13 May 2020

Via Electronic Submission

Therapeutic Goods Administration
PO BOX 100
WODEN ACT 2606
Australia

Re: Consultation – Scope of Regulated Software-Based Products

Dear Sir or Madam:

Roche has a rich history of being a global leader in healthcare research and innovation. Over the last decade, Roche has invested in pioneering technologies and built data ecosystems that are transforming healthcare. Roche remains committed to develop digital solutions focused on evidence-based, efficient and prevention focused clinical decision support tools, as well as, digital solutions for patients in chronic disease management.

Advances in computing technology, as well as the fast-paced, iterative nature of the development, delivery, and frequency of innovation in software, have given rise to a rapidly evolving environment of many new Software as a Medical Device (SaMD) products as well as many health-based software products. Only a subset of software used in healthcare meets the definition of a device (i.e. qualifies as a medical device), and it is therefore important to clarify how such qualification determinations are made.

Roche applauds TGA's goal to address appropriate qualification of software products in order to support a risk-based, fit-for-purpose regulatory paradigm for software. This approach will allow TGA to focus its resources on those products that present the highest risk to patients while ensuring innovative, low-risk technologies reach users more quickly. Software qualification also provides needed clarity to software developers regarding which software does or does not qualify as a medical device and should be regulated.

We recognise TGA for an approach consistent with those taken by Canada, the United States, and the EU, and which supports our shared goals of global convergence. We specifically commend TGA's thoughtful and forward-thinking consideration of exclusion and exemption of certain software functions, which allows a more tailored and risk-based approach to these products, especially around clinical decision support. We provide our specific recommendations to TGA's approach and responses to questions in Appendix A.

Thank you for the opportunity to provide comments on this important issue. Roche is committed to working with TGA to support a risk-based, fit-for-purpose regulatory framework that brings safe, effective digital technologies into healthcare at a pace that matches the speed of what's possible – and that patients deserve – while also accommodating the shorter timelines and unique agility of software development.

Yours sincerely

Roche Diagnostics Australia Pty Limited

Appendix A: Roche Comments on Software Qualification

In order to best address the questions posed in this consultation, we have summarised our proposal in the table below:

Excluded from all device regulation	**Exempted** from some device regulation, but still regulated as a device	**Regulated** as a device
Not subject to TGA regulation. - No registration requirement in ARTG - No TGA assessment of any type required - No monitoring for ongoing safety	**Subject to some TGA regulation*** - No registration requirement for ARTG but: ü Must meet relevant essential principles for safety and performance ü Must report adverse events to TGA ü TGA can take regulatory action for false advertising * exemption conditions can be prescribed in the regulation	**Subject to TGA regulations.**
Software intended for: - Administrative support of a health care facility - Management of prescription information - Medication/adherence (treatment regimens) - Electronic patient records - Electronic patient record keeping - Clinical workflow and support - Education, training, or guidance - Transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results - Processing tools for secure info storage - Communication tools (between HCPs, patients, labs) such as telemedicine - Health information management/ database systems - Maintaining and encouraging a healthy lifestyle	Software intended for: Clinical decision support that meets three of the four following criteria: • it is not intended to acquire, process, or analyse a medical image or a signal from a hardware medical device or an in vitro diagnostic device, - it is intended for the purpose of displaying, analysing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines); - it is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; - it is intended for the purpose of enabling such health care professional to independently review the basis and	Software intended to: · Diagnose of an individual's disease or condition · Monitor an individual's disease or condition · Provide therapy to an individual · Control other medical devices · Is an accessory to a medical device · Recommend or specify a treatment or intervention specific to an individual · Generate virtual anatomical or physiological models

Excluded from all device regulation	**Exempted** from some device regulation, but still regulated as a device	**Regulated** as a device
- Extracts data from clinical trials/patient records - Monitoring or management of health IT systems - Medi-alerts not intended to monitor a specific disease or condition - Standard IT equipment with no therapeutic claims - Travel medicine tools - Predictive analysis* - Archetype editor - Laboratory Information Systems - Helps patients self-manage a specific disease/condition - Helps patients manage stress for mental health - Monitors a condition* - Software that provides "class-based analyses" rather than patient-specific diagnosis or management* - Clinical decision support* *Assuming the four criteria associated with "Clinical Decision Support Software" are met - it is not intended to acquire, process, or analyse a medical image or a signal from a hardware medical device or an in vitro diagnostic device, - it is intended for the purpose of displaying, analysing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines), and - it is intended for the purpose of supporting or providing recommendations to a health care professional about prevention,	input(s) for such recommendations and such recommendations are intended only as one of several pieces of information a health care professional can use in making a clinical diagnosis or treatment decision regarding an individual patient." and, has a risk categorization deemed "less important" for independent review (based on IMDRF's N12 risk categorization and IMDRF's N41 clinical evaluation guidances)	

Excluded from all device regulation	**Exempted** from some device regulation, but still regulated as a device	**Regulated** as a device
diagnosis, or treatment of a disease or condition, and - it is intended for the purpose of enabling such health care professional to independently review the basis and input(s) for such recommendations and such recommendations are intended only as one of several pieces of information a health care professional can use in making a clinical diagnosis or treatment decision regarding an individual patient." 		

