[redacted]

GSKCH response to:

ACMS Meeting, November 2019

Agenda item 1.1: Paracetamol
Submission from the Delegate to amend the Schedule 2 and Schedule 4 entries for liquid paracetamol

Document type:	**GSKCH Response to: Submission from the Delegate to amend the Schedule 2 and Schedule 4 entries for liquid paracetamol** **ACMS Meeting November 2019 – 1.1 Paracetamol**
Submitted by:	[redacted] GlaxoSmithKline Consumer Healthcare, Australia and New Zealand
Release date:	26 Sept 2019
Number of pages:	18 Pages

September 26, 2019

Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration
Sent via email: medicines.scheduling@health.gov.au

Re: ACMS Meeting November 2019
Item 1.1. Paracetamol (liquid) proposed scheduling amendment

Background

Paracetamol (CAS no. 103-90-2) is one of the most widely used OTC analgesics and antipyretics in both adults and children. Paracetamol is listed in the World Health Organization's List of Essential Medicines, providing international recognition of its efficacy and safety profile when used as directed.

Paracetamol has a long-standing history of use in Australia. It was first used commercially in Australia in 1956. Paediatric paracetamol products have been available in Australia for over 40 years (first registration 1976), and the 100 mg/mL dose strength has been available for over 35 years (first registration 1984).

The Scheduling Policy Framework aims to facilitate access to medicines and support appropriate self-care while minimising risks and protecting public health interests. The paracetamol entries in Schedules 2, 3 and 4 of the Poisons Standard aim to minimise the risk of accidental paracetamol poisoning by limiting the total dose in a pack. However, there is no formal limit on the amount of paracetamol that can be supplied in the liquid form in Schedule 2.

The current TGA delegate initiated proposal therefore seeks to amend the Schedule 2 and Schedule 4 entries for liquid paracetamol with the intent to limit the volume or maximum paracetamol mass in Schedule 2 paracetamol liquid preparations.

Specifically, the proposal seeks to:

I. Amend the schedules such that all oral liquid paracetamol preparations are a Schedule 4 medicine, except when included in Schedule 2; and

II. Amend Schedule 2 by imposing limits on oral liquid paracetamol preparations with the following wording, or otherwise they will be deemed a Schedule 4 medicine:

"Liquid preparations for oral use containing no greater than 50 mg per mL of paracetamol in 100 mL with a maximum of 50 g paracetamol per container"

GlaxoSmithKline Consumer Healthcare (GSKCH) welcomes the opportunity to comment on this proposal.

GSKCH position

GSKCH understands that the reasoning for this delegate-initiated agenda item was to address concerns noted by the delegate during consideration of paracetamol for use in animals.[i] In that interim determination the delegate stated the following:

> *"In relation to the separate matter of paracetamol for human use; having reviewed the current Poisons Standard I have decided that a future delegate initiated application is appropriate to restrict the volume of liquid paracetamol available for human use in Schedule 2."*

In principle, GSKCH is not opposed to setting a limit on the **total amount** (volume) of paracetamol that is available per container of liquid preparations to bring it in line with solid dose formulations. However, GSKCH does not agree with the proposed wording of the amendment to the scheduling of liquid paracetamol preparations *as presented* in the agenda item, on the basis that:

1. We believe that a mathematical error may have occurred in the drafting of the proposed revised wording.
2. The proposal will have a significant but unnecessary impact on existing liquid paracetamol products currently available in Schedule 2:
    a. by excluding 100 mg/mL preparations, and
    b. by limiting pack sizes to "no greater than 50 mg per mL of paracetamol in 100 mL" (i.e. no more than 5000 mg [5 grams] per container).

[i] Source: https://www.tga.gov.au/book-page/31-interim-decision-relation-paracetamol

3. The proposal is in discord with both the paracetamol N2 OTC monograph and the Australian Regulatory Guidelines for over the counter medicines (ARGOM) documents issued by the TGA.
4. There are no known safety signals in Australia to warrant a need to eliminate 100 mg/mL liquid paracetamol preparations (nor to limit pack size to 100 mL) to safeguard public health.

Below we provide a detailed justification regarding the above concerns and outline a practical option to achieve the intent of the TGA's proposal whilst avoiding the ensuing confusion and alarm that has been created due to the proposed wording.

