KEY NOTE PRESENTATION AT SWISSMEDIC 10TH ANNIVERSARY SYMPOSIUM "THE CHALLENGES OF REGULATION AND CHANGING REGULATION PARADIGMS"

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Your Excellency, Federal Councillor Alain Berset
Ms Christine Beerli, Chairwoman, Swissmedic Council
Mr Juerg Schnetzer, Executive Director, Swissmedic
Distinguished friends and colleagues

Thank you for the privilege to share some thoughts with you this morning on the changes and challenges that we face as health product regulatory authorities. It gives me great pleasure to be here with my colleagues to celebrate Swissmedic's 10th anniversary. On behalf of the Health Sciences Authority of Singapore, I would like to extend our heartiest congratulations on this milestone anniversary. We look forward to continuing collaboration and strengthening our valuable ties with Swissmedic in the years to come.

2. Ties between HSA and Swissmedic are strong, and we work particularly closely in the Consortium that comprises our two agencies, together with Health Canada and Australia's TGA. This partnership is grounded on the similar values and regulatory philosophies shared by the consortium partners. We have advanced in key collaborations over the past few years:

- A standardised approach to Benefit-Risk assessment of medicines is being developed to facilitate joint reviews;
- HSA and Swissmedic have completed a parallel review involving a New Drug Application and one Minor Change Application. Our reviewers have been enriched through learning about one another's perspectives, and we look forward to more such collaborations;
- We have started work sharing initiatives for new and generic drug reviews through sharing of assessment reports, and are working towards joint reviews; and

- We continue to promote staff attachments between our agencies.

Changing Landscape

3. From that context, let me now share some perspectives on the changing global landscape in health products regulation, and Singapore's approaches to address the associated regulatory challenges.

4. Since the turn of the century, the world has become increasingly connected. Information flows easily through the Internet and social media platforms. Drug and device regulators are facing a landscape that is dynamically changing in response to globalization, technological advancements, rising stakeholder expectations, and greater resource and expertise demands. However, our mission as regulators remains unchanged – we must still continue to ensure that health products available to our populations are safe, efficacious and of good quality.

5. The global supply chain has become more complex. Products are rarely fully manufactured in a single country. Regulators face challenges in regulating diverse distribution channels. These include the Internet, which facilitates direct purchase by consumers of products of uncertain origin and quality, and which can be detrimental to health or deadly.

6. Innovative drugs and new medical technologies are blurring the lines between product categories, and between products and professional practice, thus challenging our traditional regulatory frameworks. Although there are initiatives to harmonize technical and regulatory requirements within and across regions, completeness of implementation continues to be a challenge due to differing national and legal requirements. But with such a global economy, increasing regulatory interdependence is inevitable, necessary and something to be pursued.

7. The industry expects regulatory certainty, shortened time-to-market and no unnecessary barriers. Healthcare professionals expect quicker access to new and innovative therapies. And patients and the public look for faster access, prompt

responses, and better regulatory transparency and efficiency. This requires coordination amongst government entities since increasingly interconnected issues mean that single agencies cannot fully address them in isolation. In Singapore, we have a “no wrong door” public sector policy. This requires the agency that receives initial feedback or inputs to follow up and co-ordinate an integrated response from other agencies involved - even if the issue is not necessarily the main responsibility of the first contact point.

8. To meet the more complex scope of regulated products, we need to ensure that our regulatory expertise is equally cutting edge. Various initiatives are aimed at lowering market entry barriers with greater emphasis on post-market measures. This requires redesign of processes, and re-alignment of resources and expertise. Engaging stakeholders in policymaking can make for more robust policies with greater ownership of solutions. Here, international collaboration amongst national regulators is vital to “co-create” solutions to the new challenges we face.

Singapore’s Perspective

9. Let me now share some Singapore perspectives. HSA’s unwavering focus is on ensuring quality, safety and efficacy of health products, and protecting public health. At the same time, we recognise that no health product can be guaranteed as 100% safe. Singapore’s population is about 5 million, and HSA has about 900 staff, one third of whom are involved in product regulation. In spite of our relative smallness, we must always apply international best practices and good science in regulation. To address our regulatory challenges, we apply four key approaches and principles:

- Calibration of risk controls;
- Leveraging on reference agencies;
- Harnessing the power of technology; and
- Exploring new paradigms in regulation.

(A) Calibrating Risk Controls

10. Let me start with calibration of risk controls. Drugs and devices encompass a wide range of low to high risk products. We need to maintain a balance that does not result in over or under-regulation. As we all know, the regulatory pendulum may swing to either extreme, influenced by factors such as high profile adverse events and industry lobbying. We always need to find a mid-range of sound and rational regulation that ensures health products are safe, efficacious and of good quality; are accessible through appropriate channels that ensure proper use; are subject to robust post-marketing vigilance and enforcement; and are supported by accurate and truthful information.

