Perrin K, Beasley R. Proposed MHRA changes to UK children's paracetamol dosing recommendations: modelling study. Journal of the Royal Society of Medicine. 2012;105:263-9

3 Playfor S, Jenkins I, Boyles C, et al: Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med 2006; 32(8):1125-1136.

4 Goldman RD, Ko K, Linett LJ, et al: Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. Ann Pharmacother 2004; 38(1):146-150.

5 Perrott DA, Piira T, Goodenough B, et al: Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. Arch Pediatr Adolesc Med 2004; 158(6):521-526

6 Berde CB & Sethna NF: Analgesics for the treatment of pain in children. N Engl J Med 2002; 347(14):1094-1103.

7 Cranswick N & Coghlan D: Paracetamol efficacy and safety in children: the first 40 years. Am J Ther 2000; 7(2):135-141

8 de Martino M, Chiarugi A. Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain Ther. 2015;4:149-680

9 Temple AR, Temple BR, Kuffner EK. Dosing and antipyretic efficacy of oral acetaminophen in children. Clin Ther. 2013;35(1361–75):e1–45

Question 4: The proposed paracetamol dosing table provides one dose per age/weight bracket that is calculated from the maximum recommended dose for the low-end weight of the age/weight bracket (ie, 15 mg/kg). This means that a minimum dose of 10 mg/kg is achieved for the high-end weight of the age/weight bracket – Do you think that this is appropriate?

Table 8: Proposed dosing table

The following table is the proposed dosing table for paracetamol when sold in a liquid oral dose form.

Age	Average body weight (kg)	Single dose (mg)	Strength: 120 mg/5 mL		Strength: 250 mg/5 mL	
			Volume – absolute (mL)	Volume – rounded (nearest 0.5 mL)	Volume – absolute (mL)	Volume – rounded (nearest 0.5 mL)
1–3 months	4–6	60	2.5	2.5	1.2	1.2*
3–6 months	7–8	105	4.4	4.5	2.1	2.0
6–12 months	9–10	135	5.6	5.5	2.7	2.5
1–2 years	11–12	165	6.9	7.0	3.3	3.5
2–3 years	13–14	195	8.1	8.0	3.9	4.0
3–4 years	15–16	225	9.4	9.5	4.5	4.5
4–5 years	17–18	255	10.6	10.5	5.1	5.0
5–6 years	19–20	285	11.9	12.0	5.7	5.5
6–7 years	21–22	315	13.1	13.0	6.3	6.5
7–8 years	23–25	345	14.4	14.5	6.9	7.0
8–9 years	26–28	390	16.3	16.5	7.8	8.0
9–10 years	29–32	435	18.1	18.0	8.7	8.5
10–11 years	33–36	495	20.6	20.5	9.9	10.0
11–12 years	37–41	555	23.1	23.0	11.1	11.0
>12 years	42–60	630	26.2	26.0	12.6	12.5
>12 years	Over 60 kg: 500 to 1000 mg. Dosage should not exceed 4 g in 24 hours.		20.8–41.7	21–41.5	10–20	10–20

* This dose has not been rounded as rounding down would lead to an underdose and rounding up to an overdose.

Table 9 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	57	79.2	50	84.7	4	40	3	100
	No	11	15.3	6	10.2	5	50	0	0
	Not answered	4	5.6	3	5.1	1	10	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

The majority of healthcare professionals agreed with the proposal. Most comments concerned the issue of knowing the child's weight and if the weight for age used in the table was still correct. Additional suggestions included having a QR code link to a dose calculator, using the term 'up to' within the age/weight ranges and reducing the dose to 10mg/kg for the 1-3 month age bracket. It was felt that having exact volumes of what to give is straight forward and decreases the risk of medication errors by users. Comments were made on improving the readability of the table with the suggestion below (Table 10) which was trialled on consumers.

Table 10: Proposed dosing table from the Paediatric Society

Proposed dosing table from the P&T SIG of the Paediatric Society 2020

The following table is the proposed dosing table for paracetamol when sold in a liquid oral dose form.

Age	Average body weight (kg)**	Single dose (mg)	Strength: 120 mg/5 mL Volume – rounded mL	Strength: 250 mg/5 mL Volume – rounded mL
1–3 months	4–6	50mg	2mL	1mL
3–6 months	7–8	105	4.5	2
6–12 months	9–10	135	5.5	2.5
1–2 years	11–12	165	7	3.5
2–3 years	13–14	195	8	4
3–4 years	15–16	225	9.5	4.5
4–5 years	17–18	255	10.5	5
5–6 years	19–20	285	12	5.5
6–7 years	21–22	315	13	6.5
7–8 years	23–25	345	14.5	7
8–9 years	26–28	390	16.5	8
9–10 years	29–32	435	18	8.5
10–11 years	33–36	495	20.5	10
11–12 years	37–41	555	23	11
>12 years	42–60	630	26	12.5
>12 years	Over 60 kg: 500 to 1000 mg. Dosage should not exceed 4 g in 24 hours.		20-40	10–20

* This dose has not been rounded as rounding down would lead to an underdose and rounding up to an overdose.

**Never dose up if your child's weight is more than the average weight listed for their age range (i.e. use your child's age range for dosing, not their weight range)

Comments were made that the two different strengths on the table should be colour coded in some way to make people more aware of checking which strength they have before they give the dose, (eg, pink for the 120 mg/5 mL strength and orange for the 250 mg/5 mL strength) as people can just glance at the dosing table and may only 'see' the amount for the wrong strength and thereby under or overdose their child. If you are a sleep-deprived, stressed parent who has been awake half the night with a sick child it is an easy mistake to make.

Comments from Industry

Positive comments from industry included agreement that dosing should be by weight but that including the age-based dose when the weight is not known helps minimise a child getting an incorrect dose. A review of age-based paracetamol dosing guidelines was cited that found that underweight children (ie, those in the 9th centile) are at risk of overdosing and overweight children (ie, those in the 91st centile) are at risk of underdosing. It follows that dosing tables combining age and weight are preferred. The current and the proposed tables both provide appropriate, narrow age and weight bands.

A number of problems were raised with the proposed changes which are grouped into subheadings below.

No evidence that a change is needed

No evidence was provided that the current table causes consumers a problem. The current table with its age/weight range and corresponding dose range ensures that a consumer gives the same recommended 15 mg/kg dose of paracetamol to their child no matter which row they look at.

Specific problems with the proposed table

The ages and weights in the table deviate from NZ-WHO growth charts.

There are two different average body weights for children of the same age in the crossover between bands. For example, in the first age bracket (1-3 months), the 3-month-old child is given the average weight of 6kg. In the second age bracket (3-6 months), the average weight of a 3-month-old child is increased by 1kg to 7kg (Table 11).

Table 11: Problems with the proposed dosing table

	Current table		Proposed table		*Proposed table with correct weight*
	Row 1	Row 2	Row 1	Row 2	*Row 2*
Age	3 months	3 months	3 months	3 months	*3 months*
Weight	6 kg	6 kg	6 kg	7 kg	*6 kg*
Dose	90 mg	90 mg	60 mg	105 mg	*105 mg*
Dose/bodyweight	15 mg/kg	15 mg/kg	**10 mg/kg**	**15 mg/kg**	*17.5 mg/kg*
Comment	Internal consistency between rows.		*Lack of internal consistency in weight between rows leading to over dosing.*		

Current dosing table	Proposed dosing table
Child aged 1-3 months Weight: 4-6 kg Dose: 60-90 mg	Child aged 1-3 months Weight: 4-6 kg Dose: 60 mg
Child aged 3-6 months Weight: 6-8 kg Dose: 90-120 mg	Child aged 3-6 months Weight: 7-8 kg Dose: 105 mg
A 3-month-old is consistently dosed with 90 mg	*A 3-month-old infant is dosed with either 60 mg or 105 mg at the parent's discretion*

If a caregiver has a 3-month-old child and they do not know the weight, the carer must choose between two possible doses on the label – either 60 mg (as the upper limit for 1-3 months) or 105 mg (as the lower limit for 3-6 months age bracket). The difference between these two doses is significant – it is almost two-fold.

