

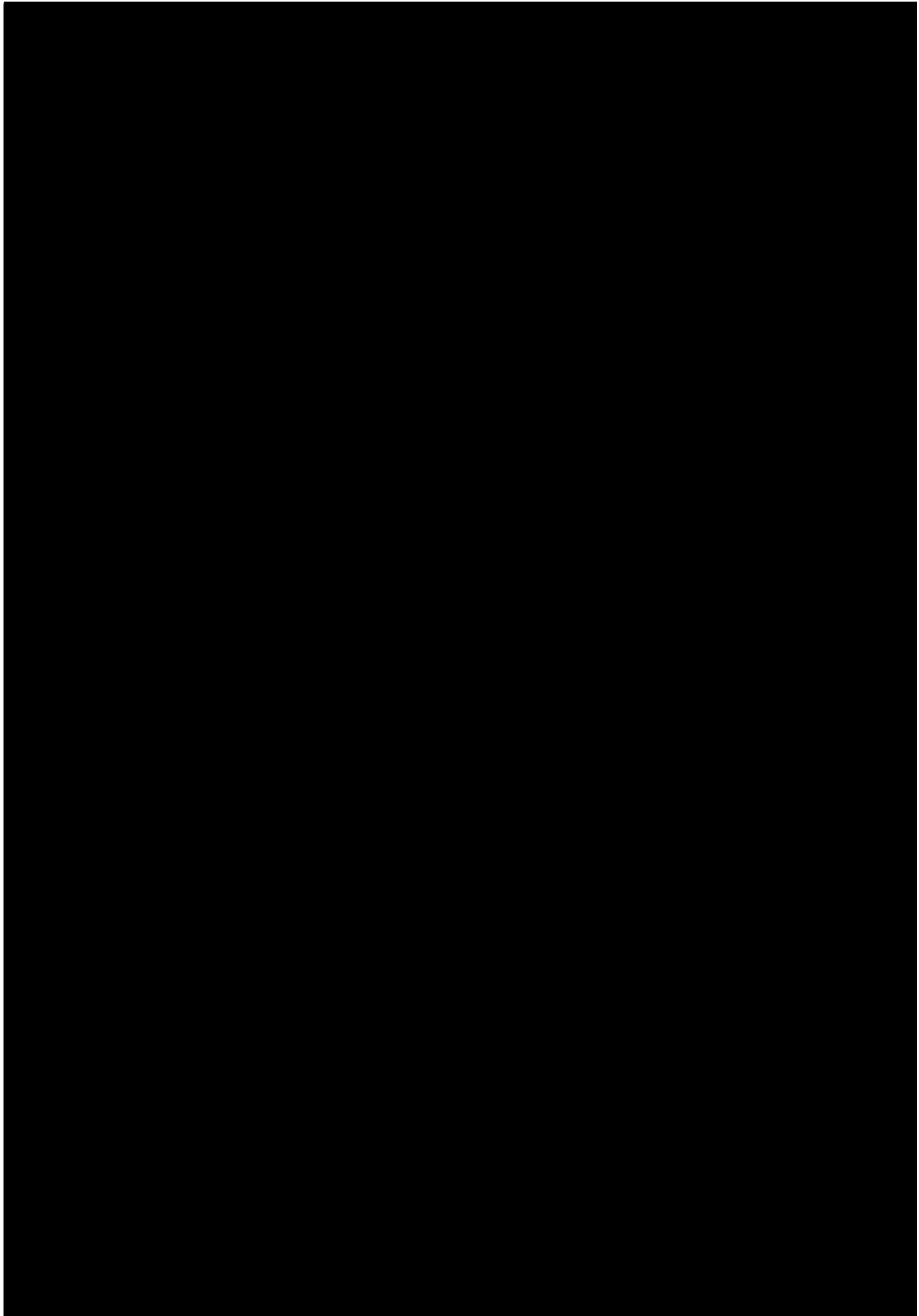


Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

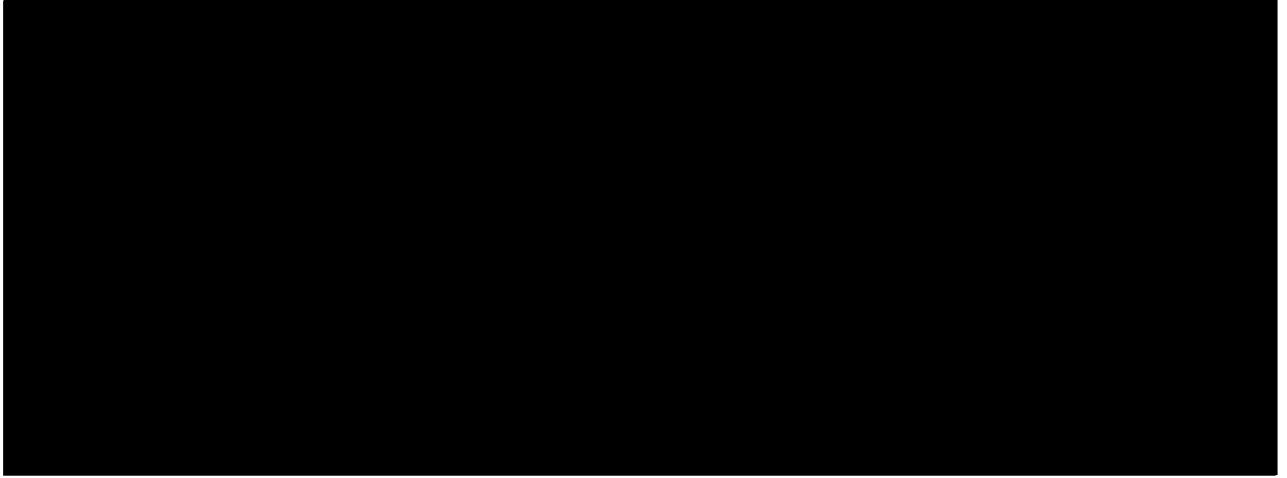
**Advisory Committee
on the
Safety of Medicines**

**Minutes of the
8th Meeting
15 July 2011**

ParkRoyal Hotel – Melbourne Airport







TGA staff in attendance:

