AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

October 2019

Review of medicine name similarity for monoclonal antibodies and tyrosine kinase inhibitors

Professor Lynne Emmerton, School of Pharmacy Curtin University, has prepared this report on behalf of the Australian Commission on Safety and Quality in Health Care

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Preface

This preface has been written by the Australian Commission on Safety and Quality in Health Care to provide context and background to the main report that follows. The main report was written by an expert from Curtin University, Perth, Western Australia.

Background and purpose

The Commission works in partnership with patients, carers, clinicians, the Australian, state and territory health systems, the private sector, managers and healthcare organisations to achieve a safe, high-quality and sustainable health system.

Key functions of the Commission include: developing national safety and quality standards, developing clinical care standards to improve the implementation of evidence-based health care, coordinating work in specific areas to improve outcomes for patients, and providing information, publications and resources about safety and quality.

The Commission works in four priority areas:

- Patient safety
- Partnering with patients, consumers and communities
- Quality, cost and value
- Supporting health professionals to provide care that is informed, supported and organised to deliver safe and high-quality care.

The Commission is responsible for the development and stewardship of the *National Tall Man Lettering List* (the List). The Commission completed and published a revised List in 2017 to reflect the changes to the Australian Register of Therapeutic Goods (ARTG), International Tall Man lettering lists, International Harmonisation of Ingredient Names and reported adverse incidents or near misses from hospital networks across Australia.

In completing the review of the List, the Commission identified an outstanding piece of work relating to the potential for selection error relating to a class of medicines referred to as monoclonal antibodies which end with the suffix ‘mab’. In addition, advice from medication safety stakeholders prompted the Commission to add another class of medicines to this review: tyrosine kinase inhibitors (ending with the suffix ‘nib’).

There is ongoing expansion of the number of medicines listed on the ARTG within both of these therapeutic classes.

Overview of safety and risk of medicine name confusion

Medication errors are one of the most commonly reported clinical incidents in acute healthcare settings. While rates of serious harm are low, the prevalence of medication errors is a concern, particularly as many are preventable. Medication incidents related to ‘look-alike, sound-alike’ (LASA) medicine names are one of the most common type of medication error.

With several new medicines entering the market each year and in the absence of an effective pre-marketing screening method, LASA medicine names continue to pose a risk to patient safety nationally and internationally.

The subject of this report has been prompted by recent changes to Tall Man lettering lists published by other countries, and reported adverse incidents or near misses from hospital

networks across Australia involving the following therapeutic classes of immuno-modulating medicines:

- Monoclonal antibodies (MABs) (commonly ending in the suffix ‘mab’)
- Tyrosine kinase inhibitors (TKIs) (commonly ending in the suffix ‘nib’).

These classes of medicines require particular risk management due their potency, complexity of their names (both written and verbally), similarity in clinical indication, and recent expansion of these therapeutic classes.

Overview of findings and recommendations

Review of name similarity for the identified therapeutic classes of immune-modulator medicines has included the theoretical risk of confusion within these classes of medicines in clinical practice, including the similarity in clinical indication, with a view to producing a specialised Tall Man List for these medicines for use in oncology practice.

Semi-automation software developed for the Commission by Dr Colin Curtain and successfully trialed in 2017, was used to facilitate the review by computing name similarity scores for these medicines to identity the risk of confusion. The analysis also included potential for confusion of the MABs and TKIs with any other specialist medicines of similar product presentation or brand names, including medicines with a ‘gib’ suffix (for example, soNIDEGib).

Issues likely to influence confusion in medicine selection were considered as follows:

- Indication
- Shelf/storage location
- Similarity in packaging/formulation
- Proximity in an electronic medication management system drop-down list.

As a result of this review, two MAB medicines (infliximab and rituximab), which were included in the original 2011 Tall Man Lettering List, were not retained due to low significance of their alphabetical clustering and proximity.

One non-‘mab’ non-‘nib’ medicine was retained given similarity scores, and alphabetical clustering and drop down list proximity with two ‘nib’ medicines.

A prioritised list of thirty one (31) medicines was distilled into a meaningful list of grouping pairs and trios of medicine names with the suffixes ‘mab’, ‘nib’ and ’gib’.

Table 1 shows the final list and their Tall Man representation which were endorsed by the Commission’s Health Services Medication Expert Advisory Group (HSMEAG).

‘mab’	‘nib’ / ‘gib’
beNRALizumab beVACizumab beZLOTOXumab	aFATinib aXITinib
eCULizumab eFALizumab eMICizumab	bARICITinib biNIMEtinib
oBINUTUZumab oFATUMumab	cABOZANtinib cOBIMEtinib
oCRELizumab oMALizumab	daBRAFEnib daSATinib
pANITUMumab pERTUZumab	laPAtinib leNVAtinib
raMUCIRumab raNIBIZumab	pAZOPanib pONATinib
	soNIDEGib[1] soRAFENib sUNITinib
	tOFACitinib tRAMEtinib

Table 1. Final list of 31 medicines and their Tall Man representation

Use and limitations of this review

The review outcomes provided objective evidence and identification of a prioritised list of 31 medicines recommended for application of Tall Man lettering.

Whilst the Commission receives advice from states and territories on concerns and near misses relating to these and other classes of medicines, the review did not examine formally recorded adverse events or incidents related to LASA medicines in Australia.

Commission response to findings and recommendations

This document contributes to the emerging national conversation on the use of Tall Man lettering as a LASA risk reduction strategy, and has facilitated the Commission’s stewardship role to regularly review the *National Tall Man Lettering List*.

The Commission supports the overall findings and has published a supplementary list of medicines with Tall Man lettering representation as recommended within this report.

The Commission will disseminate the findings and recommendations to state and territory governments, the private hospital sector, primary care providers and the medical software industry. This will support organisations to refine their approaches to medication safety, as they continue to implement various risk reduction strategies, including electronic medication management systems, and ensure safe on-screen display of medicines information.

Sharing this information will assist the health sector in its approach to medication safety by implementing LASA risk reduction strategies, and contribute to improved patient safety nationally.