1) What kinds of software-based products should be exempted from inclusion in the ARTG? What are they and why should they be exempted?

We believe certain low-risk clinical decision support software that is not outright excluded from the ARTG could be eligible for exemption based on meeting certain criteria, as outlined below:

Clinical decision support that meets three of the four following criteria:

- it is not intended to acquire, process, or analyse a medical image or a signal from a hardware medical device or an in vitro diagnostic device,
- it is intended for the purpose of displaying, analysing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
- it is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition;
- it is intended for the purpose of enabling such health care professional to independently review the basis and input(s) for such recommendations and such recommendations are intended only as one of several pieces of information a health care professional can use in making a clinical diagnosis or treatment decision regarding an individual patient."

and,

has a risk categorization deemed "less important" for independent review (based on IMDRF's N12 risk categorization and IMDRF's N41 clinical evaluation guidances).

Such a construct would allow certain low-risk CDS software to be exempt from submission of an application for review to TGA while also ensuring the CDS is subject to certain aspects of regulatory oversight.

We present the below example of a product that would fall within this exemption category according to the above criteria:

Example: Software that aggregates data from continuous glucose monitoring, activity trackers, and food logs to help insulin-dependent type 2 diabetic patients identify potential lifestyle triggers for hypoglycemic events and recommends corrective treatment options (e.g., timing of insulin dosing). The recommendations made by the software are based on published guidelines and are easily reviewable and understandable by the patients to which they are provided. With respect to IMDRF's N12 Risk Categorization framework, this software is intended to inform clinical management for a serious situation or condition.

Response: Since this software is CDS, it must first be evaluated by the developer to determine if it meets the CDS criteria for exclusion. When reviewing the example in the context of the CDS criteria provided on page 16 of the Consultation, it does not meet the following criterion:

- *it is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition*

The software function described is intended for the purpose of informing patients, not healthcare professionals, about disease treatment. It therefore does not meet the CDS criteria for exclusion from the ARTG.

However, the software **could meet the proposed CDS exemption criteria**.

The software is clinical decision support software and meets three of the four following criteria:

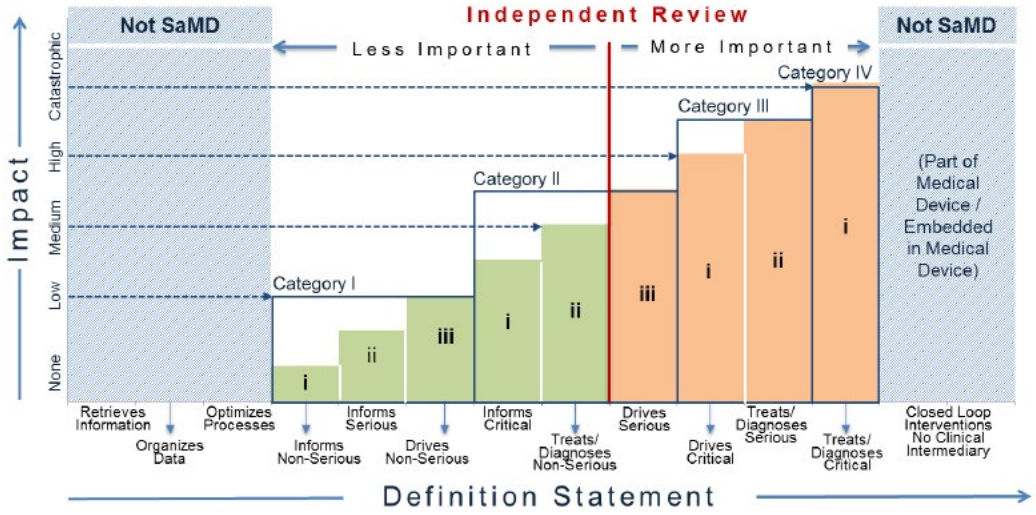
- it is not intended to acquire, process, or analyse a medical image or a signal from a hardware medical device or an in vitro diagnostic device; (Yes)
- it is intended for the purpose of displaying, analysing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines); (Yes)
- it is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; (It does not meet this criterion)
- is intended for the purpose of enabling such health care professional/(user) to independently review the basis and input(s) for such recommendations and such recommendations are intended only as one of several pieces of information a health care professional can use in making a clinical diagnosis or treatment decision regarding an individual patient." (Yes, in the context of the "user" being a patient, and not a HCP).