Ms Elspeth Kay

Secretary

Dr Megan Keaney

Principal Medical Advisor

Dr Jane Cook

Head (A/g), Office of Product Review

Dr Nick Simpson

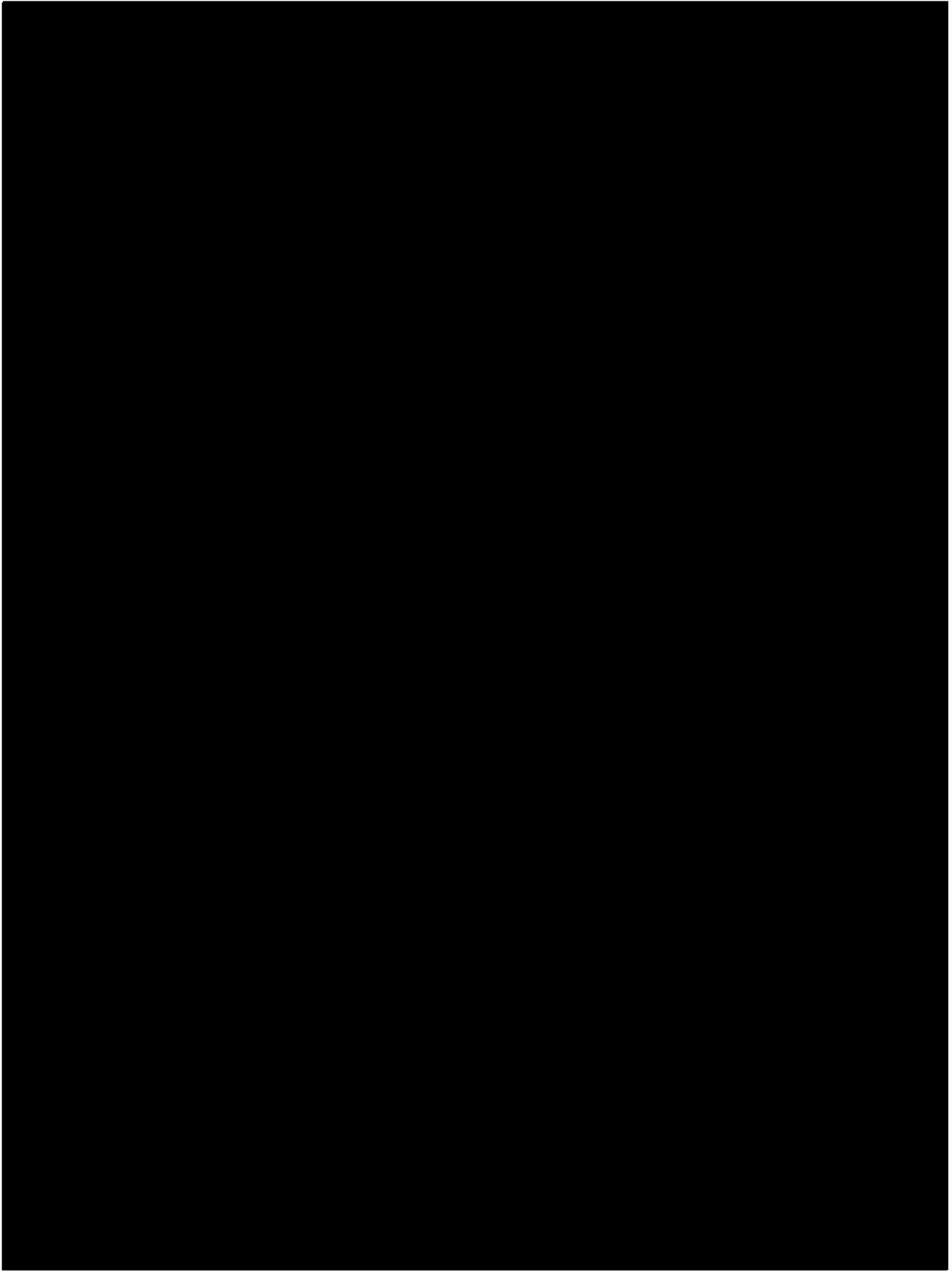
Medical Officer, Office of Product Review