[1] The only non-‘mab’, non-‘nib’ medicine included in the prioritised list.

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Acknowledgements:

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For development of the semi-automation software used in this project for the Commission and production an updated spreadsheet of medicine name similarity scores in March 2019, using end-February 2019 Australian Medicines Terminology (AMT) data.

Mr Daniel Lalor
Director of Pharmacy
The Canberra Hospital
For clinical expertise and advice in confirming the final prioritised list of medicines.

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Final Report for the Australian Commission on Safety and Quality in Health Care

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Background

The Australian Commission on Safety and Quality in Health Care ('the Commission') has undertaken a program of activity relating to risk management for look-alike, sound-alike (LASA) medicines. Since 2011, this activity has encompassed:

1. Development and publication of the National Tall Man Lettering List (2011)[1] , with confusable medicines identified from international and Australian reports of errors inv0lving medicines confusion, and reports of near misses. Confusable medicine pairs and groups were subjected to manual calculation of their name similarity, and consideration of the similarity in their product characteristics. A risk matrix then assisted with identification of a priority list, for which Tall Man Lettering was deduced.

2. Ongoing national and international environmental scans of error and near-miss reports involving medicine confusion, to identify further LASA medicine pairs.

3. International literature review, confirming the ongoing use of Tall Man lettering in a number of developed countries, albeit in the absence of a more advanced protocol for prioritisation of LASA medicines for Tall Man lettering.

4. Development and validation of Australian software for automated screening of name similarity for LASA pairs[2], based on American software ('POCA')[3] for screening of the uniqueness of proposed proprietary medicine names.

5. Revision of the National Tall Man Lettering List (2017)[1], informed by national and international error and near-miss reports, computed name similarity scores, consideration of environmental risks for LASA errors, and consideration of similarity of product characteristics within pairs/groups of confusable medicines.

Recent work by the Commission proposed that two classes of immuno-modulating agents – monoclonal antibodies (MABs) (commonly ending in the suffix '**mab**') and tyrosine kinase factor (alpha) inhibitors (TKIs) (commonly ending in the suffix '**nib'**) – require particular risk management. This relates to the potency of these agents, complexity of their generic medicine names (both written and verbally), similarity in clinical indications[4], and recent and ongoing expansion of these therapeutic classes.

The current report explores name similarity within groups of generic 'mab' and 'nib' medicines, and hence, the theoretical risk of confusion within these groups of medicines in clinical practice, with a view to producing a specialist Tall Man List(s) for use in oncology.

Methods and Findings

1. Production of an updated all-against-all name database of name similarity scores, using the entire April 2019 Australian Medicines Terminology, limited to generic names, by Dr Colin Curtain (UTas)

Dr Curtain produced an updated spreadsheet of medicine name similarity scores in March 2019, using end-February 2019 AMT data.

The complete AMT generic medicines output file comprises 2,123 name pairs with composite similarity scores ≥0.6500. This is a more conservative threshold than for the 2017 research, where 'moderate' similarity was defined as ≥0.6600. Further reduction is possible if required.

2. Reduction of the all-against-all name similarity database to the currently-available MABs and TKIs

All medicine names including the string 'mab' or 'nib' were searched for and highlighted, to select monoclonal antibodies and tyrosine kinase inhibitors, respectively.

All matches between 'mab' and 'nib' medicines with non-chemotherapy/immunotherapy medicines were deleted. Matched names **deleted** were: nicotinic, nicotine, aprotinin (n=4), framycetin, rifaximin, tretinoin, adenosine, ezetimibe, cimetidine, olanzapine, lubricating, and tranexamic. Matched non-mab and non-nib names **retained** were: sonidegib, nilutamide, vindesine, bortezomib, pomalidomide, carfilzomib.

The reduced list, prior to expert consultation, comprised 351 name pairs with composite similarity scores ≥0.6500: 192 'high' similarity (≥0.6900), and 159 'moderate' similarity (0.6500-0.6899). The more conservative cut-off for 'moderate' similarity of 0.6500 was selected on account of the modest number of data. Analysis proceeded for all 351 name pairs.

The highest similarity score, 0.8570, was for **eculizumab** vs **efalizumab**.

A total of 93 unique medicine names were implicated in similarity scores ≥0.6500. This total comprised 55 'mab', 32 'nib', and six other name suffixes ('gib', 'amide', 'esine', 'omib' x 2, and 'omide').

The top 20 most frequently implicated medicine names comprised 16 'mab' and four 'nib' medicines. Whether 'mab' medicines present greater opportunity for confusion in clinical practice depends on their frequency of use, familiarity with these medicines, and numerous environmental factors. The most frequently implicated medicine names were:

eculizumab (n=22 matches ≥0.6500 in original master list)
daclizumab *(discontinued)* (n=21)
omalizumab (n=21)
afatinib (n=20)

Names in red font above were identified in red font within the data output file.

3. Addition to the reduced database

a) available product presentations (e.g. powder vs liquid, injection strengths and volumes)

Recent research by Her et al.[5], using multivariate logistic regression to predict the likelihood of name pair confusion, confirmed that matching product characteristics increased the risk of confusion between medicines. The most significant predictor was "same manufacturer", suggestive of look-alike medicine packaging as a risk for 'picking' errors from storage units.

Previous work by the Commission[6] had indeed acknowledged the similarity in product characteristics as a risk for medicine confusion.

Available product presentations for the retained 'mab' and 'nib' medicines were sourced from the online (current) *Australian Medicines Handbook* (*AMH*). Information was not available in the *AMH* for 18 of the 93 implicated medicines. Missing data were completed using NPS Medicinewise, manufacturers' websites, Consumer Medicines Information and international sources.

Review of dosage form data confirmed that all 'mab' medicines were only available as injections (solution or powder), while 'nib' medicines were available as tablets or capsules.

Apart from this consistency in dosage forms, the strengths and volumes/numbers were remarkably unique, and did not present any apparent risk in addition to the confusable medicine names.

Furthermore, while particular characteristics could be included in the computed similarity scores, the computational load would be impractical, the computation would be restricted to proprietary names or branded generic medicines, and an arbitrary algorithm would need to be introduced to assign a weighting to the product characteristics versus name similarity.