1. Ambiguous and unclear draft wording

The proposed amendment to the Schedule 2 entry for liquid paracetamol preparations is confusing and unclear. It can readily be deemed to seek to restrict the total amount of paracetamol by stipulating that preparations should contain a dose strength of no greater than 50 mg/mL; imposes a maximum pack size of 100 mL; yet on the other hand permits pack sizes of up to 50 g per container. These three elements are incongruent and impose both impractical and unsupported restrictions on the currently available liquid paracetamol preparations.

It is understood from correspondence provided to GSKCH by the industry association Consumer Healthcare Products Australia (CHP) that from a TGA perspective "*As outlined in the published reasons, the intent of the proposal is to place a restriction on the total amount of paracetamol that is available per bottle of formulated liquid preparations for human use. There is no intention for the proposed amendments to lower the total volume of liquid paracetamol in products currently available on the market*." However, the three limits proposed (i.e., a maximum concentration of 50 mg/mL; a maximum volume 100 mL; and a maximum 50 g paracetamol per container), as written, are incompatible with the intent of the proposed amendment.

By way of example the various permutations of the proposed amendments could be construed as follows:

a) *Paracetamol liquid preparations at a concentration of 50 mg/mL in a maximum pack size of 100 mL equates to:*
   = 50 mg/mL paracetamol concentration x 100 mL

= 5000 mg total dose of paracetamol per 100 mL container
= 5 g total dose of paracetamol per 100 mL

Therefore, effectively imposing a limit **10-fold LOWER** than the 50 g presumably intended by the proposed wording.

b) *Paracetamol liquid preparations in a maximum pack size of 100 mL and containing 50 g paracetamol equates to:*
= 50 g total dose of paracetamol in 100 mL
= 50,000 mg total dose of paracetamol in 100 mL
= 500 mg/mL paracetamol concentration

Therefore, effectively permitting a content **10-fold HIGHER** than the 50 mg/mL specified by the proposed wording.

c) *Paracetamol liquid preparations in a maximum dose strength of not greater than 50 mg/mL equates to an exclusion from Schedule 2 for 100 mg/mL liquid paracetamol preparations even though products in the marketplace are found in only up to 20 mL containers:*
= 100 mg/mL paracetamol concentration x 20 mL
= 2000 mg total dose of paracetamol per 20 mL container
= 2 g total dose of paracetamol per 100 mL

Therefore, effectively imposing a limit **25-fold LOWER** than the 50 g presumably intended by the proposed wording.

If the intent of the proposal is (as the TGA suggests) *to place a restriction on the total amount of paracetamol that is available per bottle of formulated liquid preparations* in the Schedule 2 paracetamol entry it is therefore not unreasonable to ask that the TGA set an upper limit that accommodates all the currently supplied liquid paracetamol products and is consistent with other paracetamol dose forms in the same schedule, and set this limit at 50 g.

Taking into account single ingredient paracetamol preparations with different strengths that are currently available, this would translate to the following:

Current strength	Current maximum volume	Current maximum total dose	Meets the proposed ≤ 50 g limit
24 mg/mL	500 mL	12,0000 mg = 12 g	YES
48 mg/mL	500 mL	24,000 mg = 24 g	YES
50 mg/mL	1000 mL	50,000 mg = 50 g	YES
100 mg/mL	20 mL	2000 mg = 2 g	YES

Therefore the intent of the proposal can be achieved, while at the same time correcting the ambiguity and mathematical errors, by simply revising the wording of the proposed amendment to read as follows:

> ***"Liquid preparations for oral use containing ~~no greater than 50mg per mL or paracetamol in 100 mL with~~ a maximum of 50 g paracetamol per container"***

2. Negative impact on access of currently supplied liquid paracetamol products

If the above considerations are not taken into account and the existing proposed wording is to progress as is, it would substantially impact the continued availability and use of currently approved liquid paracetamol preparations.

2.1 Unintended upscheduling (to Schedule 4) of half of the currently registered liquid paracetamol product variants

According to the ACMS #28 agenda item, there are currently 17 liquid paracetamol containing permutations of different strengths and different bottle sizes available as Schedule 2 medicines. As demonstrated in Table 1 below, the proposed changes would effectively result in the upscheduling (to Schedule 4) of 11 of these dose/pack size permutations (denoted in red), thus retaining only 6 dose/pack size permutations.