And,

The CDS has a risk categorization deemed "less important" for independent review (based on IMDRF's N12 risk categorization and IMDRF's N41 clinical evaluation guidances). (Yes, explanation below.)

The software function described in the example is intended to inform clinical management for a serious situation or condition (diabetes). Given this risk categorization, Figure 13 of IMDRF's *Software as a Medical*

Device (SaMD): Clinical Evaluation guidance can be reviewed to understand the importance of independent review for a software function falling in this risk category:



(Reproduced from IMDRF Software as a Medical Device (SaMD): Clinical Evaluation guidance)

As can be seen in this figure, independent review is "less important" for a software function that informs a serious situation or condition.

As such, the software function described within this example meets three of the four CDS criteria and has a risk categorization whereby independent review is "less important" according to IMDRF's *Software as a Medical Device (SaMD): Clinical Evaluation* guidance. Therefore, this software function would be eligible for exemption from inclusion in the ARTG according to the framework proposed above.

Such a model for exemption of software functions would allow TGA continued oversight of certain low-risk software functions while reducing the burdens, both to TGA and software developers, imposed by premarket review. Additionally, an approach whereby patient-focused CDS may be exempt while healthcare professional-focused CDS may be excluded (please see our proposal in the Exclusion section of this response) is consistent with the approach TGA has taken elsewhere to differentiate the risk profile of patient- vs. healthcare professional-centric software. For example, as described in Table 1 of this Consultation, software applications providing information to an "individual" have a higher class than software applications providing information to a "relevant health professional."

2) What kinds of software-based products should be excluded from regulation by the TGA? What are they and why should they be excluded?

We agree that the software functions TGA has listed on pages 13 – 14 of the Consultation paper should be excluded from regulation, as they do not meet the definition of a medical device under the current application of the Therapeutic Goods Act. These software functions are shown in black font in the "Excluded" column of the above table.

In addition to these functions, we recommend that the additional software functions we have provided in red, underlined font in the "Excluded" column of the above table also be excluded from TGA regulation. Our rationale for each of these is provided below:

a) Laboratory Information Systems (LIS): As TGA noted on page 12 of its Consultation, laboratory information systems (LIS) or laboratory information management systems (LIMS) are intended for the input, storage, and retrieval of clinical information. Such software can also be used for ordering of laboratory tests, samples with labels, and sorting, and for the management of data regarding samples, technical validation, and quality controls. All of these functions do not meet the medical device definition. For this reason, such software functionality is not considered to be a medical device in the US (as described in the US FDA's *Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act* guidance) or in the EU (as described in MDCG 2019-11, *Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR*). If any LIS modules or algorithms have an intended purpose that does fulfill the definition of a medical device, then they should be subject to applicable regulatory requirements regardless of their use environment.

b) Helps patients self-manage a specific disease/condition: As described in the Consultation, these software functions assist patients in managing their own health and often provide educational information. Many mobile applications currently on the market provide patients with tools to organise and track health information without providing recommendations to alter or change a previously prescribed treatment or therapy. Examples include apps that provide simple tools for patients with specific conditions or chronic disease (e.g., obesity, anorexia, arthritis, diabetes, heart disease) to log, track, or trend their events or measurements (e.g., blood pressure measurements, drug intake times, diet, daily routine or emotional state, average blood glucose) and share this information with their health care provider as part of a disease-management plan. Such software functionality should be excluded from regulation because it is intended for logging, tracking, and trending data and for education and is not intended for diagnosing or monitoring a disease or recommending a treatment or therapy.

c) Helps patients manage stress for mental health: We believe software functions such as those that provide daily motivational tips to promote a positive mental outlook or direct mindfulness activities are intended to maintain or encourage a healthy lifestyle and thus belong within the category of "general wellness" software. Such software typically falls within one of two categories: 1) The software has an intended use that relates to maintaining or encouraging a general state of health or health activity; or 2) The software has an intended use that relates the role of the healthy lifestyle with helping to reduce the risk or impact of certain chronic diseases and conditions and where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition. With respect to mental health software, the role that factors such as a positive mental outlook play in managing mental health stress are well understood and accepted. Therefore, we believe that such mental health software, as described, should be considered as general wellness software and should be excluded from regulation by TGA. We also believe that TGA should apply a similar approach to other areas where the relationship between healthy lifestyle choices and a disease or condition is well understood (for example, the role healthy lifestyle choices play in living well with diabetes). The US FDA's guidance document *General Wellness: Policy for Low Risk Devices* may serve as a helpful model.