A more pragmatic solution is expert review of error and near-miss reports and highest-risk name pairs to consider name similarity, product characteristics and other environmental risks (e.g. co-located storage).

b) identifiers for those MABs and TKIs already in the Tall Man Lettering List (INFLIximab, RITUximab) and/or flagged in other safety alerts

Only INFLIximab (3 instances) and RITUximab (4 instances) had been represented in the 2011 Tall Man Lettering List.

These two medicines were considered 'retained' for the purposes of a new, specialised list(s). Their Tall Man representation was also retained as a starting point for the new list.

4. Determination of whether orthographic or phonetic similarity (or both) is the more significant issue in the highest name similarity scores for MABs and TKIs

The orthographic (look-alike) similarity scores (average of BI-SIM and LED) for the 351 retained names averaged 0.6458 (range 0.5000-0.8182). Considering only the look-alike scores, 148 pairs had a computed look-alike score of ≥0.6500, 89 of which were 'high' similarity.

The phonetic (sound-alike) similarity scores (ALINE) averaged 0.7675 (range 0.6598-0.9237). Considering only the sound-alike scores, all 351 pairs have a computed look-alike score of ≥0.6500, 326 of which are 'high' similarity.

This suggested *sound*-alike risks for medicine name confusion theoretically exceeded look-alike risks.

5. Consultation workshop with oncology specialists including safety and quality pharmacists to determine priorities for clinical practice

A consultation workshop (1h 40min) was held with oncology specialists (nursing and pharmacy) and safety and quality pharmacists via videoconference on 23rd May 2019. Representatives for the Therapeutic Goods Administration (TGA) also attended.

In order to determine priorities for clinical practice, the consultation initially focused on:

a) computed name similarity scores
b) clinical factors (e.g. storage, preparation)
c) potential for confusion of MABs and TKIs with any other specialist medicines of similar product presentation or brand names.

Participants were identified in consultation with, and invited by, the Commission.

The workshop attendees were:

Name	Specialty/Title	Organisation
Helen Dowling **(Chair)**	Senior Project Officer	Commission
Julia Shingleton	Pharmacist, eviQ Content Manager	Cancer Institute NSW
Barbara O'Callaghan	Clinical Nurse Consultant, Haematology/Oncology	Fiona Stanley Hospital
David Lui	Cardiology Pharmacist	Sir Charles Gairdner Hospital
Kerry Fitzsimons	Pharmacist, Medication Safety Pharmacy Advisor, Medication Safety	Fiona Stanley Hospital WA Health
Michael Cain	Pharmacist, Oncology Lead	Sir Charles Gairdner Hospital
Julie Adams (SHPA representative)	Oncology Pharmacist and Managing Director	Chemo At Home
Sarah Walton	Pharmacist, Clinical Evaluation Unit	Therapeutic Goods Administration (TGA)
Jessie Howard (alternate for Dr Deborah Emms)	Transparency Reforms and Evaluation Support Section	TGA

Ethical approval was not required for this stage, as it was considered consultation with stakeholders rather than data gathering. The discussions summarised below are not attributed to particular participants.

Prof Emmerton presented the background to the work, followed by a series of guided discussion points and questions, which were put to the workshop participants (Appendix 1).

A summary of the actions and outcomes emanating from each discussion point or question are summarised along with a number of 'post-workshop notes' in the following pages.

Confirmation of the 'master list' of name pairs

The master list, extracted from the all-against-all computation of generic name similarity, using the February 2019 *AMT*, had been produced by removing names with similarity to non-'mab' and non-'nib' medicines, but retaining names with similarity to other anti-cancer agents.

Action:
Three of the deleted non-'mab', non-'nib' matches (tretinoin, ezetimibe, olanzapine) were suggested by participants as potentially relevant for reintroduction to the master list, due to their potential for confusion with 'nib' medicines. Discussion ensued around the settings in which these medicines were prescribed/dispensed; these and TKIs might be dispensed in community pharmacies by staff less familiar with the LASA TKI name.

Outcome:

- tretinoin: demonstrated similarity to trametinib (0.6661)
- ezetimibe: demonstrated similarity to gefitinib (0.6583)
- olanzapine: demonstrated similarity to lenvatinib (0.6569)

None of the similarity scores was considered significant enough for reintroduction of the name pairs to the master list. However, if trametinib, gefitinib and/or lenvatinib were identified as confusable according to other criteria (see point 6 below), relevant pairs could be considered for Tall Man lettering.

Retention of the 50:50 weighting of orthographic:phonetic scores, or variation to suit clinical practice?

LASA risks vary with the clinical setting. Medicines selected from electronic lists are more prone to *look*-alike confusion than sound-alike confusion; however, 'mab' agents are more likely to be presented in electronic lists as *regimens* than individual medicines for selection. One participant suggested recomputing similarity scores with the common suffix (-lizumab, -tuzumab, -atinib etc) deleted, as this is how these medicines might be colloquially referred to in specialist clinical settings. Discussion ensued around how look-alike medicine names can be confused; the eye tends to be drawn to the start and end of a word. The risk of look-alike errors might therefore increase if the similar medicine names start with the same letter(s). Furthermore, when stored alphabetically, these medicines might be in close proximity, increasing the risk of 'picking' errors.

Two potential sources of *sound*-alike errors were identified: verbal orders from a consultant to a registrar (although there would be checking mechanisms in place before administration of that medicine); and patients verbally reporting their medication history with mispronunciation of medicine names, leading to erroneous documentation by clinical staff.

On balance, a 50:50 weighting of orthographic and phonetic similarity scores seemed appropriate.

Action:
Re-compute the name similarity scores excluding the common suffixes, adding another column into the master list to consider re-prioritisation of name pairs.