Importantly, it would completely remove from Schedule 2 (and force into Schedule 4) all 100 mg/mL 'infant drops' products, all pack sizes greater than 100mL, and the

combination product (paracetamol plus dextromethorphan), which cannot meet what are deemed to be the quite incongruent criteria of the TGA proposal.

Unfortunately, the overall (unintended) outcome of this ambiguous proposal is that consumers would be required to:

a) attend a doctor's surgery to obtain a prescription (for a medicine that is only available under a restricted benefit on the PBS), or

b) deal with the confusion of selecting a liquid paracetamol preparation in a dose strength that is not ideally suited to the age of their child, or

c) re-purchase these medicines at more frequent intervals, or

d) in some instances purchase medicines in larger pack sizes than has previously been necessary.

These scenarios, especially the need to change to a different dose/pack size could therefore increase the potential for dosing confusion and harm from misadventure rather than mitigating it.

*Table 1. Impact of proposed changes on current liquid paracetamol product variants – **Products upscheduled from Schedule 2 to Schedule 4 denoted in red**.*

			Proposed amended criteria for liquid paracetamol products		
Current strength	Current maximum volume	Current maximum total dose	Volume limit 100 mL	Strength limit 50 mg/mL	Dose limit 50 g
24 mg/mL	50 mL	1200 mg = 1.2g	YES	YES	YES
24 mg/mL	100 mL	2400 mg = 2.4 g	YES	YES	YES
24 mg/mL	200 mL	4800 mg = 4.8 g	NO	YES	YES
24 mg/mL	500 mL	12000 mg = 12 g	NO	YES	YES
*32.5 mg/mL	120 mL	3900 mg = 3.9 g	NO	YES	YES
*32.5 mg/mL	240 mL	7800 mg = 7.8 g	NO	YES	YES
*32.5 mg/mL	360mL	11700 mg = 11.7 g	NO	YES	YES

48 mg/mL	50 mL	2400 mg = 2.4 g	YES	YES	YES
48 mg/mL	100 mL	4800 mg = 4.8 g	YES	YES	YES
48 mg/mL	200 mL	9600 mg = 9.6 g	NO	YES	YES
48 mg/mL	500 mL	24000 mg = 24 g	NO	YES	YES
50 mg/mL	60 mL	3000 mg = 3.0 g	YES	YES	YES
50 mg/mL	100 mL	5000 mg = 5.0 g	YES	YES	YES
50 mg/mL	200 mL	10000mg = 10 g	NO	YES	YES
50 mg/mL	1000 mL	50000 mg = 50 g	NO	YES	YES
100 mg/mL	5 mL	500 mg = 0.5 g	YES	NO	YES
100 mg/mL	20 mL	2000 mg = 2 g	YES	NO	YES

* Combination product also containing dextromethorphan 1 mg/mL.

2.2 Insufficient product volume to meet current treatment guidelines

In addition to deleting more than half of the currently available liquid paracetamol product variants, the products remaining would be small packs containing a maximum volume of 100 mL. The advice to consumers from the TGA is that liquid paracetamol:

- Should be dosed at 15 mg per kg, which can be given every four to six hours as required, with no more than four doses in 24 hours.[ii]
- Should not be given for more than 48 hours without a doctor's advice.[iii]

Yet, with the restrictions imposed it would mean that for many children the available age-appropriate pack would not provide sufficient medicine for this maximum 48-hour dosing period. This is illustrated in Table 2 below; the blue boxes denote instances where the total volume in a bottle of liquid paracetamol would be

[ii] Sourced from: https://www.tga.gov.au/community-qa/recommended-paracetamol-doses
[iii] Sourced from: https://www.tga.gov.au/alert/paracetamol-information-consumers

insufficient to provide 8 doses over a 48-hour period at the recommended dose of 15 mg/kg.