When age-correct average weights are applied the dosing table fails to provide a 15 mg/kg dose in any age bracket (Table 12).

Table 12: Recalculation of dose after weight adjustment

Table 3. Sub- and supra-therapeutic paracetamol dosing using the parameters in the proposed dosing table.

	Proposed				Proposed with NZ-WHO corrected average body			
Age bracket	Average body weight (kg)	Single dose (mg)	Dose per kg bodyweight		Average body weight (kg)	Singe dose (mg)	Dose per kg bo	
			Lower age band	Upper age band			Lower age band	U
1-3 months	4-6	60	15 mg/kg	10 mg/kg	4-6	60	15 mg/kg	
3-6 months	7-8	105	15 mg/kg	13.1 mg/kg	6-8	105	17.5 mg/kg	
6-12 months	9-10	135	15 mg/kg	13.5 mg/kg	8-10	135	16.9 mg/kg	
1-2 years	11-12	165	15 mg/kg	13.75 mg/kg	10-12	165	16.5 mg/kg	
2-3 years	13-14	195	15 mg/kg	13.9 mg/kg	12-14	195	16.25 mg/kg	
3-4 years	15-16	225	15 mg/kg	14 mg/kg	14-16	225	16 mg/kg	
4-5 years	17-18	255	15 mg/kg	14.1 mg/kg	16-18	255	15.9 mg/kg	
5-6 years	19-20	285	15 mg/kg	14.25 mg/kg	18-20	285	15.8 mg/kg	
6-7 years	21-22	315	15 mg/kg	14.32 mg/kg	20-22	315	15.75 mg/kg	
7-8 years	23-25	345	15 mg/kg	13.8 mg/kg	22-25	345	15.7 mg/kg	
8-9 years	26-28	390	15 mg/kg	13.5 mg/kg	25-28	390	15.6 mg/kg	
9-10 years	29-32	435	15 mg/kg	13.6 mg/kg	28-32	435	15.5 mg/kg	
10-11 years	33-36	495	15 mg/kg	13.75 mg/kg	32-36	495	15.5 mg/kg	
11-12 years	37-41	555	15 mg/kg	13.5 mg/kg	36-41	555	15.4 mg/kg	
*>12 years**	*42-60*	*630*	*15 mg/kg*	*10.5 mg/kg*	*41-60*	*630*	*15.4 mg/kg*	

There is variation, with no proportionality, in the mg/kg bodyweight dose across all upper weights for each of the age and weight brackets.

The dosage information for age >12 years is inconsistent with the dosing information on solid oral dosage forms. For children over 12 years, the recommended dose for solid oral dose forms is 500 mg – 1000 mg, whereas the proposed dose for liquids is 630 mg; this may cause confusion. Note also that many adults

weigh less than 60 kg, and the recommended 630 mg dose is equivalent to 10.5 mg/kg bodyweight for a 60 kg person.

Therapeutic dose is 15mg/kg

The table does not achieve a dose of 15mg/kg for all ages and weights. The dose of 15mg/kg is universally considered to be the optimal safe and effective dose.[10] The published literature highlights that the use of a single dose of paracetamol within specified age for weight bands poses a significant limitation, particularly if these bands are very wide. A single dose undermines the accuracy of dosing in children who are in age groups that overlap. Changing this to a single dose provides the consumer with a choice of two different doses.

A dose of 15mg/kg allows an earlier onset and longer duration of effect (than lower doses). A dose of 15mg/kg is well below the level of single dose toxicity; toxicity in children tends to occur after administration of single doses ranging from 120 to 150 mg/kg.

The sub-therapeutic doses are also of relevance because associated perceived lack of efficacy has the potential to encourage more frequent re-dosing, resulting in an inadvertent overdose. Although there is no evidence that this is certain to occur, Medsafe should be alert to this possibility.

Need for consistency

Changing to a dose range would necessitate changes to NZ formulary, consumer educational materials, online calculators (eg, https://www.healthnavigator.org.nz/tools/p/paracetamol-dose-calculator/) and is against BPAC advice. These will need changing with the current table, what algorithms can be used by calculators to enable dosing is compliant with the label? Healthcare professionals are likely to prescribe different doses to those on the OTC label, this will lead to confusion.

Consumer testing and understanding

Changes to the dosing table should not be made without consumer testing.

Medsafe Response

No evidence that a change is needed

As outlined above healthcare professional responses to the consultation agreed that there is the potential for error with the dose range provided in the current table. The MHRA uses one dose for an age range so the proposal is not unprecedented.

In the current dosing table children aged 1 to 6 months might get a dose greater than 15 mg/kg. The lowest dose is 10 mg/kg for children aged 1 to 3 months (Table 13).

10 De Martino M, Chiarugi A. Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain Ther. 2015 Dec; 4(2): 149-168

Table 13: Problems with the current dosing table

			mg/kg dose			
Age	Average body weight	Dose (mg)	Low dose/low weight	High dose/low weight	Low dose/high weight	High dose/high weight
1 - 3 months	4 - 6	60 - 90	15	22.5	10	15
3 - 6 months	6 - 8	90 - 120	15	20	11.25	15
6 - 12 months	8 - 10	120 - 150	15	18.75	12	15
1 - 2 years	10 - 12	150 - 180	15	18	12.5	15
2 - 3 years	12 - 14	180 - 210	15	17.5	12.85	15
3 - 4 years	14 - 16	210 - 240	15	17.14	13.125	15
4 - 5 years	16 - 18	240 - 270	15	16.875	13.33	15
5 - 6 years	18 - 20	270 - 300	15	16.66	13.5	15
6 - 7 years	20 - 22	300 - 330	15	16.5	13.64	15
7 - 8 years	22 - 25	330 - 375	15	17	13.2	15
8 - 9 years	25 - 28	375 - 420	15	16.8	13.39	15
9 - 10 years	28 - 32	420 - 480	15	17.14	13.125	15
10 - 11 years	32 - 36	480 - 540	15	16.875	13.33	15
11 - 12 years	36 - 41	540 - 615	15	17.08	13.17	15
> 12 years	Not specified	500 - 1000	n/a	n/a	n/a	n/a

Specific problems with the proposed table

Medsafe agrees that the overlapping age ranges in the proposed table are not desirable. The proposed table does not lead to overdoses (Table 14).

Table 14: Proposed dosing table - dose by weight

Age	Weight (kg)	Dose (mg)	mg/kg dose – bottom of weight range	mg/kg dose - top of weight range
1 - 3 months	4 - 6	60	15	10
3 - 6 months	7 - 8	105	15	13.125
6 - 12 months	9 - 10	135	15	13.5
1 - 2 years	11 - 12	165	15	13.75
2 - 3 years	13 - 14	195	15	13.9
3 - 4 years	15 - 16	225	15	14.06
4 - 5 years	17 - 18	255	15	14.166
5 - 6 years	19 - 20	285	15	14.25
6 - 7 years	21 - 22	315	15	14.32
7 - 8 years	23 - 25	345	15	13.8
8 - 9 years	26 - 28	390	15	13.928
9 - 10 years	29 - 32	435	15	13.59
10 - 11 years	33 - 36	495	15	13.75
11 - 12 years	37 - 41	555	15	13.54
>12 years	42 – 60	630	15	10.5
>12 years	>60 kg	500 - 1000	n/a	n/a

All doses fall within 10-15 mg/kg. Only 6 kg and 60 kg children get a 10 mg/kg dose. Doses only fall outside of this range if a different weight is assigned to age as shown above in the industry comments.

Excluding the issue with the overlapping age ranges the weight ranges are aligned with the current dosing table for the upper bound. The weights are appropriate for the age bands, as far as we can tell. The NZ-WHO growth charts only go to five years old and are separate for boys and girls. The weights for children aged 6-12 years are taken from the Pfizer growth charts, which are endorsed by the Australasian Paediatric Endocrine Group (APEG) (Table 15). It is not possible to capture all children in the weight range for a given age, which is why weight-based dosing is important. The proposed label statements include an instruction to use the dose for your child's weight, and to only dose based on age when the weight isn't known.