Outcome:
Re-computation of similarity scores was carried out for the top 20 matches. Suffixes were commonly multi-syllabic (e.g. -lizumab, -limumab, -tuzumab). Deletion of identical suffixes truncated the medicine names to between one and four letters, in many cases rendering the similarity score invalid because these remaining letters often shared nothing in common. Considering that abbreviated medicine names (i.e. a prefix) should never form part of a written medication record or medicine list, this exercise suggests the entire word should be used for computation of similarity scores. It should also be noted that transformation of the *AMT* dataset for the all-against-all screening reduced multiple-word names (e.g. medicines with a conjugate) to the first word, which positively skews name similarity; this is discussed later.

Confirmation of the main clinical and/or environmental risks of confusion

Software presentations (selection errors from drop-down lists): Participants reported variable uptake by software vendors in their adoption of Tall Man lettering. *iPharmacy* produces patient-facing labels, which are not appropriate for Tall Man representation. As noted above, 'mab' agents are often presented in electronic lists as regimens rather than individual medicines, and the medication management process (prescribing → dispensing → administration) involves stringent checks due to the potency of these medicines. Inclusion of Tall Man lettering in electronic lists may therefore be more appropriate for the 'nib' rather than 'mab' medicines, particularly with the potential for TKIs to be prescribed in hospital and dispensed in community pharmacy by staff less familiar with the medicines.

Mis-spelling and/or mishearing: Oral 'nib' medicines would be more likely handwritten or typed in prescriptions than 'mab' medicines. Verbal orders of 'nib' medicines (which might be misheard) could result in confusion, although checks should be in place. Medicine names starting with the same letter(s) were noted as a particular risk for 'picking' errors from shelves or electronic lists.

Close proximity in storage areas: Small storage areas (e.g. refrigerators) offer less opportunity for physical separation of medicines. Shelving labels are/can be used in refrigerators.

Look-alike packaging: Prepared syringes present risks for look-alike selection errors, due to their packaging.

Similar strengths/sizes/volumes: Investigation of the available strengths/volumes/quantities has revealed little commonality between medicine pairs with similar names. Identical route of administration (oral) warrants consideration.

Higher – or lower – volume of dispensing: Greater familiarity with a medicine, due to high dispensing volumes, may lead to lax practices and errors; however, less familiarity with a medicine may lead to lack of recognition of a LASA error. Participants recognised that the volume of dispensing could work either way as a risk factor.

Action:
Prioritisation within the master list could be assisted by highlighting name pairs with the same route of administration, and commencing with the same letter(s).

Outcome:
Suffixes were retained for computation of name similarity. However, medicine pairs commencing with the same letter(s), ending in the same suffix, and sharing the same dosage form, strength or pack size/volume, were identified as:

eculizumab vs efalizumab injection (0.8570)
afatinib vs axitinib tablets, both available in packs of 28 (0.8213)
ocrelizumab vs omalizumab injection (0.7449)
ceritinib vs crizotinib capsules (0.7331)
eculizumab vs emicizumab injection (0.7175)
ramucirumab vs ranibizumab injection (0.7147)
efalizumab vs evolocumab *(later deleted due to use in cardiology)* injection (0.7050)
sonidegib vs sunitinib capsules (0.7033)
efalizumab vs emicizumab injection (0.7010)
baricitinib vs binimetinib tablets (0.6839)
pazopanib vs ponatinib tablets, both available in packs of 30, also in the ISMP list (0.6614)
tofacitinib vs trametinib tablets (0.6614)
panitumumab vs pertuzumab injection (0.6605)
daclizumab *(discontinued worldwide)* vs dupilumab injection (0.6594)
cabozantinib vs cobimetinib tablets, both available as 20mg (0.6578)
carfilzomib vs certolizumab injection (0.6556).

Names in red font above were prioritised in red font in the master list.

Is there the need to increase prioritisation of any 'moderate' name matches?

Action:
Participants identified two medicines with 'moderate' matches whose names had been truncated from two-word conjugate names, and could be deleted: brentuximab (known as brentuximab vedotin) and trastuzumab (known as trastuzumab emtansine). As indicated above, daclizumab has been discontinued worldwide, and could be deleted. Idarucizumab is reportedly rarely used, but has potential for confusion with other medicines, so it was recommended to check for the number and significance of matches with this medicine. The cholesterol-lowering 'mab' medicines in the list (evolocumab, alirocumab) are used mainly for cardiology outpatients under stringent prescribing protocols, and could be deleted (for later review).

Outcome:
Brentuximab, trastuzumab, evolocumab and alirocumab were deleted from the master list. Medicines pairing with brentuximab, trastuzumab, evolocumab and alirocumab remained paired with other medicines in the master list, and were therefore retained. Matches involving idarucizumab were with bevacizumab (0.7127), daratumumab (0.6874), tildrakizumab (0.6772), emicizumab (0.6730), palivizumab (0.6643), ramucirumab (0.6632) and pertuzumab (0.6630). Due to this number of matches and reportedly rare use of idarucizumab (suggesting lack of familiarity and potential for confusion), this medicine was retained in the master list. The reduced master list at this point comprised 313 medicine pairs.

Should there be a joint list, or separate list(s) for 'mab' and 'nib' medicines?

No preference was identified; a single list could be the starting point, and if unmanageable, separated into 'mab' and 'nib' medicines, or by route of administration (parenteral vs oral). Medicines prioritised for (or within) the list could be those names most frequently implicated in 'at least moderate' matches, headed by eculizumab (n=20 matches in the reduced master list) and omalizumab (n=20).

Post-workshop Note 1:
Review of the latest Institute for Safe Medication Practices (ISMP) communiquè revealed a *List of Confused Drug Names*[7] (updated February 2019, comprising 741 proprietary and generic medicines) for which Tall Man lettering had been applied to a selection of 160 names. This approach could be replicated in Australia. The ISMP's selection criteria for application of Tall Man lettering were not revealed. The advantages of a 'Tall Man list within a master list' are the ability to reprioritise medicines within that list, and maintain control over a broader list of confusable medicines, which would be useful for safety and quality communications. Included in the ISMP list of 741 medicines are 11 'mab' and 'nib' medicines. The eight names in red font below were retained for consideration for an Australian list. The ISMP's Tall Man representation was retained where relevant, but may be changed depending on the constitution of an Australian list.