11. We calibrate risk according to various factors. In relation to Premises and Players, there are differing knowledge levels and operational standards. Manufacturers and dealers of different product categories have varying levels of competence. We also need to consider the realities of prevailing business practices and the supply chain. All these determine the mix of regulatory tools, communication and costing strategies, and resourcing.

12. Users and Consumers are end recipients. High risk products like biologicals, cell & tissue therapy and high risk medical devices should not have direct access by patients who are not in a position to make fully informed risk decisions. Here, physicians and pharmacists function as gatekeepers, and the framework needs to recognize and interact with them to define appropriate regulation. But a lighter pre-market touch can be applied for low risk products. Here, a caveat emptor approach can be used, taking into account risk thresholds and appetites that will change over time.

13. While many factors influence our regulatory approach, product risk remains a fundamental factor. The principles are not new but we have tried to crystallize them in a way that can be more clearly shared internally and externally with stakeholders. We aim to maintain a twin focus on the intrinsic and extrinsic risks of products. Intrinsic risks are inherent to products based on declared composition and intended use. They are related to factors such as ingredients and mode of administration. A product's intrinsic risk is assessed based on disclosures by product owners or on

current scientific knowledge. However, at the point of product approval, there may be still unknown intrinsic risks, and we must put in place plans and measures to manage these uncertainties.

14. Extrinsic risks are not attributable to the declared composition or intended use. Such risks are usually unknown but may be predicted from trends or past experience, and include adulteration, contamination and unsubstantiated therapeutic claims.

15. In determining the appropriate regulatory approach, intrinsic risks are mostly managed by pre-market controls through requirements imposed during product evaluation or post-approval conditions. Extrinsic risks are primarily managed through post-market measures such as post-approval surveillance, audit, vigilance and enforcement.

16. To further clarify our product risk stratification, this is a matrix representation of how we classify different product categories according to intrinsic and extrinsic risk. This helps us to better target pre- and post-market measures. However, there are other considerations that are not included here, such as maturity of the industry, competency of players, and knowledge levels of patients and consumers.

17. The most rigorous pre-market requirements are naturally focused on products with the highest intrinsic risk, namely drugs and cell & tissue therapy. These are subject to the strictest evaluation and licensing requirements. A high risk product registry exists for products identified to be in this risk category. Conversely, low risk cosmetic products only require online notification with immediate clearance and no licensing.

18. Over time, complementary health products have proven to be of higher extrinsic risk of being adulterated and marketed with unsubstantiated therapeutic claims. More proactive post-market activities are therefore targeted at this group, especially on the highest risk sub-group of lifestyle products related to slimming or sexual performance.

19. We have also applied a similar regulatory approach for medical devices that came under full regulatory control at the beginning of this year. This followed phasing in of measures over five years. The intrinsic risks of medical devices result from an interplay of factors that include duration of device contact with the body, degree of invasiveness, and local or systemic effects.

20. Medical devices are categorized from highest risk Class D to the lowest risk Class A devices. More vigorous pre-market requirements are imposed on Class C and D devices, while non-sterile Class A devices of lowest risk are exempt from product registration. We continue to monitor extrinsic risk factors to build up more experience to further rationalize our post-market measures.

(B) Leveraging on Reference Agencies

21. The following illustrate Singapore's regulatory approach to using referencing or benchmark information in order to optimise pre-market processes.

22. For new drugs, three routes are available to companies:

- The full evaluation route introduced in 1998 is a full dossier route for innovative products that have not been approved elsewhere at the point of submission. This route requires submission of the full quality, non-clinical & clinical dataset.
- The abridged evaluation route introduced in 1987 leverages on approval by another competent agency. This confidence-based approach focuses on full quality and clinical evaluation and abridge evaluation of non-clinical and early phase studies.
- The verification route introduced in 2003 is the fastest route. It is also a confidence-based approach but for products that have been approved by at least two of HSA's reference agencies. The same dataset as the abridged route is required with the additional requirement for an

unredacted assessment report from the reference agency. Evaluation focuses on the assessments done by the reference agencies.

23. Full and abridged evaluation routes also exist for medical devices. From this month onwards, we further enhanced the registration process for lower risk Class B medical devices. Depending on prior independent approvals from reference agencies and the safety history, Class B devices may qualify for expedited or immediate registration in Singapore.