Dr Luigino Apollonio

Minute Secretary, Committee Support Unit

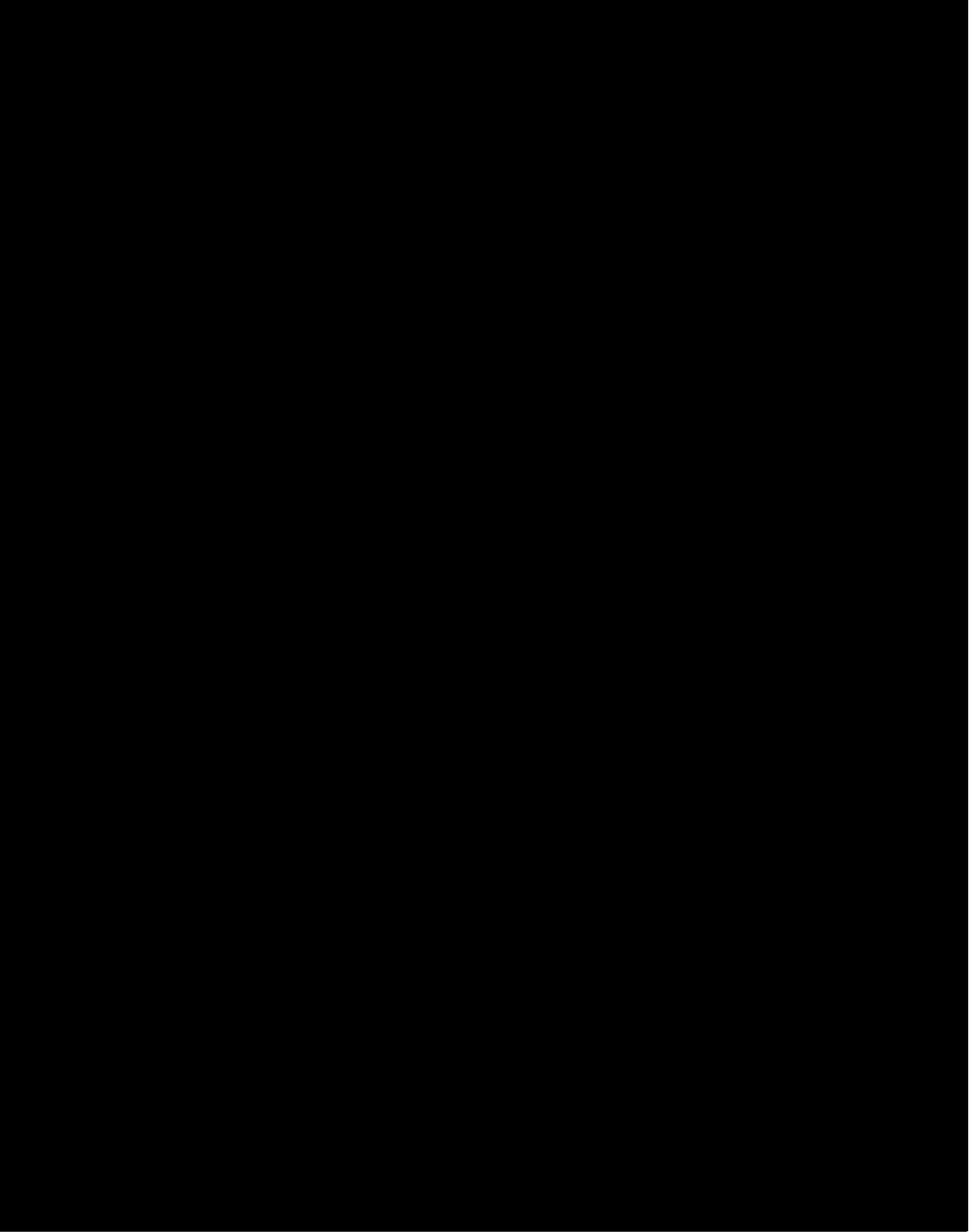
Ms Heather Lane

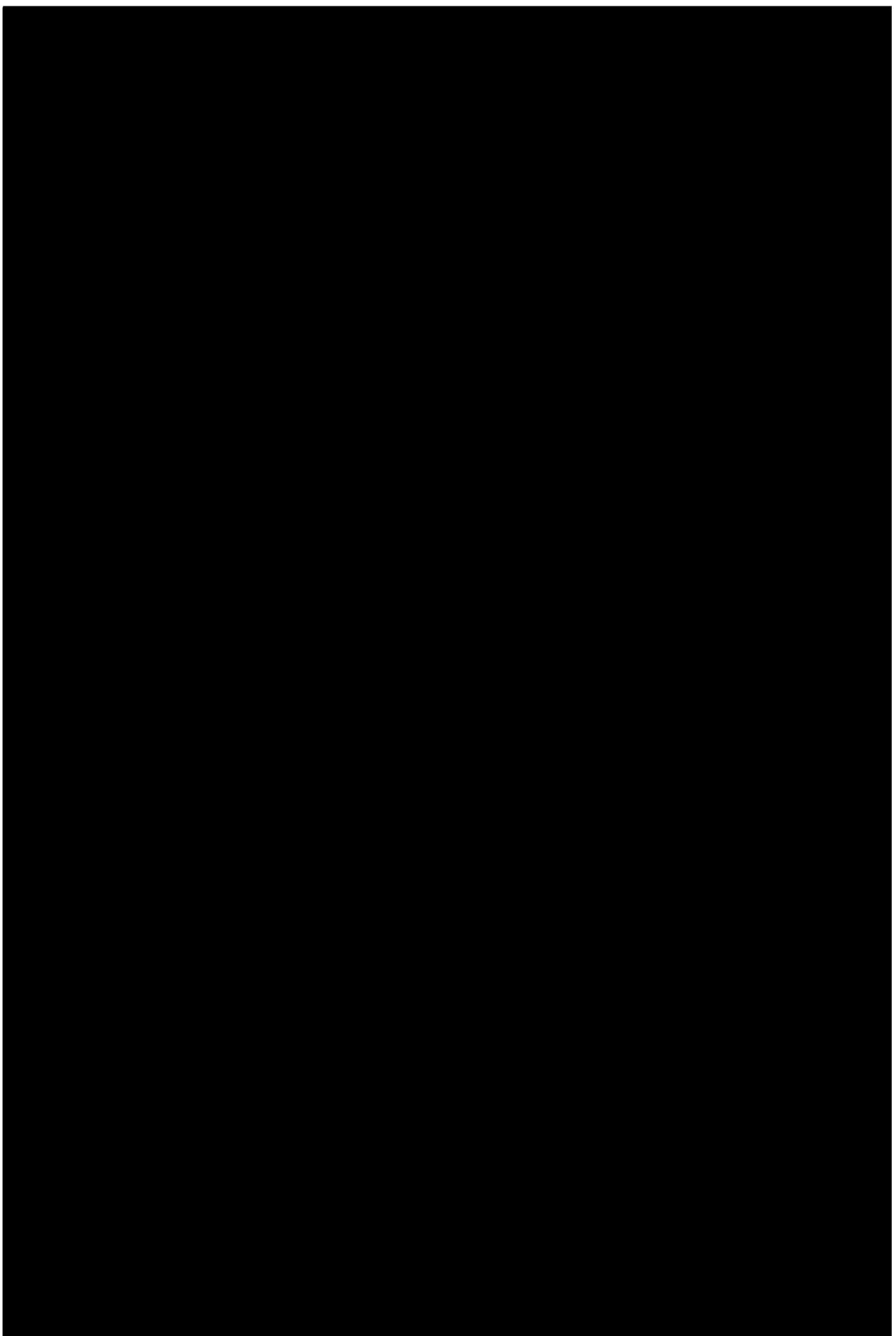
Minute Secretary, Committee Support Unit