Table 15: Weights for age

NZ-WHO growth charts

	Girls weight percentile (kg)			Boys weight percentile (kg)		
Age	9th	50th	91st	9th	50th	91st
1 m	3.4	4.1	4.9	3.6	4.4	5.2
3 m	4.9	5.8	6.9	5.4	6.4	7.4
6 m	5.7	6.8	8.6	6.4	7.4	9.2
1 y	7.6	9.0	10.5	8.3	9.6	11.1
2 y	9.8	11.5	13.6	10.4	12.1	14.2
3 y	11.7	13.9	16.5	12.2	14.3	16.8
4 y	13.5	16	19.5	13.8	16.3	19.4
5 y	15	18.3	22.4	15.3	18.3	22

Pfizer growth charts

	Girls weight percentile (kg)			Boys weight percentile (kg)		
Age	10th	50th	90th	10th	50th	90th
6 y	16	20.5	25.5	18	21	25.5
7 y	19	23	29	14.5	23	24
8 y	21	26	33	22	26	32.5
9 y	23.5	29	38	24	24	37
10 y	26.5	38	44	26	32	42
11 y	30	37.5	50	29	36	48
12 y	33	42	56	32.5	41	54

New Zealand labels do not appear to be currently aligned with the TGA OTC monograph. The Australian includes different strengths: 24 mg/mL, 48 mg/mL, and 100 mg/mL, compared with the 24 mg/mL and 50 mg/mL strengths used in New Zealand. Therefore, the current situation is one where there is no harmonisation between Australia and New Zealand.

The UK dosing table is based on age only and doses are in 2.5 mL increments. The age brackets are wider than the proposed table. Sweden and Finland use dosing based on a range of 10 – 15 mg/kg with one dose for each age/weight band.

Therefore, Medsafe considers that the principle of using single doses for an age/weight bracket in the proposed table is consistent with paracetamol dosing in other countries.

Table 16: TGA Liquid paracetamol dosing table

Age	Average body weight (kg)	Single dose (mL) 24 mg/mL oral liquid	Single dose (mL) 48 mg/mL oral liquid	Single dose (mL) 100 mg/mL oral liquid
1 – 3 months	4 – 6	-	-	0.6 – 0.9 mL
3 – 6 months	6 – 8	-	-	0.9 – 1.2 mL
6 – 12 months	8 – 10	-	-	1.2 – 1.5 mL
1 – 2 years	10 – 12	6 – 8 mL	3 – 4 mL	1.5 – 1.8 mL
2 – 3 years	12 – 14	8 – 9 mL	4 mL	-
3 – 4 years	14 – 16	9 – 10 mL	4 – 5 mL	-
4 – 5 years	16 – 18	10 – 11 mL	5 – 6 mL	-
5 – 6 years	18 – 20	11 – 13 mL	6 mL	-
6 – 7 years	20 – 22	13 – 14 mL	6 – 7 mL	-
7 – 8 years	22 – 25	14 – 16 mL	7 – 8 mL	-
8 – 9 years	25 – 28	16 – 18 mL	8 – 9 mL	-
9 – 10 years	28 – 32	18 – 20 mL	9 – 10 mL	-
10 – 11 years	32 – 36	20 – 23 mL	10 – 11 mL	-
11 – 12 years	36 – 41	23 – 26 mL	11 – 13 mL	-

Therapeutic dose is 15mg/kg

Medsafe review of the literature indicates that the therapeutic dose is 10mg – 15 mg/kg. The reference cited regarding a faster onset for 15mg/kg[11] concludes that a dose of 15 mg/kg/dose is a safe and effective dose. The therapeutic dose for paracetamol was discussed in the previous question. We agree that a single dose of 15 to 20 mg/kg is below the threshold for toxicity, however, we are also concerned about chronic overdosing leading to toxicity.

Need for consistency

Medsafe agrees that consistency is desirable. However, we note and expect that for many medicines there are differences between the non-prescription and the prescription dose. We note that the prescribed dose of paracetamol is only current for the short period the child remains at the same weight.

Consumer testing and understanding

The table provided by the Paediatric Society above was consumer tested and found to be understandable.

Overall comments

Taking all the comments into consideration we conclude that a dosing table can be constructed with a single dose for narrow weight/age bands that delivers a therapeutic dose. The table below has been constructed using the comments kindly provided in the consultation.

11 de Martino M, Chiarugi A. Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain Ther. 2015;4:149-680

Outcome

The dosing table is shown below. This is not the final version as we have added two rounding options (discussed below) and two columns showing the actual dose range for the weight range (based on the dose volumes). See Appendix 1 for the final dosing tables. The ages have been adjusted to remove overlap. The first row has a smaller age and weight range and lower dose as recommended by the Paediatric Society. Some rounding has been adjusted to maintain a dose of 10 – 15 mg/kg. The 12-year-old dosing is not included as this is discussed below.

Age	**Body weight (kg)**	**Single dose (mg)**	**Strength: 120 mg/5 mL**		**Strength: 250 mg/5 mL**		**Dose range**	
			Volume - rounded to 0.2 mL	**Volume - rounded to 0.5 mL**	**Volume - rounded to 0.2 mL**	**Volume - rounded to 0.5 mL**	**Lowest dose/kg (mg)**	**Highest dose/kg (mg)**
1 - 2 months	4 - 5	50	2	2	1	1	9.6	12.5
3 – 6 months	6 - 7	90	3.8	3.5	1.8	1.5	10.7	15.2
7 – 11 months	8 - 9	120	5	5	2.4	2	11.1	15
12 – 23 months	10 - 12	150	6.2	6	3	3	12	15
2 years	13 - 14	195	8	8	4	4	13.7	15.4
3 years	15 - 16	225	9.4	9.5	4.4	4.5	13.8	15.2
4 years	17 - 18	255	10.6	10.5	5	5	13.9	15
5 years	19 - 20	285	12	12	5.6	5.5	13.8	15.2
6 years	21 - 22	315	13	13	6.4	6.5	14.2	15.5
7 years	23 - 25	345	14.4	14.5	7	7	13.8	15.2
8 years	26 - 28	390	16.4	16.5	7.8	8	13.9	15.4
9 years	29 - 32	435	18	18	8.6	8.5	13.3	14.9
10 years	33 - 36	495	20.6	20.5	10	10	13.8	15.2
11 years	37 - 41	555	23	23	11	11	13.4	14.9

Question 5: The proposed paracetamol dosing table provides an additional age/weight bracket for consumers >12 years with a weight between 42 kg and 60 kg in line with Martindale. This is in order to better capture those consumers whose weight is not high enough to take a full 1 g adult dose – Do you think that this is appropriate?

Table 17: Proposed dosing for 12 year old children

11–12 years	37–41	555	23.1	23.0	11.1	11.0
>12 years	42–60	630	26.2	26.0	12.6	12.5
>12 years	Over 60 kg: 500 to 1000 mg. Dosage should not exceed 4 g in 24 hours.		20.8–41.7	21–41.5	10–20	10–20

Table 18 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	61	84.7	54	91.5	4	40	3	100
	No	7	9.7	2	3.4	5	50	0	0
	Not answered	4	5.6	3	5.1	1	10	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Respondents agreed with having a category for people >12 years with a weight between 42 kg and 60 kg as many teenagers do not get to higher weights for several years and a dose of 1000 mg should be reserved for people 65 kg and over. Respondents thought the table could be better designed (eg, '>12', should be changed to '12 years and older').

It was noted that the dose is a large volume of liquid especially for the 120mg/5ml strength, so it may be better not to include doses for older children for this strength of paracetamol and children of 12 years can take tablets. It was also noted that units should be consistent, the dose is given in mg but the total daily dose in g.