(C) Harnessing the Power of Technology

24. The third approach we use focuses on IT systems. In Singapore, our Adverse Event (AE) reporting channels have developed over the years to increasing reliance on IT generated reports. We have been receiving AE reports directly from electronic databases in our healthcare institutions for the past 5 years. According to WHO's Uppsala Monitoring Centre, Singapore has taken the world lead in terms of number of valid reports per million inhabitants submitted to the WHO global database. The quality of reports received can be further improved. Nonetheless, the completeness of our electronic AE reports is very useful for detecting clusters of AEs which can provide insights for batch-related issues, AEs following introduction of new products, as well as changes in AE trends from products under close surveillance. Although the number of reports in the local database is small compared to that of larger regulatory agencies, we are looking into mining the data for potential safety signals that reflect uncertainty in intrinsic risk, and to some extent extrinsic risks like product adulteration. There have also been many cases of adulterated complementary health products detected through reported AEs.

25. Singapore's Ministry of Health is also looking into online notification of infectious diseases from family physicians and community hospitals. HSA is leveraging on these new IT projects to boost AE reporting rates from these additional sources. Electronic health records are a rich source of drug-safety signals that can be further exploited, and we see harnessing IT infrastructure and data mining as an important tool to further strengthen detection of drug safety signals.

(D) Exploring New Paradigms

26. Finally, let me touch on new paradigms. Together with our colleagues in the US FDA, EMA and the Health Canada, as well as industry representatives, HSA is partnering with MIT's Centre for Biomedical Innovation in the NEWDIGS project. This is an initiative intended to catalyze innovations in the pharmaceutical drug development paradigm. One key aspect of NEWDIGS activities is focused on 'adaptive licensing' (AL) approaches, based on the recognition that the knowledge of drugs is not binary but evolves with time.

27. In adaptive licensing, licensing decisions are based on proactively planned, step-wise evidence development and learning about the risks and benefits of products throughout their life cycles. After initial conditional authorisation, regulators systematically reassess the benefits and risks of drugs, based on efficacy and safety data obtained under real world conditions of use. Early use is limited to patients most likely to derive the greatest benefit. The patient population can be expanded, contracted, or modified based on new data.

28. As eloquently described by expert colleagues such as Professor Hans-Georg Eichler from the EMA, the *traditional drug licensing model* involves a single "magic moment" between pre- and post-licensing, where use of a drug is tightly controlled in the narrowly defined pre-licensing population. But then this is almost totally relaxed for use in the real-world post-licensing population. In *Adaptive Licensing*, this artificial dichotomy of pre- and post-licensing phases ("magic moment") is replaced by graded, more tightly managed, but more timely market entry of products. Adaptive licensing therefore seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with securing long-term, real world information on benefit and harm. This allows better and more informed patient care decisions to be made.

29. I see AL as an important measure to augment the current system, especially in an environment of high drug development costs and insufficient effective products to meet unmet medical needs. The potential benefits of AL include:

- Reduced development cost and time-to-market;
- Improved knowledge about the risks and benefits of new products in real world settings; and
- Dissemination of learning through publications, conferences, and educational programs targeting scientific and business leaders in the healthcare industry.

30. From Singapore's perspective, we see AL playing a role in situations where new drugs could benefit patients with unmet needs in Singapore, especially in the area of chronic diseases. We are still looking for a pilot product relevant to our demographic profile, and are being very judicious in identifying products we could allow under AL. Clearly, these should not be very high risk products.

31. We do need to address concerns about reduced efficacy and safety evidence. There still needs to be sufficient information about the product at point of initial conditional authorisation. The fundamental conditions of safety, efficacy and quality should still be met but with greater flexibility in licensing and timing of entry, coupled with more focused monitoring.

32. This approach also requires adequate education of patients to ensure clear informed consent and understanding of the risk-benefit ratio in using these products. We are still looking into clarifying the optimal models for doing this.

33. As post-market monitoring is an important element of adaptive licensing, it is important to have robust post-market tools in place to allow close tracking of product use after initial conditional authorisation. In this respect, our small population size and the presence of strong health IT systems is an advantage. On the other hand, our small population size also means it is important for Singapore to partner other regulators in pilot projects. This ensures sufficient patient numbers for meaningful

post-market data on risk and benefit.

Conclusion

34. I have just briefly covered these four key approaches that Singapore applies in responding to the regulatory challenges we all face. As we move into the future, regulation will continue to evolve as new unknown risks emerge and as new health products are introduced. Our regulatory frameworks will always have to adapt to new requirements and paradigms to ensure timely mitigation of risks in order to safeguard public health in our populations.

35. I firmly believe that regulatory collaboration is the way to go in the years ahead. Continual clarification of product risks will help advance global regulatory convergence. The formation and strengthening of strategic partnerships through harmonization initiatives, and with training organizations and other key players will promote complementary actions. Such partnerships will help to marshal and focus collective resources in a more effective, coordinated and sustainable manner. In this way, we will all be able to function as more effective regulators not only within our jurisdictions, but also collaborating to protect and advance the public health of the international community.

36. On that note, may I once again congratulate Swissmedic on your 10th Anniversary, and extend my very best wishes for many more exciting and inspiring years ahead. Thank you.

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