- ado-trastuzumab emtansine: not screened in the current analysis; known as trastuzumab emantasine (a conjugate), whereby the name had been truncated after the first word
- idaru**CIZU**mab: vs bevacizumab (0.7127), daclizumab *(discontinued)* (0.6994), daratumumab (0.6874), tildrakizumab (0.6772), emicizumab (0.6730), palivizumab (0.6643), ramucirumab (0.6632), pertuzumab (0.6630) → for consideration for the Australian list
- in**FLIX**imab: in the Australian Tall Man list, but as **INFLI**ximab → for consideration for the Australian list
- neratinib: not available in Australia
- nilotinib: vs erlotinib (0.7878), crizotinib (0.7064), nilutamide (0.7017), alectinib (0.6837), sunitinib (0.6768), imatinib (0.6677), ibrutinib (0.6634), bosutinib (0.6619), ceritinib (0.6598), dastinib (0.6554), binimetinib (0.6510) → for consideration for the Australian list
- **PAZOP**anib: vs ponatinib (0.6614) → for consideration for the Australian list, also due to common first letter and dosage form
- **PONAT**inib: vs sunitinib (0.7780), imatinib (0.7506), bosutinib (0.7216), dasatinib (0.7142), lapatinib (0.6983), lenvatinib (0.6939), afatinib (0.6920), trametinib (0.6659), pazopanib (0.6614), cobimetinib (0.6602), tofacitinib (0.6539) → for consideration for the Australian list, also due to common first letter and dosage form
- ri**TUX**imab: in the Australian Tall Man list, but as **RITU**ximab → for consideration for the Australian list
- **SORA**fenib: vs encorafenib (0.8059), regorafenib (0.7579), dabrafenib (0.7361), vemurafenib (0.6999) → for consideration for the Australian list
- **SUNI**tinib: vs ponatinib (0.7780), ceritinib (0.7067), sonidegib (0.7033), imatinib (0.6974), axitinib (0.6897), bosutinib (0.6800), nilotinib (0.6768), gefitinib (0.6759), osimertinib (0.6698), ruxolitinib (0.6691), binimetinib (0.6655) → for consideration for the Australian list
- trastuzumab: deleted from the master list due to truncation of the conjugate name.

Post-workshop Note 2:
The Commission forwarded a communique from *Prescrire*, detailing a number of proposed International Nonproprietary Names (INNs) in the List 120 as higher risk, due to confusion with other INNs and brand names. A number of these pairs represent conjugates. As discussed earlier, transformation of the AMT in preparation for automated screening truncates conjugate names. Therefore, these were disregarded for the current exercise. Other 'mab' and 'nib' names in their list were:

- ieramilimab vs nidanilimab: neither is available in Australia
- abrocitinib vs baricitinib: abrocitinib is not available in Australia
- abrocitinib vs ibrutinib: abrocitinib is not available in Australia
- selitrectinib vs Zelitrex® (valaciclovir): selitrectinib is not available in Australia
- teclistamab vs Tecfidera® (dimethyl fumarate): teclistamab is not available in Australia.

Post-workshop Note 3:
The National Pharmacy Association in the UK published a list of LASA items in October 2018[8]. This list comprised 379 name pairs, including brand names, with no indication of which, if any, were prioritised for Tall Man representation. Of this list, infliximab vs rituximab was the only 'mab' or 'nib' medicine pair. This pair has a computed similarity score 0.5953 (below the arbitrary cut-off of 0.6500); however, both names had been prioritised separately in the current list via matches with other 'mab' medicines.

What is the ideal length of a 'mab' and/or 'nib' medicine list(s)?

No maximum length was suggested, as it might depend on the manageability of the list. However, from the perspective of medicines safety communication, a 'short' list of high focus may be more effective than a comprehensive list. Complicating the production of a comprehensive list is the potential for multi-way matches that create conflict in the application of the mid-Tall Man rule[6]. As stated above, it may be preferable to publish a list of confusable medicines, with a selection of names in Tall Man lettering.

Action:
The following processes were utilised to create a priority list of 'mab' and 'nib' medicine names:

1. Re-analysis with common suffixes deleted → this analysis was rejected on the basis of reducing the computation to strings of one to four dissimilar letters.

2. Consideration of pairs with a common first letter(s) and identical dosage forms (or potentially confusable strengths/volumes) → this analysis identified 14 pairs of medicines for prioritisation, after deletion of two pairs for other reasons.

3. Consideration of trametinib, gefitinib and lenvatinib, which had paired with deleted medicine names that had been flagged in the workshop for potential reintroduction → the deleted medicines that had paired with these had little apparent commonality to other retained medicines; as such, the deleted medicines were not reintroduced.

4. Reference to the ISMP list (see point 5 above) → this analysis identified eight medicines of interest, along with their numerous matches that warrant consideration for an Australian list.

5. Reference to the *Prescrire* list of confusable INNs (see point 5 above) → no changes required to the Australian priority list.

6. Reference to the UK list of LASA items (see point 5 above) → no changes required to the Australian priority list.

7. Consideration of medicines most frequently implicated in matches → the reduced master list comprised 313 pairs (94 unique medicine names), of which, 26 medicines had at least 'moderate' similarity to 10 or more other medicines. **Thirty** of the 94 medicines had been highlighted using one of the criteria listed here for prioritisation for an Australian list. If these 30 medicine names were not manageable for application of Tall Man lettering, it could be considered that 13 of the 30 were represented in the shortlist of 26 medicines with at least 'moderate' similarity to 10 or more other medicines.

Ideas for implementation of a 'mab' and/or 'nib' Tall Man list(s)

As per the ISMP, the final Tall Man list(s) would be accompanied by a recommendation from the Commission to be integrated into software and labelling for non-patient-facing processes in the medication management pathway: prescribing (software, in-house protocols), dispensing (software) and shelf labelling (including inside refrigerators). If the Tall Man list is a subset of a larger 'list of confusable 'mab' and/or 'nib' medicines', the full list would be recommended for medicines safety educational initiatives.