Other comments included concerns regarding dosing in obese children. It was also noted that advice from HQSC based on an American study of paracetamol-induced hepatotoxicity in adults noted that one of the risk factors identified was bodyweight less than 50 kg weight associated with eating disorders, chronic disease or frailty.[12]

Comments from Industry

There were comments that there is no evidence that low body weight alone causes paracetamol hepatotoxicity. A variance in the weight of children > 12 years is already accounted for in the current

12 https://www.hqsc.govt.nz/assets/Medication-Safety/Watch-Updates/Medication-Safety-Watch-16-Jan-2016.pdf

recommendation of giving either a 500 mg dose or a 1000 mg dose in children > 12 years so there is no need for this addition.

It was considered that generally, a fixed-dosing regimen is potentially more convenient than a weight-adjusted dosing regimen for both patients and clinicians. It is generally accepted that children should be able to swallow a tablet by the age of 6-7 years. It follows that within the OTC setting, products for paediatric use are in liquid formats and those for use in children > 12 years and adults are in solid dose formats.

The proposed dosing table introduces the potential to provoke confusion because consumers are provided with a number of conflicting paracetamol doses for their adolescent child, depending on which product they opt to use:

- Liquid products, labelled for children 11-12 years: 555 mg dose
- Liquid products, labelled for > 12 years (42-60 kg): 630 mg
- Liquid products, labelled for > 12 years (over 60 kg): 500 mg – 1000 mg
- Solid oral dose forms, labelled for children over 12: 500 mg – 1000 mg.

Comments from Other

Providing this additional age/weight dosing bracket lessens the risk of overdose in a small for age child. In addition, it was noted that the proposal suggests that 'Medicine labels may include only a subset of the age groups'. We believe it is necessary to include the full dosing table for all age groups.

Medsafe Response/Outcome

As noted above, when a dose range is provided it is not clear that consumers and caregivers realise that the range is to cover differences in weight rather than, for example, severity of symptoms. The proposed dose of liquid paracetamol for children over 12 years and under 60 kg is for those who cannot swallow a tablet.

The proposed table includes doses for all age groups to solicit consultation responses; as clarified above only the doses relevant to the product presentation need to be included on the label.

Medsafe agrees that it is desirable to have consistent units and that the phrase 12 years and older is better understood than a symbol.

Medsafe agrees that for children aged 12 and above there is potential for confusion between the liquid and solid oral dose forms. We have adjusted the table slightly to reduce the potential for confusion.

Age	**Body weight (kg)**	**Single dose (mg)**	**Strength: 120 mg/5 mL**		**Strength: 250 mg/5 mL**	
			Volume - rounded to 0.2 mL	**Volume - rounded to 0.5 mL**	**Volume - rounded to 0.2 mL**	**Volume - rounded to 0.5 mL**
11 years	37 - 41	555	23	23	11	11
12 years and older	42 - 60	630	26	26	12.6	12.5
	Over 60	500 – 1000	20 – 40	20 – 40	10 – 20	10 – 20

Question 6: In the proposed paracetamol dosing table, should the volume be absolute or rounded to the nearest 0.5 mL (shaded column)?

Table 19: Proposed dosing table

Proposed dosing table

The following table is the proposed dosing table for paracetamol when sold in a liquid oral dose form.

Age	Average body weight (kg)	Single dose (mg)	Strength: 120 mg/5 mL		Strength: 250 mg/5 mL	
			Volume – absolute (mL)	Volume – rounded (nearest 0.5 mL)	Volume – absolute (mL)	Volume – rounded (nearest 0.5 mL)
1–3 months	4–6	60	2.5	2.5	1.2	1.2*
3–6 months	7–8	105	4.4	4.5	2.1	2.0
6–12 months	9–10	135	5.6	5.5	2.7	2.5
1–2 years	11–12	165	6.9	7.0	3.3	3.5
2–3 years	13–14	195	8.1	8.0	3.9	4.0
3–4 years	15–16	225	9.4	9.5	4.5	4.5
4–5 years	17–18	255	10.6	10.5	5.1	5.0
5–6 years	19–20	285	11.9	12.0	5.7	5.5
6–7 years	21–22	315	13.1	13.0	6.3	6.5
7–8 years	23–25	345	14.4	14.5	6.9	7.0
8–9 years	26–28	390	16.3	16.5	7.8	8.0
9–10 years	29–32	435	18.1	18.0	8.7	8.5
10–11 years	33–36	495	20.6	20.5	9.9	10.0
11–12 years	37–41	555	23.1	23.0	11.1	11.0
>12 years	42–60	630	26.2	26.0	12.6	12.5
>12 years	Over 60 kg: 500 to 1000 mg. Dosage should not exceed 4 g in 24 hours.		20.8–41.7	21–41.5	10–20	10–20

* This dose has not been rounded as rounding down would lead to an underdose and rounding up to an overdose.

Table 20 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Absolute or rounded	Absolute	10	13.9	9	15.3	1	10	0	0
	Rounded	53	73.6	46	78.0	4	40	3	100
	Not answered	9	12.5	4	6.8	5	50	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments included that rounding down is fine as it makes is more practical and safer for parents to measure. However, it was noted that rounding to 0.5 mL makes a considerable difference at the lower age range. The most common oral syringe in use has 0.2 mL increments, so doses such as 2.1ml and 2.5ml cannot be read off the syringe. Finally, the table is too complicated for the average consumer, only state the rounded dose to avoid confusion.

Comments from Industry

The Best Practice Advocacy Centre (https://bpac.org.nz/2018/paracetamol.aspx) notes that 'The paracetamol dose should be prescribed as accurately as possible, however, in practice increments of 0.5 mL

are often used.' Guidance from the American Academy of Paediatrics supports that 'Orally administered liquid medications should be dosed to the nearest 0.1, 0.5, or 1 mL, as appropriate based on the margin for safe and effective dosing, but dosing to the hundredth of a mL should be avoided.' However, there is no evidence to support that rounding to the nearest 0.5 mL would better facilitate the safe use of liquid paracetamol. It was noted that the available dosing calculators do not round the dose.

It was also noted that some groups of consumers may have difficulty in working with fractions and decimals and may find even the rounded doses hard.

Comments from Other

It was remarked that doses should be rounded to the nearest 0.5 mL and trailing zeros should be avoided (ie, 2 mL and not 2.0 mL) which could be misread as 20 mL, leading to a tenfold dosing error. Many dosing devices do not have 0.1 mL volume graduations.

Medsafe Response/Outcome

Overall there was agreement that rounding down the dose was acceptable. Medsafe notes that the dose will need to take into account the measuring ability of the device provided, this will be highlighted in the LSD.

Outcome

The doses volumes should be rounded to make dosing easier, but the capabilities of the dosing device provided need to be taken in to account. The table will display the dose as both 0.2 mL and 0.5 mL increments with instructions to use the rounding for the measuring device provided.

Question 7: If the dose is greater than the total of the syringe provided in the packaging, should this be given as two administrations (for example, if the dose is 7.5 mL should the label statement be one 5 mL dose plus one 2.5 mL dose)?

Table 21 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Agree with two administrations	Yes	36	50	33	55.9	1	10	2	66.7
	No	29	40.3	21	35.6	7	70	1	33.3
	Not answered	7	9.7	5	8.5	2	20	0	0

* See Table 1 for details of respondent categories.

Comments from Healthcare professionals

The main comment was that the device provided should be able to administer all the recommended doses. It was considered that advice to administer the dose as two part-doses would be confusing and lead to errors. Other comments were that the total volume with the two administrations in brackets should be provided on the label. It was also noted that there is also a danger that the two administrations could be split over time. The label should also state that this medicine should always be used with the measure supplied with the packaging. It was also suggested that a pictogram could be used. The language could be simplified to 'larger doses may be given in two lots'. This should also be explained by the person selling the medicine.

Comments from Industry

The appropriate device should be provided in the packaging, for larger doses this could be a medicine cup rather than a syringe. There is a risk of under or over dosing with two administrations. It is not standard practice to write instructions in this format. Doses should be kept as a single number. Pharmacists and their staff already provide thorough counselling and advice when providing paracetamol liquid over the counter. We would expect the need to give a dose in two administrations to be explained during consultation with an appropriate pharmacy staff member.