Table 2. Impact of proposed changes on current liquid paracetamol product variants – ***Products no longer able to meet minimum dose-volume requirements denoted in blue boxes.***

		Product strengths and bottle sizes available after amended scheduling					
		24 mg/mL 50 mL	*24 mg/mL 100 mL*	*48 mg/mL 50 mL*	*48 mg/mL 100 mL*	*50 mg/mL 60 mL*	*50 mg/mL 100 mL*
Age	*Average Body Weight (Kg)*	***Volume (mL) per dose: Multiply the volume by 8 to provide the maximum of 8 doses over a 48-hour period. Blue boxes denote insufficient volume in the bottle to achieve this.***					
1-3 months	*4-6*	*2.5-3.8*	*2.5-3.8*	*1.3-1.9*	*1.3-1.9*	*1.2-1.8*	*1.2-1.8*
3-6 months	*6-8*	*3.8-5.0*	*3.8-5.0*	*1.9-2.5*	*1.9-2.5*	*1.8-2.4*	*1.8-2.4*
6-12 months	*8-10*	*5.0-6.3*	*5.0-6.3*	*2.5-3.1*	*2.5-3.1*	*2.4-3.0*	*2.4-3.0*
1-2 years	*10-12*	*6.3-7.5*	*6.3-7.5*	*3.1-3.8*	*3.1-3.8*	*3.0-3.6*	*3.0-3.6*
2-3 years	*12-14*	*7.5-8.8*	*7.5-8.8*	*3.8-4.4*	*3.8-4.4*	*3.6-4.2*	*3.6-4.2*
3-4 years	*14-16*	*8.8-10*	*8.8-10*	*4.4-5.0*	*4.4-5.0*	*4.2-4.8*	*4.2-4.8*
4-5 years	*16-18*	*10-11.3*	*10-11.3*	*5.0-5.6*	*5.0-5.6*	*4.8-5.4*	*4.8-5.4*
5-6 years	*18-20*	*11.3-12.5*	*11.3-12.5*	*5.6-6.3*	*5.6-6.3*	*5.4-6.0*	*5.4-6.0*
6-7 years	*20-22*	*12.5-13.8*	*12.5-13.8*	*6.3-6.9*	*6.3-6.9*	*6.0-6.6*	*6.0-6.6*
7-8 years	*22-25*	*13.8-15.6*	*13.8-15.6*	*6.9-7.8*	*6.9-7.8*	*6.6-7.5*	*6.6-7.5*
8-9 years	*25-28*	*15.6-17.5*	*15.6-17.5*	*7.8-8.8*	*7.8-8.8*	*7.5-8.4*	*7.5-8.4*
9-10 years	*28-32*	*17.5-20*	*17.5-20*	*8.8-10*	*8.8-10*	*8.4-9.6*	*8.4-9.6*
10-11 years	*32-36*	*20-22.5*	*20-22.5*	*10-11.3*	*10-11.3*	*9.6-10.8*	*9.6-10.8*
11-12 years	*36-41*	*22.5-25.6*	*22.5-25.6*	*11.3-12.8*	*11.3-12.8*	*10.8-12.3*	*10.8-12.3*

While it could be argued that parents could simply purchase the 48 mg/mL x 100 mL or 50 mg/mL x 100 mL product variants, this is not satisfactory because **it negatively impacts both the dose volume administered *and* the dosing device available, both of which are crucial to avoiding dosing errors.** Thereby negating the risk minimisation impetus behind the proposed scheduling amendment.

Dose volume is an important aspect of the acceptability of paediatric liquid preparations. Recognising that "*High-dose volumes pose a risk of incomplete ingestion and, thus, underdosage,"* the WHO recommends *"Efforts should, therefore, be made during pharmaceutical development to minimize the dose volume while recognizing the need to ensure accurate measurements of the dose over the anticipated range."*[1]

Oral liquid 'infant' drops provide a mechanism to deliver small volumes of a drug to children and are particularly useful in very young children.[2] While it is possible to use a single formulation over a wide age range, the volume used must be acceptable to the patient and the dosing device must be fit for purpose.[2] The published literature supports that a*cceptable* volumes for liquid preparations used in children are 0.5 mL for neonates and 2.5 mL for infants aged 1-4 years[3]

Potential concerns around dose volume and dosing accuracy have been mitigated with the currently available range of liquid paracetamol age-specific dose strengths and corresponding age-appropriate dosing devices available in Australia.

- Dose volume: ***Giving a 6-month old baby a product formulated for use in older children requires a doubling of the dosing volume***. Using the age-appropriate formulation (100 mg/mL) would require that this baby be given dose of 1.2 mL, whereas using the formulation labelled for use in children aged 6-12 years (48 mg/mL) would require that this baby be given a dose of 2.5 mL, or one labelled for children aged 1-5 years (24 mg/mL) would require that this baby be given a dose of 5 mL.