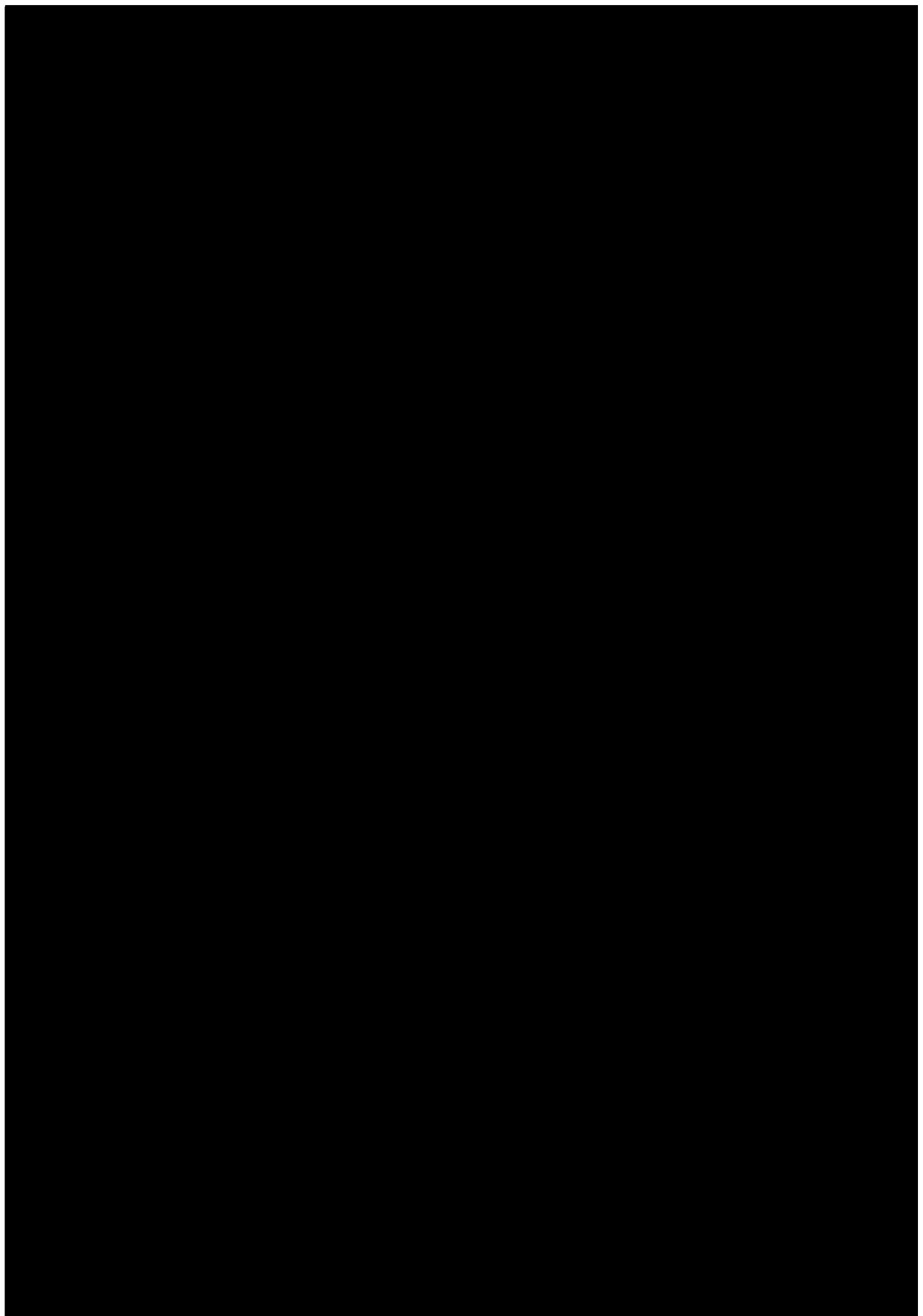


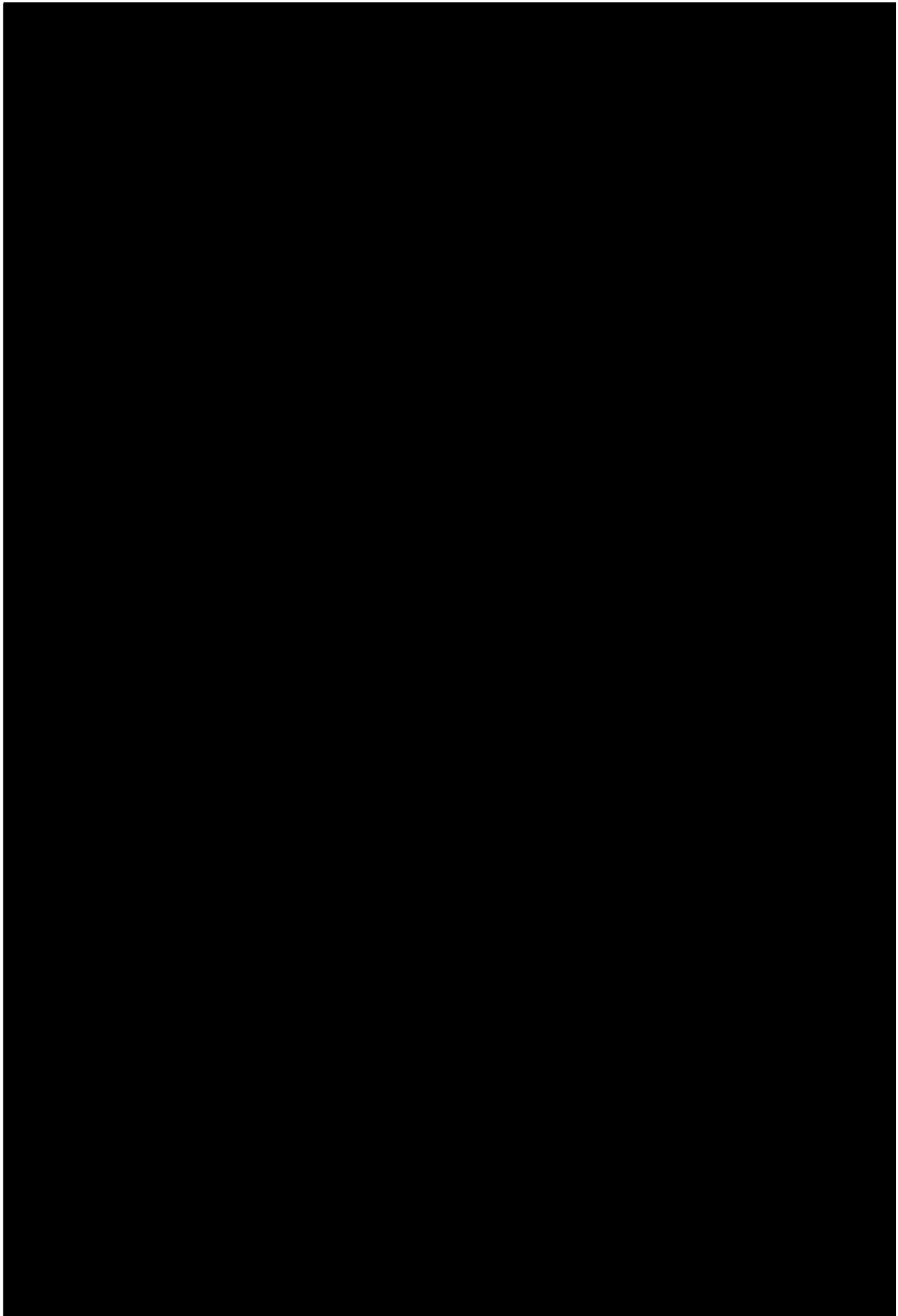
- Meeting 1, 5 March 2010, Item 6.3: *The report from the Psychiatric Drug Safety Expert Advisory Panel is to be discussed at a future meeting.*

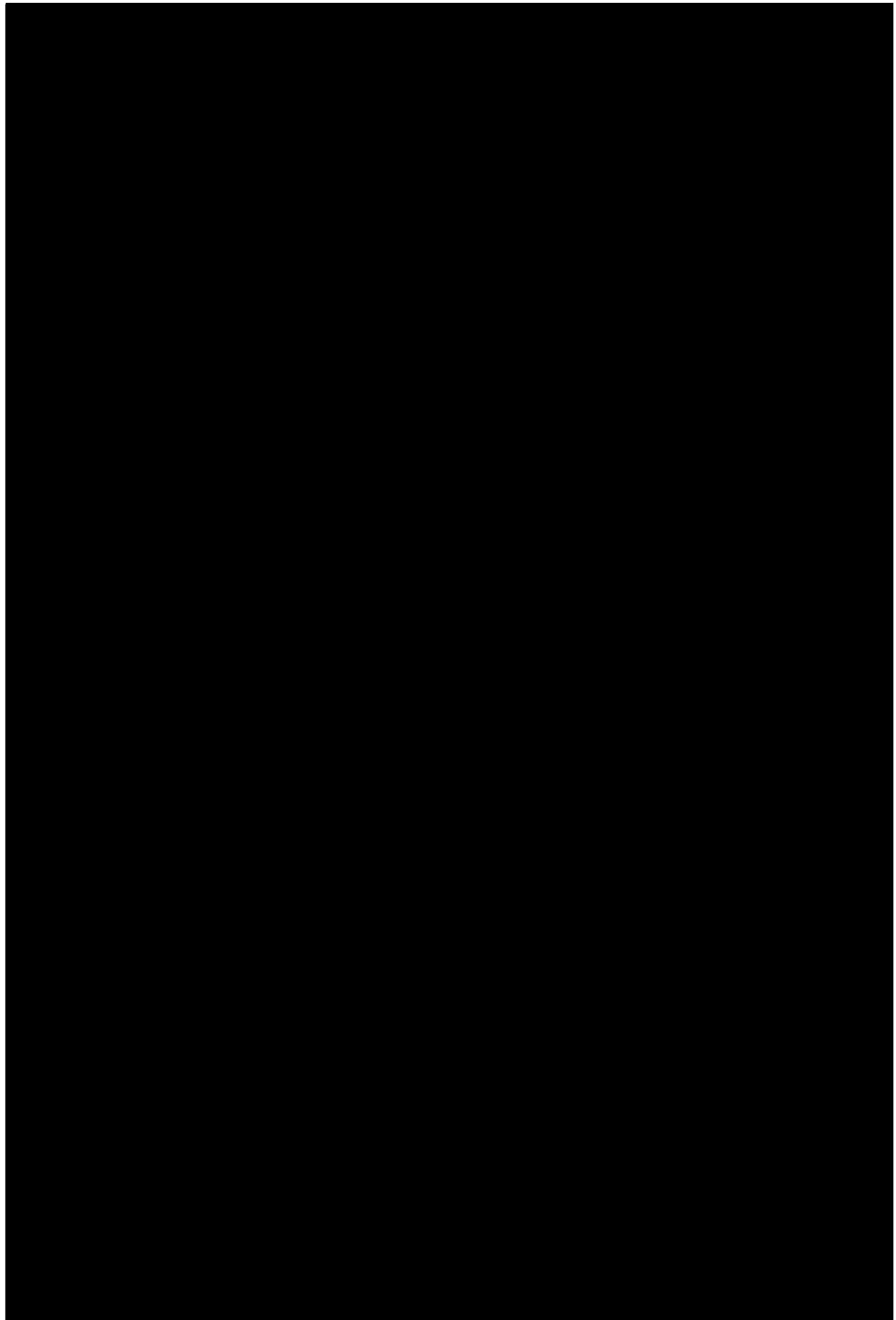
The committee was advised that OPR staff were scheduled to meet in the near future with the director of the relevant clinical evaluation unit in the Office of Medicines Authorisation to discuss actions already taken in response to the report, and identify any outstanding actions required. The committee would be advised of the outcome of these discussions.