Medsafe Response

Although the majority of respondents answered yes to this question, the comments indicated that the need for this information should be avoided by providing the correct dosing device and/or be the responsibility of the person selling the medicine to explain.

Outcome

There is no need to require information on the label that doses can be given as two administrations.

Question 8: Medsafe proposes removing the possibility for sponsors to use wider age/weight brackets on their packaging/labelling, so that only the age/weight brackets shown in the proposed paracetamol dosing table are used. This is in order to ensure that consumers receive an accurate dose – do you agree with this?

Table 22 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	65	90.3	56	94.9	6	60	3	100
	No	4	5.6	2	3.4	2	20	0	0
	Not answered	3	4.2	1	1.7	2	20	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals and other

Most comments were around the need for standardisation across all paracetamol products. A comment was made that the print size may become too small if all doses are included.

Comments from Industry

There was agreement with the concept of using narrow bands. There was disagreement regarding whether the weight bands were accurate for the age bands.

Medsafe Response

There was broad agreement with this proposal. Regarding the weights for ages, these are the approximately 50th percentile weights for age. However, there are a wide range of weights for ages and these diverge with increasing age and between sexes. For this reason, an instruction to dose based on weight where known is included in the label statements.

Outcome

The LSD will be updated to state that only the age/weight brackets in the table are allowed.

Question 9: Should packaging for liquid oral paracetamol include the measuring device to enable accurate dosing?

Table 23 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Include measuring device	Yes	65	90.3	56	94.9	6	60	3	100
	No	4	5.6	2	3.4	2	20	0	0
	Not answered	3	4.2	1	1.7	2	20	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals and other

Healthcare professional comments generally agreed and noted the problems of using domestic tea-spoons. Some caveats were also mentioned. Syringes get lost and markings wear off and it adds plastic to landfills. It may make syringes a must-buy at pharmacies. Not everyone can afford to purchase these and oral syringes are not funded.

Whenever small volumes of liquids are measured, especially viscous liquids, there can be error, including parallax error, not measuring appropriately using the meniscus of the liquid on the appropriate line on the measure, the use of lower accuracy measures such as spoons or cups, and not understanding decimal points. The use of accurate dosing devices and the availability of easy to follow instructions are recommended.

Comments from Industry

It was pointed out that a measuring device is not funded for dispensed liquid paracetamol and that in Australia liquid paracetamol products are always supplied with a dosing device. The measuring device should only be mandated with OTC products (although other comments stated this should be for all products). In a New Zealand survey, 90% (451/500) of respondents indicated that an accurate measuring device should be provided free with all liquid paracetamol products prescribed by doctors or nurses. The type of measuring device should be specified by Medsafe.

Medsafe Response

Whilst there are some caveats to providing a measuring device it was generally agreed that having one in the packaging for liquid paracetamol products purchased OTC was a good idea. The Ministry of Health has been working with pharmacists to enable the provision of measuring devices free with prescriptions.

Outcome

Provision of a suitable measuring device will be added to the LSD.

Question 10: Do you agree with the proposed changes to the paracetamol warning statements for 'when sold in liquid oral dose form'?

Proposed warning statements

Medicine/Group/Class	Conditions	Statement
Paracetamol	When sold in a liquid oral dose form	• Dose: every four to six hours when required, up to four doses in 24 hours. • Keep to the recommended dose. • Use the dose for your child's weight. Only use the dose for age if you do not know your child's weight. • If you think you may have given/taken too much paracetamol ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well. It can take time before paracetamol has a damaging effect on your liver. • Do not give or take with other products containing paracetamol. • Keep out of reach and sight of children. • Children and adolescents: Do not give/take this medicine for longer than 48 hours at a time unless advised by a doctor. • [and if intended for use in adults] Adults: Do not take this medicine for longer than a few days at a time unless advised by a doctor. • Keep this carton for future reference to the dosing table.

Table 24 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	55	76.4	48	81.4	5	50	2	66.7
	No	10	13.9	8	13.6	1	10	1	33.3
	Not answered	7	9.7	3	5.1	4	40	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Respondents asked why the Australian poisons centre number was included, suggested that the dosing table should be on the bottle as well as the carton. It was also noted that there is no mention of suppositories in this section.

Comments were made that the order of the statements could be more logical.

Comments made on the language used included that:

- the phrase 'when sold as a liquid for oral use' could be more user friendly
- the word 'container' should be used instead of 'carton' as parents will throw away cardboard packaging and only keep the bottle in the majority of cases, or change to 'Keep this packet for future doses of paracetamol.
- a few days for adults is vague, agreed with 48 hours for children or 24 hours for younger children (under 12 months) would be better.
- dosing instructions should be 'Up to and no more than 4 doses in a 24 hour period/up to four times a day, and no less than four hours between doses/do not give/take more than 4 doses in 24 hours'
- 'Doctor'' should be changed to 'healthcare professional' or 'doctor/nurse practitioner'
- The instruction 'Do not give or take with other products containing paracetamol' should have 'check with your pharmacist if you are unsure' added

- Change the wording of the overdose warning to, 'If you think you may have given/taken too much paracetamol or an overdose ring the Poisons Information Centre or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice'

Comments from Industry

Disagreement or additional comments were made on the following statements.

Keep to the recommended dose.

Concerns were raised that this statement was on a separate line due to limited space on packs especially with the need for the dosage table and multiple warning statements.

If you think you may have given/taken too much paracetamol ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well. It can take time before paracetamol has a damaging effect on your liver.

It was noted that the current statement is consumer friendly and the proposed statement is not an improvement. No scientific reference or studies were cited that indicate that this change, will have an impact on improving the safety of this product in a self-medication situation. Most people understand the term 'overdose', the words 'taken too much' are open to misinterpretation. Is 'too much' an extra dose? Is it 2 mL instead of 1.2 mL? The phrase It can take time before paracetamol has a damaging effect on your liver conveys a false sense of non-urgency, that people can wait and can take their time before seeking medical attention. People will also differ in their interpretation of 'it takes time' (ie, is it a week, two weeks, two years?).

This proposed statement is not harmonised with the existing Australian requirements. It is important to retain harmonisation with the Australian regulator.

Do not give or take with other products containing paracetamol.

Some Australian registered products carry this wording already. Double-dosing and increased frequency of dosing are implicated as contributory factors in children with paracetamol-associated liver failure. Double-dosing is a common problem. In New Zealand one of the problems is that consumers do not realise that prescribed and OTC paracetamol are the same medicine.

Keep out of reach and sight of children.

It was not considered that this adds value or improves safety. Scarce space on all labels should be devoted to key messaging, which is 'keep out of reach'. Merely seeing the product is not in itself a risk. The signal heading of 'Keep out of reach of children' is already present on the label and the proposed statement is a duplicate statement that takes up space on labels that have very little available space.

Keep this carton for future reference to the dosing table.

It was thought that the suggested concept of retaining the carton is flawed and unrealistic. Patients are not in the habit of retaining outer packaging and none is included in prescribed paracetamol which a patient receives without a dosage table, warnings or even advice on where to get further information. Technology should be used (barcodes or html addresses etc) to allow better, broader, more comprehensive safety and

dosage data being made available to the patient. Alternatively, this statement should only be required when the dosing table is not included on the label of the immediate container (bottle).

Medsafe Response

As stated above, words of similar meaning can be used, the order of statements can be changed, statements may be grouped together and there are no liquid paracetamol products labels harmonised with Australia. Suppositories are not included in this category of paracetamol products for the purposes of the LSD.

Medsafe agrees with the suggestions made to improve the statements. We note that the statement 'keep out of reach' was proposed to add 'out of sight' as young children have been known to climb to reach objects of interest that they can see. This is not a double up statement.

Medsafe welcomes the use of QR codes on package labelling to help provide information to consumer to support the safe use of paracetamol.

Outcome

The statements will be:

Dose: every four to six hours when required, no more than four doses in 24 hours.

Keep to the recommended dose

Use the dose for your child's weight. Only use the dose for age if you do not know your child's weight.

If you think you may have given/taken too much paracetamol or an overdose ring the Poisons Information Centre on 0800 764 766 or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice.