- Dose accuracy: ***Purchasing this formulation would not provide the carer with a dosing device with sufficient accuracy to measure the correct dose***. A 48 mg/mL product is often packaged with a dosing cup preferred by older children, whereas the more concentrated 100mg/mL formulation for babies is supplied with a dosing syringe for accurate measurement and ease of administration of the smaller volume.

On this basis, GSKCH questions whether eliminating 11 of the 17 of the currently available liquid paracetamol dose/pack size permutations and forcing consumers to purchase pack sizes that are not age-appropriate or do not contain an age-appropriate dosing device has any tangible value in mitigating the risk of harm from these products.

3. Current documents and guidelines

The proposed amendments are incongruent with currently established TGA documents and guidelines pertaining to liquid paracetamol.

While paracetamol was monographed by TGA in September 2013,[iv] the 100 mg/mL, 24 mg/mL and 48 mg/mL products have been listed in TGA registration guidelines (ARGOM) as the approved dose strengths since 2003. Revised registration guidelines, issued in October 2012, continue to support these three dose strengths as well as the [grandfathered] 50 mg/mL dose strength. Specifically, within ARGOM Appendix 5 (Guidelines on OTC applications for specific substances), the entry for paracetamol states:

> **Product strength and pack size - liquid preparations**
>
> Sponsors may supply any or all of the following strengths of paracetamol liquid without the need for justification: 24 mg/mL, 48 mg/mL, 50 mg/mL and 100 mg/mL. Deviation from these strengths requires justification.
>
> While not prohibited, the introduction of pack sizes larger than 200 mL will require justification.

OTC medicine applications are categorised according to risk. The OTC application categorisation framework defines five risk levels for applications for new medicines (levels N1 to N5). Lower risk levels include applications to register OTC medicines that contain well-understood active ingredients or are identical to existing OTC medicines and applications classified as N1 and N2 are deemed to pose negligible risk.

Liquid paracetamol preparations at dose strengths of 24 mg/mL, 48 mg/mL and 100 mg/mL are permitted under the N2 classification, thus, based on this framework

[iv] Source: https://www.tga.gov.au/sites/default/files/otc-argom-otc-n2-monographs-paracetamol.pdf

when supplied in accordance with the paracetamol monograph and ARGOM appendix 5 they are deemed to be of negligible risk in pack sizes of up to 200 mL (rather than the 100 mL cut-off suggested by the ACMS #28 proposal).

On this basis, GSKCH questions the rationale behind the proposed scheduling amendment for liquid paracetamol preparations, which unnecessarily upschedules 100 mg/mL dose strengths *and/or* pack sizes of 200 mL even though they fall well under the 50 g limit in the delegate's proposal, when they already meet the criteria specified in the TGA OTC paracetamol monograph and ARGOM Appendix 5.

3.1 The importance of different paracetamol OTC product strengths

The rationale behind the availability of different liquid paracetamol strength preparations is the need for different volume requirements through the different age groups, such that small children are not required to take large volumes to achieve the optimum dose. The available range of paracetamol formulation strengths in Australia is such that the highest of the current formulation strengths (100 mg/mL) is labelled for use in infants, the second highest (48 mg/mL) for children over 6 years of age and the lowest (24 mg/mL) for children in between (1-5 years).

Important issues when giving a less concentrated dose to a small child (e.g. giving the 48 mg/mL strength instead of the 100 mg/mL strength to a 6-month old baby) have been highlighted in Australian pharmacy.[4]

- Could a 6-month-old swallow 2.5 mL comfortably?
- How difficult would a carer find it to administer a 6-month-old 2.5 mL?
- Does the carer have an accurate measuring device with a graduation for 2.5 mL?

Research demonstrates that recommending oral syringes over cups, particularly for smaller doses, to reduce medication errors.[5] This would not be feasible if parents were to purchase the 48 mg/mL liquid paracetamol product for use in a child younger than 6 years of age because this dose strength variant is packaged with a measuring cup for use by older children, which does not provide sufficient accuracy to measure the small volumes that would be required.