Action:
Consider adopting the ISMP format, i.e. a list of confusable medicine pairs (generic names in red), with Tall Man lettering applied to priority medicines identified in point 6 above. The list could also be produced as a single column in alphabetical order with duplicates removed.

6. Trial induction (application) of Tall Man lettering for the prioritised MABs and TKIs, based on the conventions underpinning the 2011 Tall Man Lettering List, and noting any required breaches of those conventions

With reference to Figures 1 and 2, the Mid-Tall Man lettering convention was applied to the list of 30 prioritised 'mab' and 'nib' medicine names.

Taking two or more confusable drug names:

Step one
Working from the first letter of the drug name, take each common character to the right until two or more characters are different, and from that point on, capitalise the characters.

Thus:	Becomes:
cefuroxime	cefUROXIME
cefotaxime	cefOTAXIME
ceftazidime	cefTAZIDIME

Step two
Working from the last letter of the word, take each capitalised common character to the left until two or more characters are different, and change the capital letters to that point back to lowercase.

Thus:	Becomes:
cefUROXIME	cefUROXime
cefOTAXIME	cefOTAXime
cefTAZIDIME	cefTAZIDime

Figure 1. Mid-Tall Man lettering convention[6]

Three drug name pairs – doxorubin *vs* daunorubicin, doxorubicin *vs* idarubicin, and daunorubicin *vs* idarubicin – were all identified as having 'high' or 'extreme' risk ratings. As these three names share common orthographic elements, they were treated as a group for the construction of Mid-Tall Man names.

Step one

doxorubicin	DOXORUBICIN
daunorubicin	DAUNORUBICIN
Idarubicin	IDARUBICIN

Step two

DOXORUBICIN	DOXOrubicin
DAUNORUBICIN	DAUNOrubicin
IDARUBICIN	IDArubicin

In contrast, the three names carbamazepine, oxcarbazepine and carbimazole form a different type of group. Whilst there are some similarities between carbimazole and oxcarbazepine, there is no significant orthographic similarity between the two names. However, carbamazepine shares significant similarities with both names. Applying the Mid-Tall Man rule to the three names simultaneously:

Step one

carbamazepine	CARBAMAZEPINE
oxcarbazepine	OXCARBAZEPINE
carbimazole	CARBIMAZOLE

Step two

CARBAMAZEPINE	CARBAMAZEPINe
OXCARBAZEPINE	OXCARBAZEPINe
CARBIMAZOLE	CARBIMAZOLe

Figure 2. Application of Tall Man lettering to a group

Mid-Tall Man lettering was attempted in a pairwise fashion, documenting the precedent for each name in a separate list, in case this was contradicted by a later match with another name or required adjustment due to a group-wise match.

Existing Tall Man representation of particular names (from the ISMP or previous Australian lists) was also documented, in case of the need for updates.

Where relevant, conflicts with ISMP Tall Man representation were noted. In particular, the Australian convention retains lower-case i and upper-case L at the start or end of a string, to avoid confusion in sans serif fonts. This did not appear to be the case in the ISMP list.

Review of the complex multi-way (group-wise) matches suggested the Mid-Tall Man convention was not appropriate for the groups of 16 'nib' and 14 'mab' medicines. Consideration of all of the significant multi-way matches would lead to capitalisation of the entire suffix of medicine names, which breaches the Mid-Tall Man convention.

Post-workshop Note 4:
Consultation with a clinical expert instrumental in the preparation of the 2011 Tall Man Lettering List suggested alphabetical clustering (in pairs or trios) within the lists of prioritised medicine names would be more relevant to clinical practice than group-wise induction of Tall Man lettering. Alphabetical proximity of confusable medicines increases risk of mis-selection from electronic lists and from storage units. Review of the lists of 14 prioritised 'mab' and 16 prioritised 'nib' medicines for alphabetical clustering, followed by review of the master list for any other pairs/trios relevant to clinical practice (and their similarity scores), led to further refinement of the priority lists (Figure 3).

In summary, carfilzomib, idarucizumab, certolizumab, infliximab and rituximab were suggested for deletion from the 'mab'/'mib' list due to insignificant alphabetical clustering, and in the case of infliximab and rituximab, historical LASA pairing that has been deprioritised with the expansion of this medicine class. The following were suggested for inclusion, on account of their alphabetical clustering: obinutuzumab, ofatumumab, benralizumab, bevacizumab and bezlotoxumab. This resulted in a proposed list of 14 'mab' medicines for Tall Man lettering.

For the 'nib'/'gib' list, ceritinib, crizotinib and nilotinib were suggested for deletion, while lapatinib, lenvatinib, dabrafenib and dasatinib were suggested for inclusion to prioritise pairs with alphabetical clustering. This resulted in a proposed list of 17 'nib'/'gib' medicines for Tall Man lettering.