Do not give or take with other products containing paracetamol.

Keep out of reach and sight of children.

Children and adolescents: Do not give/take this medicine for longer than 48 hours at a time unless advised by a healthcare professional.

Adults: Do not take this medicine for longer than a few days at a time unless advised by a healthcare professional.

Keep this packet for future doses of paracetamol.

Question 11: Are there any additional warning statements you think would be appropriate to include in the proposed condition for paracetamol 'when sold in a liquid oral dose form'?

Table 25 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any additional warning statements	Yes	19	26.4	16	27.1	1	10	2	66.7
	No	46	63.9	39	66.1	6	60	1	33.3
	Not answered	7	9.7	4	6.8	3	30	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments included concerns that some medicines containing paracetamol do not clearly state that they contain paracetamol. Other warnings should be toxic in overdose, or taking more than the stated dose can cause liver damage and death, double check dose different strengths are available, explicit storage conditions as some people store in the fridge, shake well, do not give to children with liver disorders, if condition worsens contact a health professional. There should be at least four hours between doses or say it's given every 6 hours, check that other carers have not given the child a dose, do not use routinely for fever. There should only be one concentration available: 250 mg/5 mL. Add avoid alcohol for adults, seek help if an unknown dose taken, add dose for elderly patients, adults with lower body weight and patients with liver impairment.

Comments from Industry

Suggestions included ensuring the child proof cap is on the bottle and to store medicines in a locked cupboard.

Medsafe Response

Most of the suggestions from healthcare professionals are covered by the proposed statements. The dose for lower weight adults is not needed on liquid paracetamol products and as these are only sold in pharmacies a dose can be calculated by the pharmacist.

The storage conditions for medicines are checked during the pre-market assessment. Storage conditions are required on the label under the current legislation and guidelines and do not need to be mandated in the LSD.

Medsafe considers that addition of an instruction to check that the child proof cap is on the bottle should be added.

Outcome

Additional statement

Always make sure the cap is on this bottle correctly.

Question 12: Do you have any other comments about the proposed condition for paracetamol 'when sold in a liquid oral dose form'?

Table 26 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any other comments	Yes	24	33.3	20	33.9	2	20	2	66.7
	No	42	58.3	36	61.0	5	50	1	33.3
	Not answered	6	8.3	3	5.1	3	30	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

There were comments that currently paracetamol can be sold by a pharmacist as a pharmacy medicine after re-packing from a 2 litre pack whereas ibuprofen can't. There is a potential concern around dosage information being provided for young children (<6 years) for the 250 mg/5 mL strength, particularly when 250 mg/5 mL strength comes in strawberry flavour OTC but on prescription, strawberry flavour is 120 mg/5 mL. Colour coding on the table would make it easier to read. The labelling should ensure that it is read.

Comments from Industry

Industry wanted to confirm that this consultation only applies to OTC products. Concerns were raised about the LSD no longer being harmonised with Australia.

Medsafe Response

As stated above this consultation is only for OTC products and relevant to the issue of repacking this has been included in a comment to the MCC.

Outcome

No additional changes to the LSD are proposed.

Summary of comments – all other dosage forms, excluding modified release

Question 1: Do you agree with the proposed changes to the paracetamol warning statements for 'all other dosage forms, excluding modified release'?

Table 27: Proposed statements for all other dosage forms excluding modified release

Proposed warning statements

Medicine/Group/Class	Conditions	Statement
Paracetamol	All other dosage forms, excluding modified release.	• Dose: every four to six hours when required. Maximum of four doses in 24 hours. • Keep to the recommended dose. • If you think you may have taken too much paracetamol ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well. It can take time before paracetamol has a damaging effect on your liver. • Do not take with other products containing paracetamol. • Keep out of reach and sight of children. • Adults: Do not take this medicine for longer than a few days at a time unless advised by a doctor. • Children and adolescents 11 years and above: Do not take this medicine for longer than 48 hours at a time unless advised by a doctor.

Table 28 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	55	76.4	49	83.1	4	40	2	66.7
	No	11	15.3	8	13.6	2	20	1	33.3
	Not answered	6	8.3	2	3.4	4	40	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Suggestions on the statements included adding to check with your pharmacist if you are unsure, do not use more than four doses in 24 hours, do not use the maximum dose for more than 5 days in a row without advice from a health professional. The alternative wording of the overdose warning, 'If you think you may have given/taken too much paracetamol or an overdose ring the Poisons Information Centre or go to a hospital straightaway even if you feel well. the damaging effect on the liver can take time for your body to notice' was suggested. The dose should be reduced for adults under 60 kg, elderly patients and, patients with liver impairment. The use of the phrase 'a few days' was considered vague. The order of the statements should be changed.

It is not specified what the dosing should be for suppositories, as you want a standardised dose for the 125 mg, 250 mg, and 500 mg suppository strengths similar to the paracetamol liquid. They should all have the same weight-based doses depending on the strength but this statement doesn't specify this as it does for the liquid table of doses.

Comments from Industry

The specific comments made on different statements are summarised below.

Dose: every four to six hours when required. Maximum of four doses in 24 hours.

The addition of 'when required' was supported, although a request that the phrase 'do not exceed 4 g in 24 hours' is still acceptable. It was noted that the wording was inconsistent with the proposed statement for modified release paracetamol (see below).

It was also noted that if patients take one tablet as a dose, four doses is problematic as some combination products have different regimens. Patients may be combining paracetamol products and having the total quantity allows them to take up to the maximum dose. The option to express the dose as maximum number of dosage units should be allowed. Expressing the maximum as the number of dosage units is also more accurate in some circumstances given that some people might take one dosage unit (one tablet of 500 mg) instead of two; and the statement as proposed may lead some people into thinking that four dosage units (if taken as four dosage units in 24 hours) is the maximum.

Keep to the recommended dose.

This should not be on a separate line due to space constraints.

If you think you may have taken too much paracetamol ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well. It can take time before paracetamol has a damaging effect on your liver.

As above this change was not supported. The current statement was considered consumer friendly, the term 'overdose' is well understood, whereas 'taken too much' is open to misinterpretation. The statement it can take time before paracetamol has a damaging effect is open to misinterpretation and does not convey the right sense of urgency. This statement is not harmonised with Australia.

Do not take with other products containing paracetamol.

Removal of the words 'unless advised to do so by a doctor or pharmacist' was supported.

Keep out of reach and sight of children.

This was not supported, children see many products which is not in itself a risk and is unnecessary wording on already crowded labels (see above).

Children and adolescents 11 years and above: Do not take this medicine for longer than 48 hours at a time unless advised by a doctor.

It is not necessary to have '11 years and above' as the current words 'children and adolescents' already encompasses children over the age of 11 years, as adolescence is defined by the WHO as being between the ages of 10 and 19 years. The term 'children and adolescents' therefore covers children and teenagers, and this is a very well understood word in the community. The inclusion of a separate statement for children and adolescents 11 years and above on the product label was not supported because adding such an age qualification to the existing warning does not account for the available, non-liquid, dosage forms

that are labelled for use in children aged 7-12 years and therefore has the potential to create considerable confusion.

Medsafe Response

The statement on dosing only covers frequency, therefore companies have the flexibility to provide the correct information on dose for their product. Medsafe accepts that using the term 'dose' may result in some people not taking the full amount of paracetamol and that people may be combining paracetamol products. Combining products is contrary to the warning not to take with other products taking paracetamol and has the potential to lead to overdose. Medsafe does not consider that any changes are needed. Medsafe considers that the suggested changes to improve the language of the statements are helpful and has incorporated them where possible.

Outcome

The statements will be:

Dose: every four to six hours when required, no more than four doses in 24 hours.

Keep to the recommended dose

If you think you may have taken too much paracetamol, or an overdose ring the Poisons Information Centre on 0800 764 766 or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice.

Do not take with other products containing paracetamol.

Keep out of reach and sight of children.

Adolescents: Do not take this medicine for longer than 48 hours at a time unless advised by a healthcare professional.

Adults: Do not take this medicine for longer than a few days at a time unless advised by a healthcare professional.