d) Clinical decision support: Clinical decision support software fulfilling the four criteria outlined on page 16 of the Consultation should be excluded from regulation by TGA. Such an approach would allow TGA to focus its resources on software functions that pose a higher risk to patients. Further, such an approach would be consistent with the approach taken in the US and outlined in Section 520(o)(1)(E) of the Federal Food, Drug, and Cosmetic Act as well as the approach described in Health Canada's *Software as a Medical Device (SaMD): Definition and Classification* guidance document.

d1. Defining Signal
When adopting such an approach, it is important that TGA clearly define the term "signal" used in the first criterion for CDS:

- *"it is not intended to acquire, process, or analyse a medical image or a signal from a hardware medical device or an in vitro diagnostic device;"*

In the context of an in vitro diagnostic device, a signal should be defined as an electrochemical or photometric response generated by an assay and instrument that must be further processed by software to generate a clinical test result.

In the context of a hardware medical device, signal should be defined as a physiological signal that is derived from the human body and processed further by software/firmware to generate a measurement or clinical test result. An example would be the optical signal that is generated by sensors in a wearable device for cardiovascular monitoring. The software/firmware converts the optical signal into a heart rate result.

d2. Interpretation/Implementation of "Signal"
It is clear that a medical image is a clinical test result, and software that further analyzes or processes that medical image fails the first CDS criterion and remains regulated as a medical device.

In contrast, a signal from a hardware medical device or IVD is not a clinical test result. The signal is the output from hardware or a hardware/assay combination that is converted by software to a clinical test result, not the test result itself. Software that does not process a signal but uses a clinical test result as an input can still fulfill the first CDS criterion.

For example, software used in an IVD instrument to convert aphotometric signal into an HbA1C test result is the "signal" software and fails the first criterion under CDS. Such software remains regulated. Software that takes the HbA1C test result and utilizes it as input for a unique intended use meets criterion one under CDS because it is not intended to acquire, process, or analyze a signal. In contrast, a software app intended to measures a patient's ability to draw and pinch an object in order to help a clinician determine the patient's neuromotor disease progression is processing or analyzing a physiological signal and would fail criterion one for CDS.

It is important that TGA carefully define and implement the term "signal" to not include test results, measurement data, or other information that is provided by a regulated IVD or medical device. Otherwise, the unintended consequence would be to make nearly all software that uses information generated by an IVD or a signal acquisition system to be subject to regulation. We do not believe this is appropriate for such low-risk software functions, nor is it the best use of TGA's resources to provide oversight for the significant number of products this would encompass.

Alternative recommendation: If this interpretation continues to create issues, we recommend consideration of new language for CDS criteria that would establish a criterion for medical image and a separate criterion for software generating a clinical test result (removing the word "signal" entirely to avoid potential confusion):

Delete

~~*"it is not intended to acquire, process, or analyse a medical image or a signal from a hardware medical device or an in vitro diagnostic device;"*~~

Replace with:

- it is not intended to acquire, process, or analyse a medical image, and
- it is not intended to generate a clinical test result from a hardware medical device or an in vitro diagnostic device, and

d3. Transparency

In addition to careful interpretation of "signal," we believe it will be important for TGA to also clarify its interpretation regarding the fourth Clinical Decision Support criterion:

- *"it is intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient."*

In order for this criterion to be fulfilled, we believe that CDS software functions must be very transparent to the end users, such that they can readily understand the inputs as well as the basis for the resulting recommendations. Additionally, the software should "inform" their decision-making (as opposed to "drive" or "treat/diagnose," as described in IMDRF's *"Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations* guidance). Yet, there is considerable inconsistency between software developers and regulators on how to best meet this fourth criterion for CDS, based on feedback from software developers in the U.S. and Canada. As such, we recommend clarification of the language as described below:

- *it is intended for the purpose of enabling such health care professional to independently review the basis and input(s) for such recommendations and such recommendations are intended only as one of several pieces of information a health care professional can use in making a clinical diagnosis or treatment decision regarding an individual patient."*

e) Predictive analysis, monitors a condition, and software that provides "class-based analyses" rather than patient-specific diagnosis or management: Software functions falling into these categories could all be excluded from regulatory oversight if they meet the four CDS criteria outlined on page 16 of the Consultation. For example, if a software function calculates a patient's risk of developing chronic kidney disease based on information in his/her EHR, using a publicly disclosed algorithm, and describing the input and basis for the recommendation to the healthcare professional, then this predictive analysis software should be excluded from regulation by TGA. If the algorithm used in the calculation is proprietary and is not made available to the healthcare professional so that he/she can independently review the basis for the recommendation, then this predictive analysis software should not be excluded from regulation by TGA.