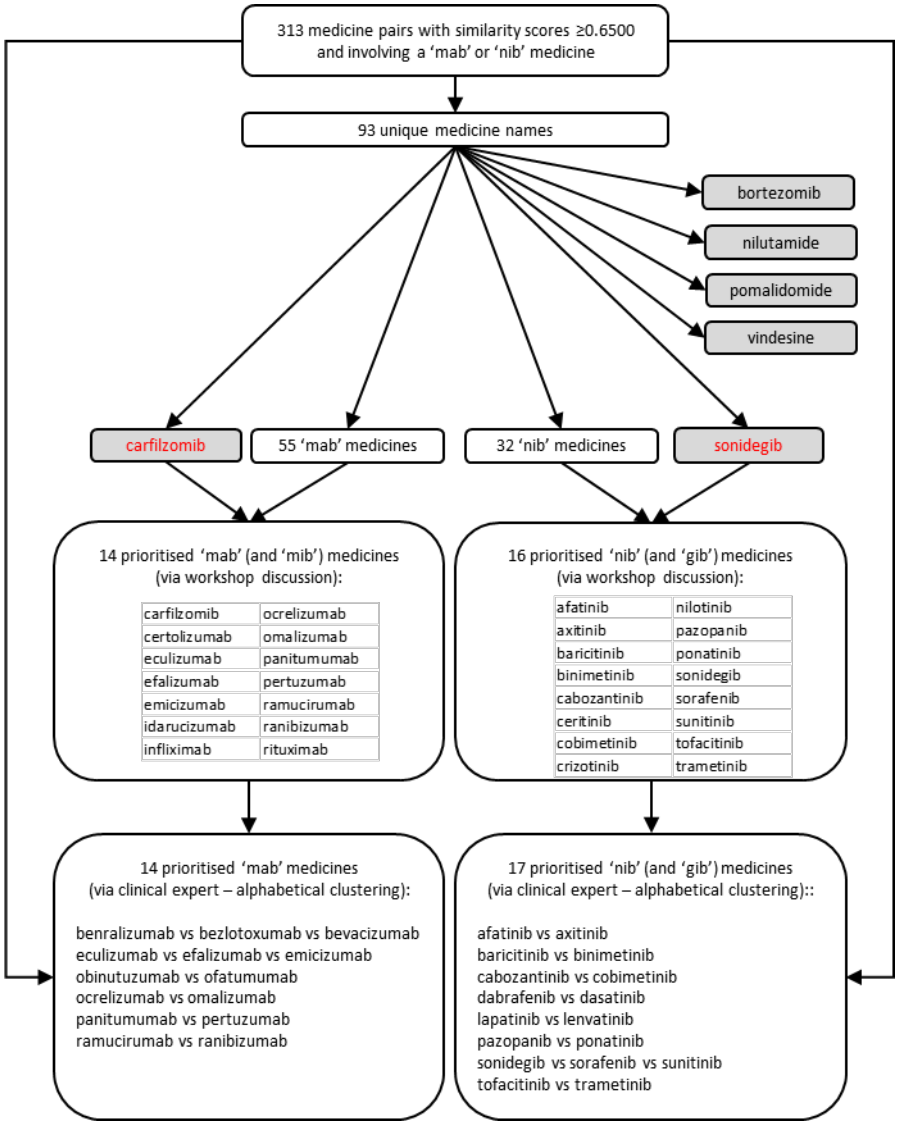

Figure 3. Data reduction summary

Post-workshop Note 5:
Iterative revisions of the prioritised medicine names suggested confirmation by the workshop participants would enhance the validity of the data reduction process. The final prioritised list of 31 medicines was distilled into a meaningful list of grouping pairs and trios of 'mab' and 'nib'/'gib' medicine names. Issues likely to influence confusion in medicine selection were considered:

- Indication
- Shelf/storage location
- Similarity in packaging/formulation etc
- Proximity in a drop-down list.

The 14 prioritised 'mab' medicines and 17 prioritised 'nib/'gib' medicines, their Tall Man representations, and a summary of the derivation of these lists, were distributed to the workshop participants for confirmation. (Figures 4 and 5)

7. Presentation of the prioritised MABs and TKIs by similarity score and proposed Tall Man presentation

The final lists are available as worksheets within a single Excel file submitted as a supplement to this report. The Excel 'sort' function can be used to alphabetise or otherwise rearrange lists.

As per the ISMP list, the final product is a list of confusable 'mab' and 'nib' (with one 'gib') medicines, with Tall Man representation of those prioritised according to the criteria described earlier in this report. Confusable pairs are also listed for the purposes of medicines safety communication.

8. Commentary around the utility of Tall Man lettering for these groups of medicines

The Mid-Tall Man convention was unable to manage complex group-wise clustering of similar names. Using the convention, groups of medicines commencing with different letters would have resulted in the entire prefix (commonly to -inib or -umab or -izumab) becoming capitalised. This was considered a breach of the Mid-Tall Man convention. Considerations leading to this approach were:

- Prioritisation of name pairs by similarity score alone does not consider the many environmental factors that may lead to LASA medicine errors.
- Prioritisation by the frequency of 'significant' matches within the master spreadsheet does not consider the frequency of dispensing of these medicines. More frequently dispensed medicines could either be more susceptible to LASA errors (due to the probability of encountering that medicine and/or confirmation bias) or less susceptible due to the pharmacist's familiarity with that product name, location and/or characteristics[9].
- Prioritisation based on similarity in dosage form was often inconclusive. For example, sunitinib is available as capsules (12.5mg, 25mg, 37.5mg, 50mg); ponatinib is available as tablets (15mg, 45mg); and pazopanib is available as tablets (200mg, 400mg). These three medicines demonstrated group-wise similarity via their pair-wise scores. The product strengths are in a similar range for sunitinib and ponatinib, albeit in different dosage forms (similarity score 0.7780). Conversely, the capsule dosage form may present a risk of confusion for ponatinib and pazopanib (0.6614).
- Prioritisation based on the same commencing letter(s) was used as the overriding logic, given risks of mis-selection from alphabetical electronic lists or storage units. For example, in an electronic list or shelf storage, ponatinib and pazopanib (0.6614) would be more closely aligned than sunitinib and ponatinib (0.7780), and was therefore prioritised.

Discussion

Commentary from oncology and medicines safety experts has confirmed the value of separate 'mab' and 'nib' Tall Man lists, as well as a master list of potentially confusable medicines within these classes. The current work has produced a list of 17 'nib'/'gib' and 14 'mab' medicines, which, using various criteria, have been identified as at risk of confusion with other medicines (Figures 4 and 5).

beNRALizumab beVACizumab beZLOTOXumab
eCULizumab eFALizumab eMICizumab
oBINUTUZumab oFATUMumab
oCRELizumab oMALizumab
pANITUMumab pERTUZumab
raMUCIRumab raNIBIZumab

Figure 4. Proposed 'mab' Tall Man list (n=14)

aFATinib aXITinib
bARICITinib biNIMEtinib
cABOZANtinib cOBIMEtinib
daBRAFEnib daSATinib
laPAtinib leNVAtinib
pAZOPanib pONATinib
soNIDEGib soRAFENib sUNITinib
tOFACitinib tRAMEtinib

Figure 5. Proposed 'nib'/'gib' Tall Man list (n=17)

Recommendations:

It is recommended that the Commission:

1. Publicise the various lists:
    - The full list of confusable 'mab' and 'nib' medicines, highlighting the prioritised (at-risk) medicines in Tall Man lettering. Users can manipulate the list according to medicines in use in their setting. [Refer to separate Excel worksheet 'Confusable pairs summary', columns A-D – within Report – Similarity scores data MABs and NIBs – October 2019: D19-31380]

    AND/OR
    - Figures 4 and 5 above, as the Tall Man representations of the prioritised medicines.
2. Maintain environmental scans of LASA errors and near misses involving these groups of medicines. Knowledge of the risk factors associated with such errors and near misses can inform revision of this initial product.
3. Review the Tall Man Lettering List every three years, taking into account the expansion of the 'mab' and 'nib' medicine groups.