Question 2: Are there any additional warning statements you think would be appropriate to include in the proposed condition for 'all other dosage forms, excluding modified release'?

Table 29 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any additional warning statements	Yes	16	22.2	15	25.4	0	0	1	33.3
	No	50	69.4	41	69.5	7	70	2	66.7
	Not answered	6	8.3	3	5.1	3	30	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments were received on the proposed statements (some were already discussed above) as well as new proposals which included:

- Check with your pharmacist if you are not sure if a product contains paracetamol.
- Avoid other cold remedies that contain paracetamol.
- Do not exceed the stated dose - this medicine can cause serious harm if used incorrectly.
- Do not take more than 8 tablets (capsules) in a 24 hour period.
- Avoid alcohol while taking paracetamol.
- Dose advice for low body weight adults and those with known liver dysfunction.
- If the condition worsens see your healthcare professional.

Comments from Industry

None were considered needed, and any further suggestions should be consulted on. It was noted that some of the statements are not appropriate for suppositories.

Medsafe Response

Most of the suggestions are variations of the proposed statements. Whilst alcohol is thought to be a factor in overdose poisoning it is not necessary to have such a statement as the overdose statement is broad and recommends calling the Poisons Centre for advice. The actual dose is not mandated in the statements only the frequency, the word 'take' in the statements can be modified for suppositories since words of similar meaning are acceptable. Therefore, these statements are applicable to combination products and suppositories. There is no need for a statement around seeing a healthcare professional if the condition worsens as this is mostly covered by the statement on seeing a healthcare professional if taking for more than a few days.

Outcome

No need for additional statements.

Question 3: Do you have any other comments about the proposed condition 'all other dosage forms, excluding modified release'?

Table 30 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any other comments	Yes	10	13.9	7	11.9	3	30	0	0
	No	57	79.2	49	83.1	5	50	3	100
	Not answered	5	6.9	3	5.1	2	20	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments were made regarding the need for a dose in elderly patients. The low health literacy in New Zealand was noted and therefore the need to keep the statements simple. One respondent noted the lack of evidence for paracetamol in back pain. It was suggested that a standardised dosing table as for the liquid was needed. The use of the word 'doctor' is outdated and should be 'healthcare professional'.

Comments from Industry

Include a dosing table. Due consideration, and consultation, is required for all paracetamol-containing products, including alternate dosage formats (eg, sachets) and combinations with other active ingredients that require different paracetamol doses (eg, with ibuprofen). Medsafe should ensure that the warning statements that are proposed can also be used for the available different dosage forms (eg, sachets containing powder for hot drinks, suppositories) and are also able to be adapted when paracetamol is combined with other ingredients and the dosage is different to 4 doses, (eg, in night-time products, day and night products, or combined with other analgesics such as ibuprofen or cold and flu ingredients).

Medsafe Response

Medsafe notes that the statements do not include the dose information. Medsafe has confirmed that the statements are compatible with combination products and formats other than tablets.

Outcome

No additional statements needed.

Summary of comments – modified release

Question 1: Do you agree with the proposed changes to the paracetamol warning statements for 'modified release'?

Proposed warning statements

Medicine/Group/Class	Conditions	Statement
Paracetamol	Modified release	• Dose: every six to eight hours when required. Maximum of six tablets in 24 hours. • Do not exceed the maximum dose. • If you think you may have taken too much paracetamol ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well. It can take time before paracetamol has a damaging effect on your liver. • Do not take with other products containing paracetamol. • Keep out of reach and sight of children. • Adults: Do not take this medicine for longer than a few days at a time unless advised by a doctor. • Adolescents: Do not take this medicine for longer than 48 hours at a time unless advised by a doctor. • Children: Do not use in children under 12 years.

Table 31 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Do you agree	Yes	56	77.8	50	84.7	4	40	2	66.7
	No	8	11.1	7	11.9	0	0	1	33.3
	Not answered	8	11.1	2	3.4	6	60	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments included that a 'few days' is too ambiguous, that healthcare professionals other than doctors can recommend paracetamol for longer term use and the order of the statements could be improved. Splitting statements for adolescents from that for children is an important change. The 12-year-old cut off is not consistent with the 60 kg cut off mentioned in the statements for liquid paracetamol. The expression of the dose is different – tablets versus doses. An age should be used not the term adolescents. Keep the use of the term overdose, for example, 'If you think you may have given/taken too much paracetamol or an overdose ring the Poisons Information Centre or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice'.

Comments from Industry

The following comments were received on the different statements.

Dose: every six to eight hours when required. Maximum of six tablets in 24 hours.

This is supported as it is harmonised with Australian requirements. The addition of when required is supported. The ability to use dose units as an alternative was requested.

Do not exceed the maximum dose.

Prefer current keep to the recommended dose, but in any case, both statements mean the same thing and should be allowed under 'words to the effect of'.

If you think you may have taken too much paracetamol ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well. It can take time before paracetamol has a damaging effect on your liver.

This statement is not supported, the term 'overdose' should be used and the phrase 'it can take time before paracetamol has a damaging effect on your liver' does not convey enough urgency (see also above).

Do not take with other products containing paracetamol.

Removal of 'unless advised to do so by a doctor or pharmacist' was supported.

Keep out of reach and sight of children.

The need to keep out of sight of children was not supported (as above).

Adolescents: Do not take this medicine for longer than 48 hours at a time unless advised by a doctor.

The harmonised wording is 'do not use modified relief paracetamol for more than 48 hours for children aged 12-17 except on medical advice'.

The importance of harmonisation was emphasised again.

Medsafe Response

Most of the comments provided were similar to those above. Therefore, the statements have been modified to be consistent with comments here and above. These products have been approved for use in children 12 years and above, despite the weight difference.

Outcome

The statement will be as follows:

Dose: every six to eight hours when required. Maximum of three doses in 24 hours.

Keep to the recommended dose

If you think you may have taken too much paracetamol or an overdose ring the Poisons Information Centre on 0800 764 766 or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice.

Do not take with other products containing paracetamol.

Keep out of reach and sight of children.

Children aged 12 to 17: Do not take this medicine for longer than 48 hours at a time unless advised by a healthcare professional.

Adults: Do not take this medicine for longer than a few days at a time unless advised by a healthcare professional.

Children: Do not use in children under 12 years of age.

Question 2: Are there any additional warning statements you think would be appropriate to include in the proposed condition 'modified release'?

Table 32 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any additional warning statements	Yes	19	26.4	16	27.1	1	10	2	66.7
	No	47	65.3	40	67.8	6	60	1	33.3
	Not answered	6	8.3	3	5.1	3	30	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Suggestions included:

- These tablets (capsules) are not suitable for use in short term or occasional pain.
- Do not crush or halve - swallow whole.
- Not appropriate for use by children under the age of 12 years unless on recommendation of GP or Pharmacist.
- Check the labels of any other medicines you are taking to ensure paracetamol is not present.
- This is a modified release product, which means it is intended to be used less often than other paracetamol products.
- Not to be taken by patients weighing less than 60 kg, heavy alcohol consumers, patients with any liver impairment, or patients suffering malnutrition or severe COPD.
- The maximum dose is 6 tablets per day.
- The term 'a few days' is too vague.

Comments from Industry

Suggestions included a statement to not crush or chew the modified release forms of paracetamol.

Comments from Other

It was suggested that an explanation of what modified release means should be included.

Medsafe Response

Some of the suggestions are included in the data sheet and CMI for these products. As these products can only be purchased from a pharmacist this information can be provided at the point of sale. Medsafe agrees that a statement around crushing or chewing should be added.

Outcome

An additional statement will be added.

Do not crush or chew these tablets.

Question 3: Do you have any other comments about the proposed condition 'modified release'?

Table 33 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any other comments	Yes	12	16.7	10	16.9	2	20	0	0
	No	54	75	47	79.7	4	40	3	100
	Not answered	6	8.3	2	3.4	4	40	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

No new comments not already discussed above.

Comments from Industry

No new comments not already discussed above

Comments from Other

No new comments not already discussed above.