The question around different liquid paracetamol formulation strengths was initially reviewed in Australia in the late 1990s as a result of the findings from the 1998 Newgreen Report.[v] Rationalization of the number of available dose strengths was undertaken in 1998 – such that for more than 20 years there have been only the well established strength formulations available on the Australian market. The follow up Newgreen Report (2003) was equally supportive of the well-established dose strengths of liquid paracetamol preparations.[vi]

Research in the Australian Pharmacy setting has demonstrated that when faced with a scenario where pharmacists were asked if the 48mg/mL (expressed as 240 mg/5 mL for 5–12 year olds) strength formulation could also be used in an infant aged 6 months **67% recommended that the customer purchase an age-appropriate paracetamol product for the younger child**, 13% calculated the dose that the 6-month old would need (based on the 48 mg/mL strength) and wrote it down for the customer and a further 16% counselled the customer on the appropriate dose of the 48 mg/mL strength.[4]

Rationalization of dose strengths has already been undertaken in the Australian market. The different available liquid paracetamol dose strengths have been labelled for over twenty years for use in specific age cohorts to account for the volume to be administered and are supplied with age-appropriate dosing devices. In addition, relevant age and weight based dosing is provided on all packs and provides specific dosing for children of all relevant ages. Practical issues supporting the need for age-appropriate dose volumes should be considered before any changes are made to the currently available dosage strengths.

On this basis, GSKCH questions the public health need to eliminate 11 of the 17 currently available liquid paracetamol dose/pack size permutations, and in particular any need to exclude the currently available 100 mg/mL dose strengths from Schedule 2.

[v] Sourced from: Review of non-prescription analgesics, 1989.
https://www.tga.gov.au/sites/default/files/review-analgesics-9802.pdf

[vi] Sourced from: Review on non-prescription analgesics. An update, 2003.
https://www.tga.gov.au/sites/default/files/review-analgesics-030411.pdf

4. Lack of safety signals with liquid paracetamol preparations

When given at the recommended maximum daily dose (≤75 mg/kg per day) paracetamol poses minimal risk of hepatotoxicity in the majority of children.[6, 7]. The approved dosing in Australia, which equates to 60mg/kg per day (15mg/kg up to 4 times a day), provides an even more significant margin of safety.

4.1 TGA Database of Adverse Event Notifications (DAEN) data

The TGA DAEN contains information from reports of adverse events that the TGA has received in relation to medicines in Australia. GSKCH has conducted an analysis of the DAEN database for the last 48 years (01 June 1971 – 01 Jun 2019) in order to better understand the extent of reports of adverse events involving liquid paracetamol preparations available in Australia.

Review of the DAEN data confirms the safety profile of liquid paracetamol preparations in Australia. Over a period of 48 years there has been a very low number of case reports (118) and 2 deaths (1 attributed to a homicide, and 1 attributed to SIDS) associated with liquid paracetamol preparations. This data is presented in the Table 3 below.

Table 3: Summary of DAEN case data for liquid paracetamol preparations over the last 48 years*

	All cases	**MedDRA reaction terms:**			
		Overdose	**Accidental overdose**	**Accidental exposure**	**Incorrect dose**
Number of reports (cases)	118	**4**	**8**	**3**	**2**
Number of cases with a single suspected medicine	108	**4**	**8**	**3**	**2**
Number of cases where death was a reported outcome	2	**1 (Homicide)**	**0**	**0**	**0**

* Medicines included in the DAEN search:

[redacted] (Ascorbic acid; chlorphenamine maleate; Paracetamol; phenylephrine tartrate), [redacted] (Paracetamol), [redacted]

(Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (children) (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (chlorphenamine maleate; Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol), [redacted] (Paracetamol)

There is no temporal relationship between the overdose exposure cases. The four recorded overdose cases occurred in separate years. The first of the accidental overdose cases was reported in 2004; there has been only one year (2005, 2 reports) in which there was more than one report in the year. This analysis of DAEN data spanning 48 years establishes that there is no significant safety signal in relation to the use of liquid paracetamol products.

On this basis, GSKCH suggests that for the majority of children liquid paracetamol products are being used appropriately and that there is no meaningful evidence to support the further need for risk mitigation beyond limiting the maximum amount per liquid paracetamol container to 50 g.

5. Conclusion

At first glance, the current proposal seeking to amend the Schedule 2 and Schedule 4 entries for liquid paracetamol products appears to be driven by an administrative decision to correct an omission specifically pertaining to these products, after consideration of the scheduling of paracetamol for animal use. However, the revised wording to the Schedule 2 entry, based on the wording proposed, goes beyond this undertaking. The current proposed wording is ambiguous, confusing and possibly impacted by a mathematical error.