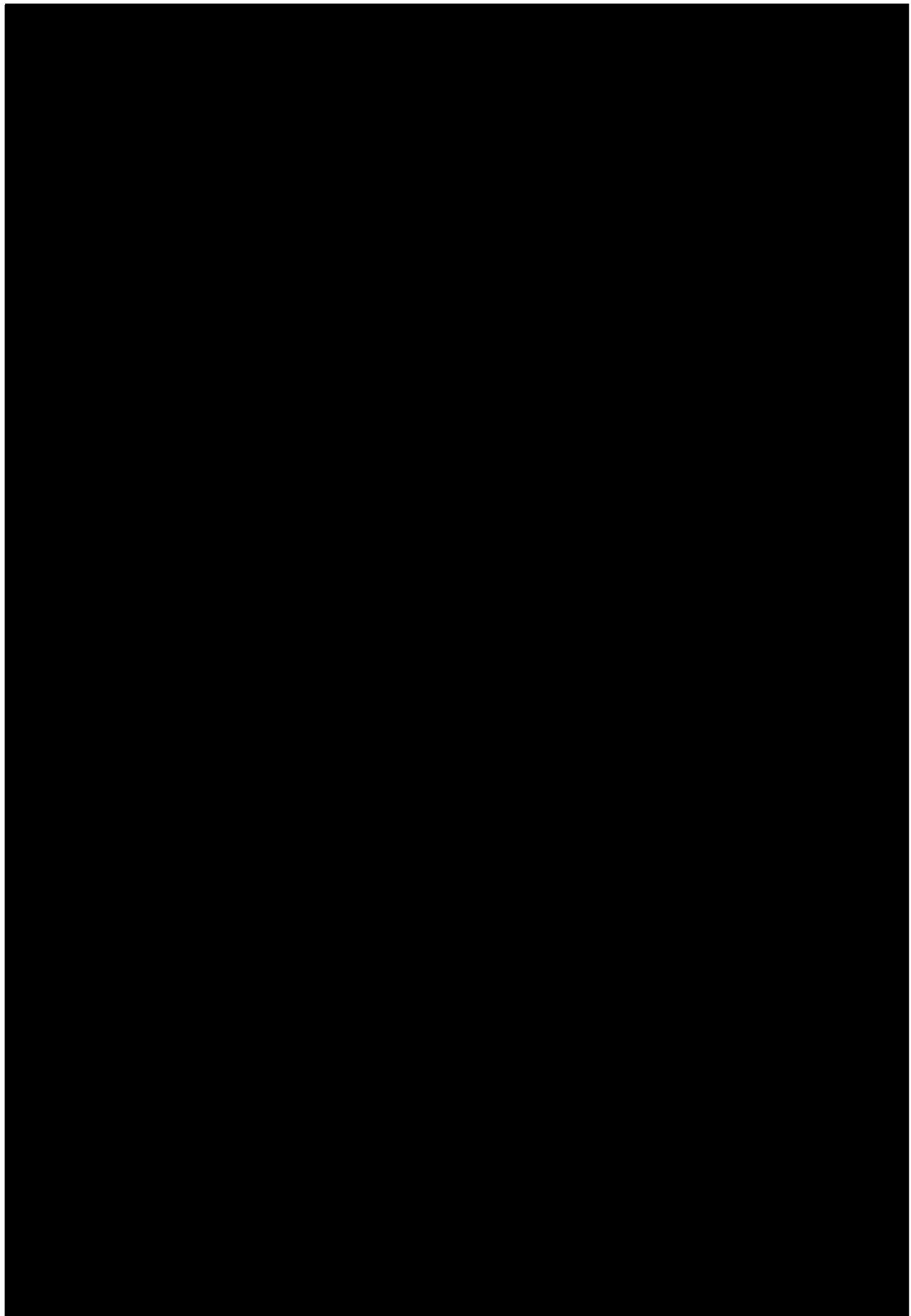


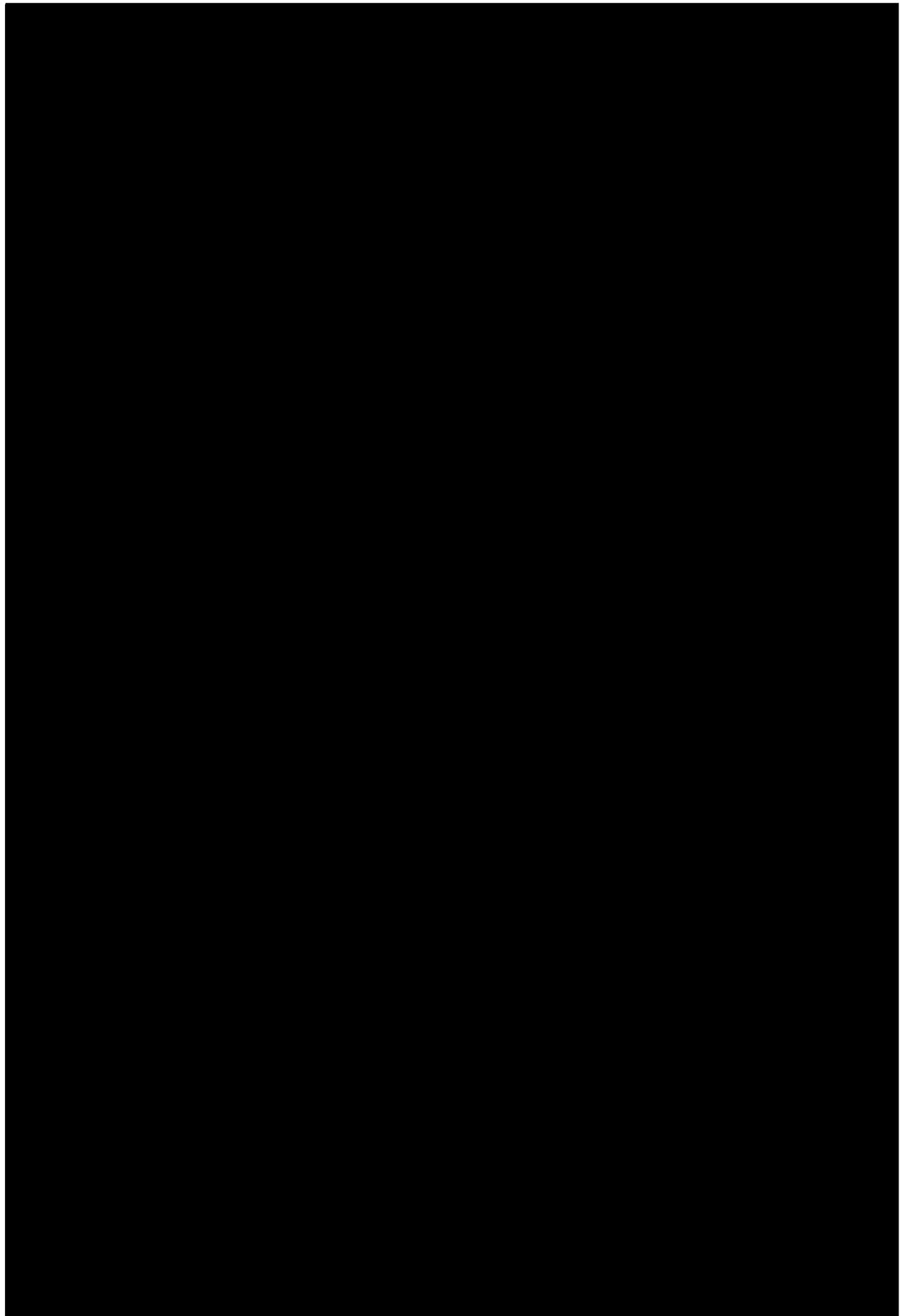


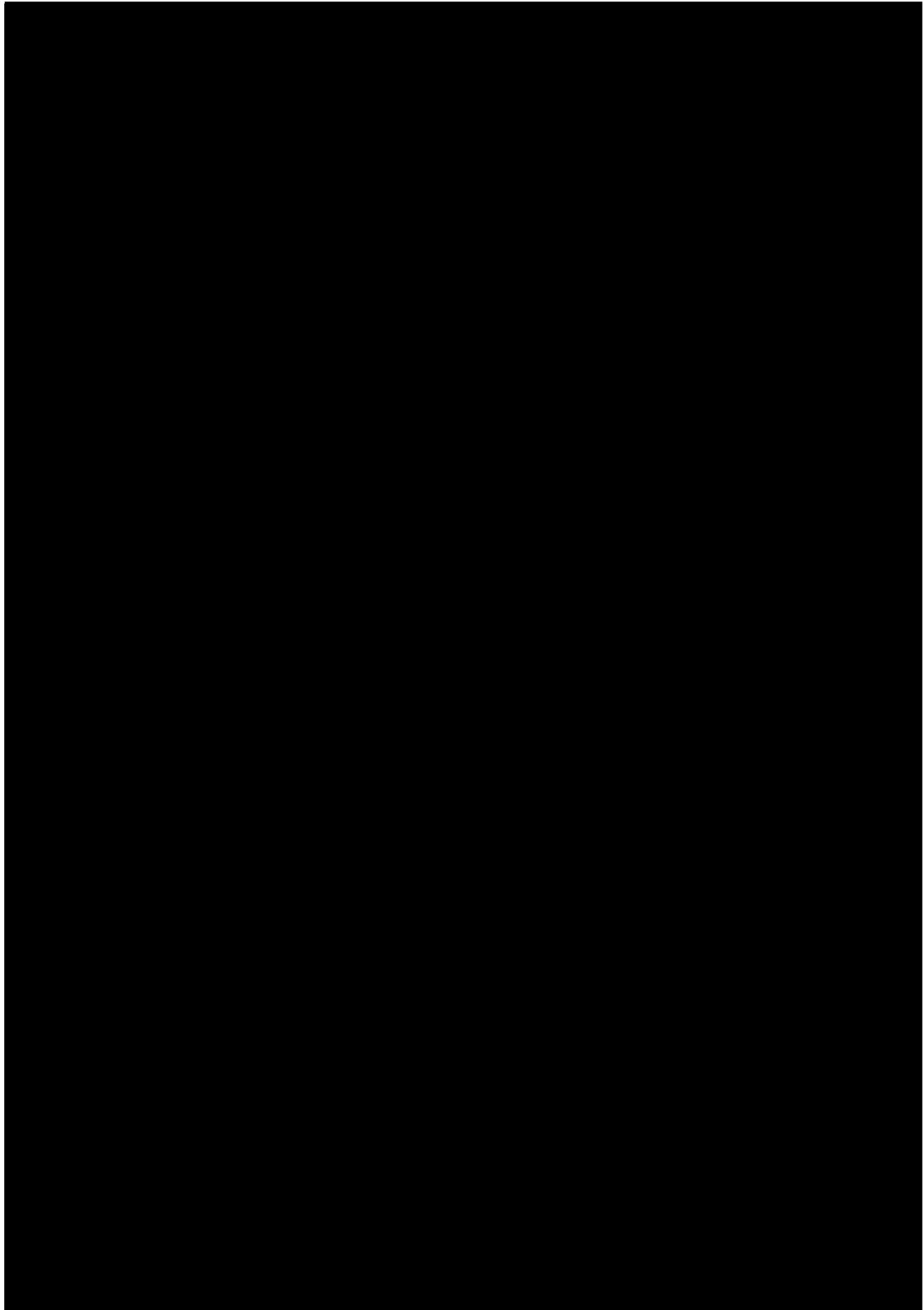


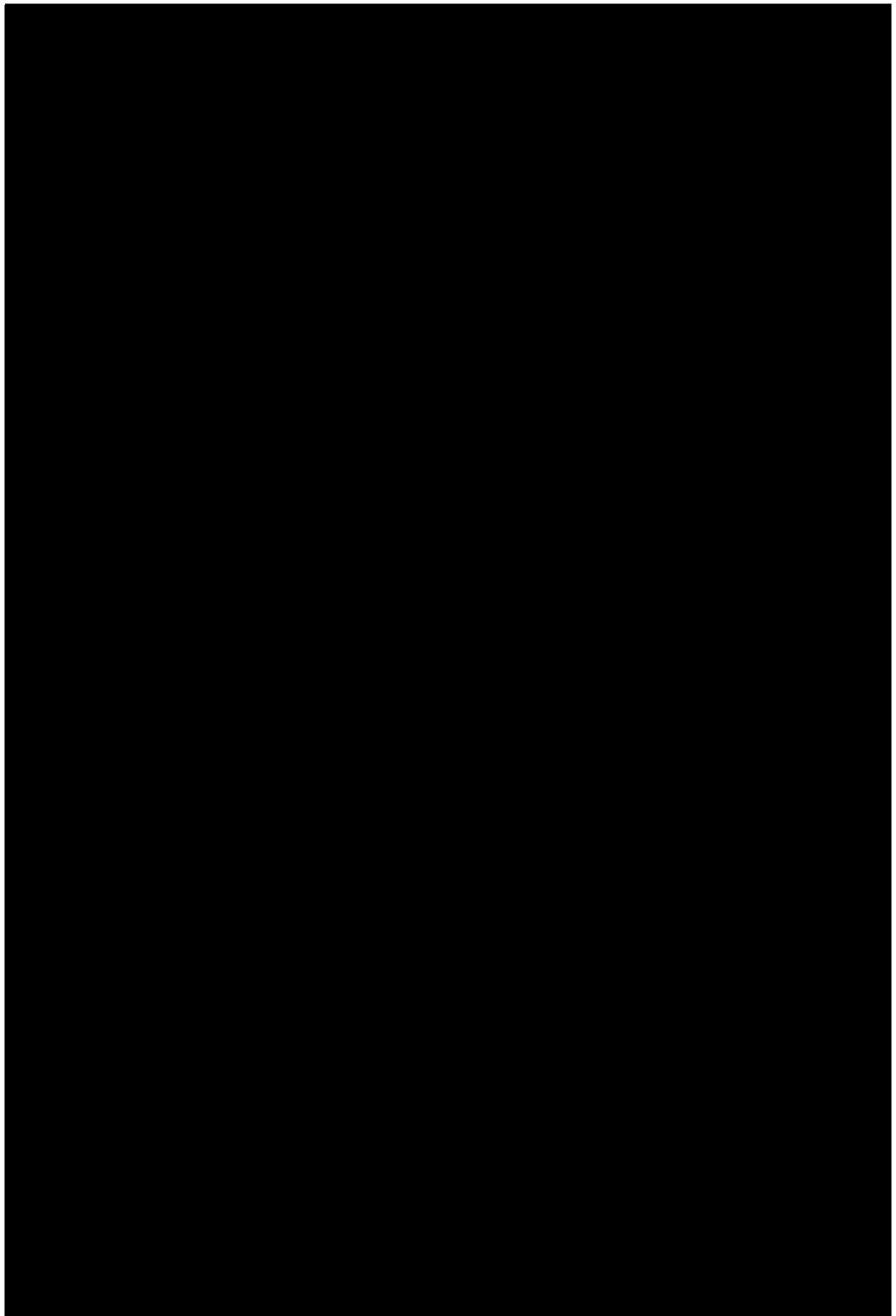


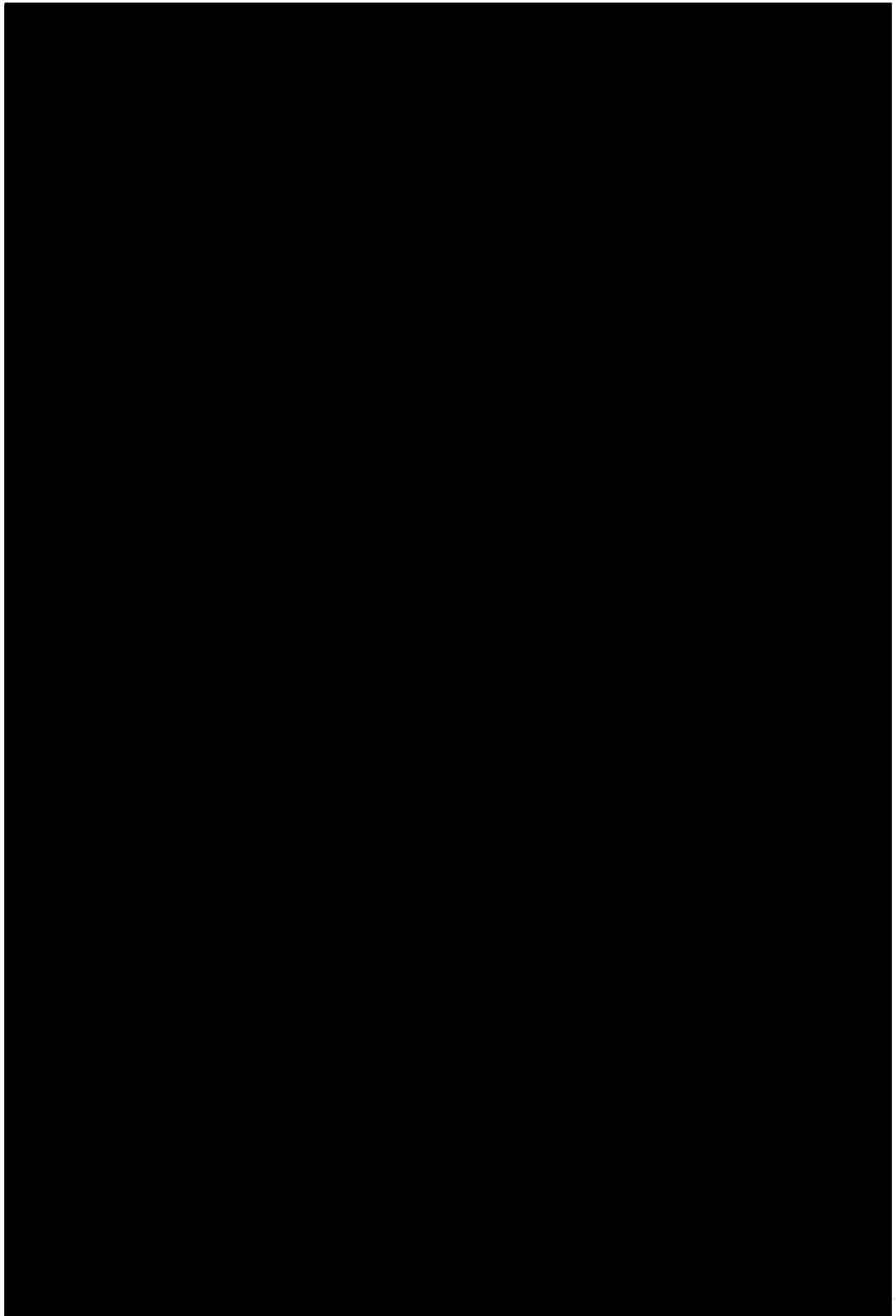


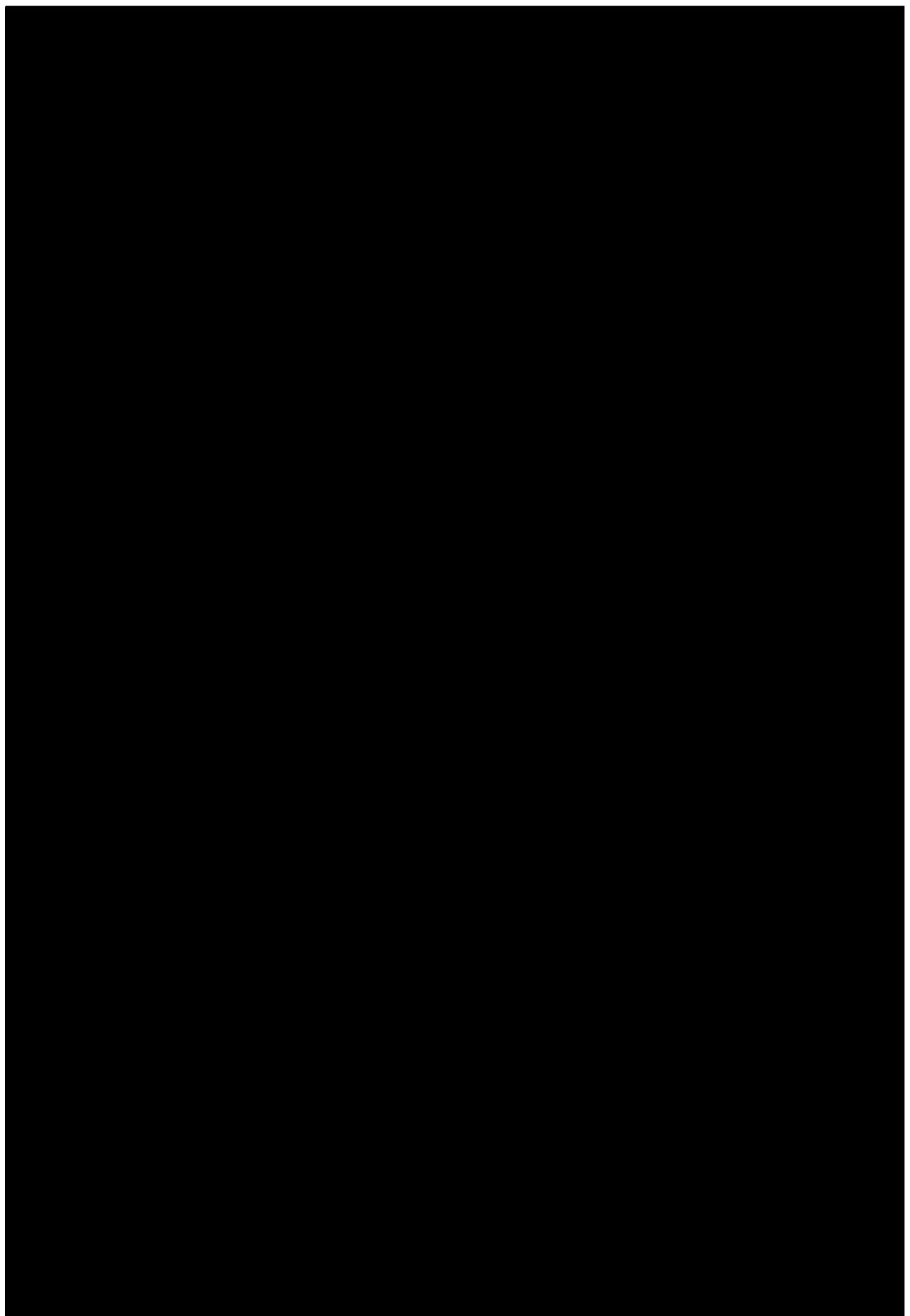












greater effect on the bioavailability of oral midazolam, as midazolam had relatively low oral bioavailability, but the bioavailability of the parenteral form was already maximal.

Members noted the evaluator's concern about the finding of study P05880 that the ethinyloestradiol AUC was decreased by 24%. They noted that there was no obvious mechanism by which boceprevir would affect the pharmacokinetics of ethinyloestradiol, so this was likely to be an effect of Pegatron. A reduction in AUC of 24% appeared unlikely to affect the contraceptive efficacy of standard combined oral contraceptives containing ethinyloestradiol, although it might affect the efficacy of low-dose combined oral contraceptives containing ethinyloestradiol at 20 micrograms.

Question 3: Are the proposed guidelines for the use of erythropoietin outlined in the 'Guidelines for the management of anaemia' (page 129 of RMP) appropriate for the Australian clinical setting? If not, then what modifications would be appropriate (eg modifications to the regimen, or reference to other clinical guidelines)?