f) It should also be noted that consumer-focused software functions (such as those described on page 15 of the Consultation) do not meet the CDS criteria outlined on page 16 of the Consultation because they provide recommendations to patients rather than healthcare professionals. Because such consumer-focused CDS software functions tend to have a greater risk profile (as described in the recent *Therapeutic Goods Legislation Amendment (2019 Measures No. 1) Regulations 2019* where, for example, software providing information to a "user" has a higher class than software providing information to a "relevant health professional"), we believe these functions should not be excluded

from regulation by TGA but may be exempted (please see our discussion on this topic in the Exemption section of our response).

3) Please provide details:

- **of any existing regulatory oversight that you consider would negate the need for the TGA to regulate particular software-based products; or**
- **describe what evidence or product characteristics could be used to determine that particular types of software pose no potential for significant harm to an individual.**

We are not aware of any existing regulatory oversight that would negate the need for the TGA to regulate particular software-based products.

Factors such as intended use (with respect to the medical device definition) and intended use population should be taken into account when determining the particular types of software that pose no potential for significant harm to an individual. Please see our responses to questions 1) and 2) for an overview of product characteristics that pose no or minimal potential for significant harm to an individual.

4) Which approaches from international jurisdictions, if any, should be used to inform the Australian approach to this issue?

Approaches from the US (including the 21st Century Cures Act and related Digital Health guidances), Health Canada, the EU, and the International Medical Device Regulators Forum (IMDRF) should be used to inform the Australian approach to this issue. We have referenced several guidance documents in our responses above.

Below, please find additional feedback regarding specific sections of the Consultation:

		Proposed Change	Specific Comment/Rationale
1	Page 14	General comment regarding "Predictive Analysis."	We believe a variety of software functions could be described as providing "Predictive Analysis," and some may fit the definition of "medical device." As such, we recommend it be clarified that predictive analysis software that meets the CDS criteria outlined on page 16 of the Consultation is excluded from regulation by TGA. Please see our further comments regarding this topic in our response to question #2.
2	Page 15	General comment regarding "monitors a condition."	The terms "mild and self-limiting" as used pose some challenge with discerning which diseases would be exempt. Vision/vision loss would be such an example that falls in a grey area with use of this term and stakeholders are characterizing differently in other markers. We recommend TGA clarify these terms if they are used in future exclusion/exemption principles.
3		Please add the following section to a future version of a TGA software qualification guidance document: "Some standalone software may break down into a significant number of applications for the user where each of these applications is correlated with a module. Some of these modules have a medical purpose, some not. Such software may be intended to cover many needs, e.g.: - Collect and maintain administrative patient details; - Keep on file the medical history of the patient; - Invoicing and other accounting functions; - Provide a link to the social security system for reimbursement;	In support of global convergence, we propose that the recommended text be included in a future version of a software qualification guidance document to ensure the understanding that, for software products with multiple functions, only those functions with medical device functionality will be regulated by TGA. This approach is consistent with approaches utilized by the US FDA (as described in the 21st Century Cures Act legislation and the supporting FDA draft guidance *Multiple Function Device Products: Policy and Considerations*), Health Canada (as described in its *Software as a Medical Device (SaMD): Definition and Classification* guidance document), and the EU (as described in MDCG 2019-11, *Guidance on Qualification and Classification of Software in*

		Proposed Change	Specific Comment/Rationale
		- Provide a link to drug prescription systems (with possible link to drug dispensing outlets); - Provide expert system assistance for medical decision making (e.g. radiotherapy dose planner). This raises the issue as to whether the whole product must be qualified as a medical device when not all applications have a medical purpose. Computer programs used in healthcare mostly have applications which consist of both medical device and non-medical device modules. The modules which are subject to the Australian Therapeutic Goods Regulation for Medical Devices must comply with the requirements of this Regulation. The non-medical device modules are not subject to the TGA medical device Regulation. It is the obligation of the developer to identify the boundaries and the interfaces of the different modules. The boundaries of the modules which are subject to the TGA medical device Regulation should be clearly identified by the manufacturer and based on the intended use. If the modules which are subject to the TGA medical device Regulation are intended for use in combination with other modules of the whole software structure, other devices or equipment, the whole combination, including the connection system, must be safe and must not impair the specified performances of the modules which are subject to the Regulation."	*Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR*).