If the intent of the proposal is to correct the current omission of liquids in the Schedule 2 paracetamol entry by specifying an upper limit to the total dose of

paracetamol available in liquid preparations, this can be achieved by simply revising the wording of the proposed amendment to read as follows:

> ***"Liquid preparations for oral use containing ~~no greater than 50mg per mL or paracetamol in 100 mL with~~ a maximum of 50 g paracetamol per container"***

However, if the intent goes beyond correction of an omission, then the TGA/Delegate need to provide evidence in support of such assertions, given the absence of any such safety signal from the TGA's own adverse event database spanning the last 48 years. The ramifications of the current proposed wording of the amendment can only work to increase risk to patients by removing the safeguards provided by the well established age-appropriate formulations, dosing devices and dosing instructions that are currently in place.

The proposal will have a significant impact on existing liquid paracetamol products available in Schedule 2, eliminating 100 mg/mL preparations and pack sizes greater than 100 mL by upscheduling them to Schedule 4. Equally, eliminating some currently available OTC liquid paracetamol preparations and causing consumers to purchase larger pack sizes of the remaining products has no tangible value in mitigating the risk of overdose.

The proposal is in discord with both the TGA's paracetamol OTC monograph and the Australian Regulatory Guidelines for over the counter medicines (ARGOM).

- Liquid paracetamol formulations can fall under the N2 classification, thus from a regulatory standpoint they are deemed to pose negligible risk.

- There is no regulatory rationale to remove existing products from the market place, when they have been safely available to consumers for 40 years or more.

There are no known safety signals to warrant a need to eliminate 100 mg/mL liquid paracetamol preparations to safeguard public health.

- Rationalization of dose strengths has already been undertaken in the Australian market.

- Practical issues supporting the need for age-appropriate dose volumes should be considered before any changes are made to the currently available dosage strengths.

- Analysis of the DAEN database (1971-2019) corroborates the published data, with only 4 cases of overdose and 8 cases of accidental overdose reported in the last 48 years. Clearly existing measures – the mandatory child-resistant closures, detailed dosing instructions for all ages, clear labelling design,[vii] and accurate, age-appropriate measuring devices – are an effective means of protecting Australian consumers.

Australian consumers and caregivers have had access to liquid paracetamol preparations for many decades, regulatory provisions are in place to ensure their safe and appropriate use and data from the pharmacy setting in which they are purchased indicates that Pharmacists are well placed to answer questions about the use of these products.

GSKCH is not opposed to setting a limit on the total amount of paracetamol that is available per bottle in liquid preparations to bring it in line with solid dose formulations. However, GSKCH does not agree with the proposed amendment to the scheduling of liquid paracetamol *as it has been presented*, on the basis that there is no meaningful, evidence-based public health rationale presented to support removal of any of these products from the market through rescheduling.

Yours sincerely,

[redacted]

[redacted]

GlaxoSmithKline Consumer Healthcare, Australia and New Zealand

vii Sourced from: Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines https://www.legislation.gov.au/Series/F2016L01287

References

1. WHO. Development of paediatric medicines: points to consider in formulation. WHO Expert Committee on Specifications for Pharmaceutical Preparations WHO Technical Report Series No 970;Forty-sixth report 197-225. Annexe 5. *Available from:* https://wwwwhoint/medicines/areas/quality_safety/quality_assurance/Annex5TRS-970pdf. 2012. [Accessed 24 Sept 2019]
2. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *British journal of clinical pharmacology*. 2015;79:405-18.
3. Mistry P, Batchelor H, project SP-U. Evidence of acceptability of oral paediatric medicines: a review. *J Pharm Pharmacol*. 2017;69:361-76.
4. Macfarlane B. Safe paracetamol use for all children: Practice pointers from mystery shopping. *AJP*. 2014;95:52-5.
5. Yin HS, Parker RM, Sanders LM, et al. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. *Pediatrics*. 2016;138:e20160357.
6. Lavonas EJ, Reynolds KM, Dart RC. Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics*. 2010;126:e1430-44.
7. Heard K, Bui A, Mlynarchek SL, et al. Toxicity from repeated doses of acetaminophen in children: assessment of causality and dose in reported cases. *Am J Ther*. 2014;21:174-83.