Outcome

No changes to the LSD.

Summary of comments – Implementation date

Question 1: Do you agree with the proposed implementation timeframe of 18 months following the publication of the consultation outcome on the Medsafe website?

Table 34 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Agree with timeframe of 18 months	Yes	51	70.8	45	76.3	4	40	2	66.7
	No	17	23.6	12	20.3	4	40	1	33.3
	Not answered	4	5.6	2	3.4	2	20	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Comments were generally to the effect that 18 months was too long, over labelling by pharmacists was suggested, although RACP agreed with the time frame.

Comments from Industry

Comments were that a minimum of 24 or 36 months were required. The justification is multiple steps are needed before new labelling can be implemented, including preparing label copy, internal company approvals and sign off, submission and approval by Medsafe, production planning and production, which may pose additional challenges given the lower New Zealand only volumes, release for supply and shipping to New Zealand (depending on the location of the manufacturing site).

Medsafe Response/Outcome

Medsafe considers that the changes requested for solid oral dose forms and suppositories are generally modifications of existing statements. Medsafe notes that label updates are submitted relatively frequently for these products and therefore considers that a time frame of 18 months is appropriate. For liquid oral paracetamol the changes to the dosing table are more extensive, therefore Medsafe considers that a timeframe of 24 months is appropriate.

Summary of comments – Other comments

Question 1: Do you have any other comments?

Table 35 Summary of responses

		Respondent category*							
		All (n=72)		**HCP** (n=59)		**Industry** (n=10)		**Other** (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any other comments	Yes	20	27.8	14	23.7	4	40	2	66.7
	No	45	62.5	40	67.8	4	40	1	33.3
	Not answered	7	9.7	5	8.5	2	20	0	0

* See Table 2 for details of respondent categories.

Comments from Healthcare professionals

Medsafe should produce a patient leaflet or have the new information as a sticker until the labels are changed. Multiple paracetamol product use is a concern encountered and is often due to a lack of understanding of what is in the products people are taking. Every paracetamol-containing product should be labelled in bold letters, 'THIS PRODUCT CONTAINS PARACETAMOL'. This should stand out on the label and should help consumers avoid using multiple paracetamol products.

Comments from Industry

Children often receive sub-therapeutic doses of paracetamol due to the wide range of dosage choices currently on bottles. The proposed changes will also help to prevent accidental overdoses where children are inadvertently given too much paracetamol. Mandatory child-proof caps will help to improve safety by preventing accidental consumption of large volumes of paracetamol. The proposed changes are long overdue and our hope is that they will all be implemented.

Comments from Other

We would like to acknowledge the work of Medsafe in revising the paracetamol warning and advisory statements. The proposed changes along with a standardised dosing table for liquid oral paracetamol will help toward addressing some of the above issues.

Medsafe Response

Other comments provided but outside the scope of the consolation were discussed in the section on general comments above. Medsafe agrees that there is value mandating a statement CONTAINS PARACETAMOL for products where paracetamol is not part of the trade name.

Outcome

Addition of the statement

CONTAINS PARACETAMOL

Appendix 1: Final Statements

Paracetamol warning statements for 'when sold in liquid oral dose form'

Dosing table for 120 mg/5 mL liquid oral paracetamol				
Age	**Body weight (kg)**	**Single dose (mg)**	**Volume rounded to 0.2 mL**	**Volume rounded to 0.5 mL**
1 - 2 months	4 - 5	50	2 mL	2 mL
3 – 6 months	6 - 7	90	3.8 mL	3.5 mL
7 – 11 months	8 - 9	120	5 mL	5 mL
12 – 23 months	10 - 12	150	6.2 mL	6 mL
2 years	13 - 14	195	8 mL	8 mL
3 years	15 - 16	225	9.4 mL	9.5 mL
4 years	17 - 18	255	10.6 mL	10.5 mL
5 years	19 - 20	285	12 mL	12 mL
6 years	21 - 22	315	13 mL	13 mL
7 years	23 - 25	345	14.4 mL	14.5 mL
8 years	26 - 28	390	16.4 mL	16.5 mL
9 years	29 - 32	435	18 mL	18 mL
10 years	33 - 36	495	20.6 mL	20.5 mL
11 years	37 - 41	555	23 mL	23 mL
12 years and older	42 - 60	630	26 mL	26 mL
	Greater than 60	500 - 1000	20 mL – 40 mL	20 mL – 40 mL

Select the part of the table relevant to the indications and adjust the dose volume to the capabilities of the dosing device which must be provided.

Dosing table for 250 mg/5 mL liquid oral paracetamol				
Age	**Body weight (kg)**	**Single dose (mg)**	**Volume rounded to 0.2 mL**	**Volume rounded to 0.5 mL**
1 - 2 months	4 - 5	50	1 mL	1 mL
3 – 6 months	6 - 7	90	1.8 mL	1.5 mL
7 – 11 months	8 - 9	120	2.4 mL	2 mL
12 – 23 months	10 - 12	150	3 mL	3 mL
2 years	13 - 14	195	4mL	4 mL
3 years	15 - 16	225	4.4 mL	4.5 mL
4 years	17 - 18	255	5mL	5 mL
5 years	19 - 20	285	5.6 mL	5.5 mL
6 years	21 - 22	315	6.4 mL	6.5 mL
7 years	23 - 25	345	7 mL	7 mL
8 years	26 - 28	390	7.8 mL	8 mL
9 years	29 - 32	435	8.6 mL	8.5 mL
10 years	33 - 36	495	10 mL	10 mL
11 years	37 - 41	555	11 mL	11 mL
12 years and older	42 - 60	630	12.6mL	12.5 mL
	greater than 60	500 - 1000	10 mL – 20 mL	10 mL – 20 mL

Select the part of the table relevant to the indications adjust the dose volume to the capabilities of the dosing device which must be provided.

Dose: every four to six hours when required, no more than four doses in 24 hours.

Keep to the recommended dose.

Use the dose for your child's weight. Only use the dose for age if you do not know your child's weight.

If you think you may have given/taken too much paracetamol, or an overdose ring the Poisons Information Centre on 0800 764 766 or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice.

Do not give or take with other products containing paracetamol.

Keep out of reach and sight of children.

Children and adolescents: Do not give/take this medicine for longer than 48 hours at a time unless advised by a healthcare professional.

Adults: Do not take this medicine for longer than a few days at a time unless advised by a healthcare professional.

Keep this packet for future doses of paracetamol.

Always make sure the cap is on this bottle correctly.

CONTAINS PARACETAMOL

Required when the name of the medicine does not include the word paracetamol.

Paracetamol warning statements for 'all other dosage forms, excluding modified release'

Dose: every four to six hours when required, no more than four doses in 24 hours.
This statement should be amended for combination products.

Keep to the recommended dose.

If you think you may have taken too much paracetamol, or an overdose ring the Poisons Information Centre on 0800 764 766 or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice.

Do not take with other products containing paracetamol.

Keep out of reach and sight of children.

Adolescents: Do not take this medicine for longer than 48 hours at a time unless advised by a healthcare professional.

Adults: Do not take this medicine for longer than a few days at a time unless advised by a healthcare professional.

CONTAINS PARACETAMOL
Required when the name of the medicine does not include the word paracetamol.

Paracetamol warning statements for 'modified release'

Dose: every six to eight hours when required. Maximum of three doses in 24 hours.

Keep to the recommended dose.

If you think you may have taken too much paracetamol, or an overdose ring the Poisons Information Centre on 0800 764 766 or go to a hospital straightaway even if you feel well. The damaging effect on the liver can take time for your body to notice.

Do not take with other products containing paracetamol.

Keep out of reach and sight of children.

Children aged 12 to 17: Do not take this medicine for longer than 48 hours at a time unless advised by a healthcare professional.

Adults: Do not take this medicine for longer than a few days at a time unless advised by a healthcare professional.

Children: Do not use in children under 12 years of age.

Do not crush or chew these tablets.

CONTAINS PARACETAMOL
Required when the name of the medicine does not include the word paracetamol.