Appendix 1

Workshop Discussion Guide

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Confusable MABs and TKIs: Do we need a specific Tall Man list?

Prof Lynne Emmerton
School of Pharmacy and Biomedical Sciences

Background

- 2011: National Tall Man Lettering List for LASA medicines introduced by the Commission – derived using manual algorithm for medicine similarity
- 2011 onwards: Ongoing international environmental scan of LASA risks, with notifications to health professionals
- 2016: International literature review revealed no further innovations to maintain Tall Man lists; however, FDA software available to screen medicine names
- 2017: Revised Tall Man List published, following review by Expert Panel and HSMEAG
- 2017: FDA software replicated and validated in Australia, drawing on the Australian Medicines Terminology database

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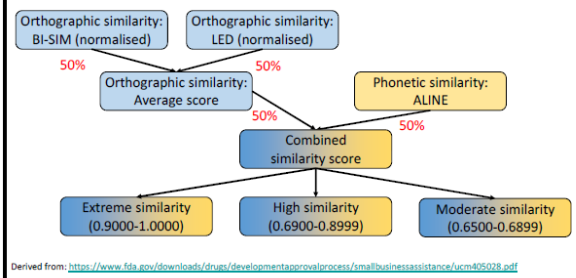
LASA v2: Look-alike sound-alike Automated Screening Application



Derived from: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm405028.pdf

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Conclusions from the 2017 Trial

- Automated screening offers a proactive approach to identification of name similarity
- Automation offers high sensitivity, but with a cost of 'noise' in the data
- *LASA v2* software can be used alongside incident reports to update the Tall Man List
- However, a large number of specialist high-risk LASA medicines are not accommodated in the Tall Man List

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Objectives of this Workshop

- To determine clinical and environmental factors that can lead to confusion within MABs and TKIs
- To confirm which MABs and TKIs are most confusable
- To explore the viability of a specialist Tall Man List(s) for MABs and TKIs

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Work Completed to Date

- Re-run of name similarity screening, limited to generic medicines (February 2019 AMT)
  → 2,213 name pairs with similarity ≥0.6500
- Retention of MABs and TKIs with similarity to other medicines of ≥0.6500…

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Question 1

Highest similarity: vs pertuzumab (0.6713)

MAB/TKI-matched names deleted		MAB/TKI-matched names retained	
nicotinic nicotine aprotinin (n=4) framycetin rifaximin tretinoin adenosine ezetimibe cimetidine olanzapine lubricating tranexamic	Should any still be considered as risks for confusion?	sonidegib nilutamide indesine bortezomib omalidomide carfilzomib	Should any be deleted?

Highest similarity: vs certolizumab (0.6556)

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Work Completed (cont'd)

- Current list of matches involving MABs and TKIs: 351 pairs
  - →192 'high' similarity (scores 0.6900-0.8999)
  - →159 'moderate' similarity (scores 0.6500-0.6899)

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Question 2

- Are the 'high' similarity pairs logical? Top matches:

0.8570*	eculizumab	efalizumab
0.8424	mepolizumab	vedolizumab
0.8336	belimumab	golimumab
0.8256*	afatinib	dasatinib
0.8213	afatinib	axitinib
0.8160	efalizumab	omalizumab
0.8150	elotuzumab	inotuzumab
0.8146*	inotuzumab	obinutuzumab
0.8119*	adalimumab	belimumab
0.8091	cetuximab	rituximab
0.8088*	belimumab	ipilimumab

*Phonetic similarity score component is 'extreme' (≥0.9000)

… but are these names more commonly written or spoken?

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Question 3

- What are the main clinical and/or environmental risks of confusion with MABs and TKIs?
  - Selection from drop-down lists?
  - Mis-spelling?
  - Mishearing?
  - Close proximity in storage areas?
  - Look-alike packaging?
  - Similar strengths, sizes? (appear unique)
  - Higher – or lower – volume of dispensing?

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Question 4 *(see Excel spreadsheet)*

- Which of the 159 'moderate' pairs should be prioritised due to these risks of confusion?
- 135 of these 'moderate' matches have 'high' phonetic similarity ... but are these names more commonly written or spoken?

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Question 5

- The top 20 most frequently implicated medicine names comprise 16 MABs and 4 NIBs
- Most frequently implicated medicine names:

  eculizumab (n=22 matches ≥0.6500)
  daclizumab (n=21)
  omalizumab (n=21)
  afatinib (n=20)
- Should we focus on MABs or NIBs in a single Tall Man List, or explore separate lists, or only work on MABs for now?

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Question 6

- The National Tall Man List was limited to <100 names (suggested max 150) to avoid alert fatigue
- If we produce a Tall Man List(s) for MABs and/or TKIs, what would be the ideal length?

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Question 7 (last one!)

- If we produce a Tall Man List(s) for MABs and/or TKIs, how do you envisage it might be implemented in practice?
  - Software?
  - Shelf labels?
  - Medicines information resources?

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Summary of Outcomes – What Next?

1. Confirmation of the 'master list' of name pairs
2. Retention of 50:50 look-alike:sound-alike scores, or variation to suit clinical practice?
3. Confirmation of the main clinical and/or environmental risks of confusion
4. Up-prioritisation of 'moderate' name matches?
5. Joint or separate list(s) for MABs and NIBs?
6. Ideal length of a MABs/NIBs list(s)?
7. Ideas for implementation of a MABs/NIBs list(s)

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