The committee agreed that it seemed reasonable to recommend adopting the same approach to using erythropoietin as was used on the clinical trials of boceprevir, and that this approach appeared to be consistent with international guidance promoted in Australia (such as the European Association for the Study of the Liver clinical practice guidelines). However, it questioned whether it would be possible to include this recommendation in the PI for boceprevir given that it was not an approved use of erythropoietin.

Additional Comments

The committee agreed that the advice for the management of overdose should be updated to reflect current practice, including reference to contacting the Poisons Centre.

The committee shared the concern of the OPR evaluator in the boceprevir is used with two other drugs, peginterferon alfa and ribavirin, but the combination is not addressed in the RMP.

Furthermore, the committee believed that education programs designed for quality use of boceprevir should encompass risks associated with peginterferon alfa and ribavirin.

Item 5 Vaccines

5.1 Update on vaccine safety activity

TGA Principal Medical Advisor Dr Megan Keaney advised the committee on the following issues relating to vaccine safety.

The Horvath Review

The Review of the Management of Adverse Events associated with Panvax and Fluvax (the Horvath Review) had been publicly released. Its recommendations included that options be considered to improve the system of governance of vaccine safety monitoring. A Governance Committee was scheduled to meet for the first time in August, and would consider options for establishing a vaccine safety committee. The TGA's preferred position was that a statutory vaccine safety committee be established, rather than a subcommittee of ACSOM. The TGA would await the recommendations of this committee before beginning to establish a committee.

CSL audit

The FDA provided a letter to CSL Biotherapies Ltd outlining the findings of their audit of CSL's Quality Management Systems (QMS). The TGA had also conducted an audit, and both the TGA

and FDA were not satisfied with some of the QMS elements in place. A joint TGA and FDA media publication was posted on the TGA website discussing CSL's investigation processes into post-manufacturing deviations and adverse events. TGA was in consultation with CSL to resolve the issues outlined in the audits.

Adverse reactions to seasonal influenza vaccine

OPR advised that they continued to monitor reports of adverse drug reactions for seasonal vaccines and had provided a report to the National Immunisation Committee (NIC). There had been reports of adverse events, however, none of these were unusual cases. The reports showed a significant number of injection site reactions, fever and malaise with the use of Fluvax.

Pneumovax 23

The TGA updated the committee on issues relating to Pneumovax 23. The published advice recommending against revaccination was to remain in place. The issue was scheduled to be reviewed by Australian Technical Advisory Group on Immunisation (ATAGI) at its June 2011 meeting. Subsequently, advice from ATAGI would be used to provide guidance for populations needing a second dose of Pneumovax 23. It was anticipated that the advice will likely contain text modifications regarding patient groups that will need revaccination (immunocompromised) to align it more closely with the PI.

A member queried if the TGA would support the implementation of a life-long vaccine register. TGA indicated that it would be supportive were a program implemented; however, this type of program was outside the scope of TGA functions.

A member queried how the TGA monitored the distribution and utilisation of vaccines. The TGA advised that it could obtain information about distribution of vaccines at a State level but not on individual usage, apart from usage in children aged under 7 years, through the Australian Childhood Immunisation Register.

Item 6 Reports to ACSOM

6.1 Report from the Chair

The Chair advised of the upcoming conflict of interest workshop to be held on Tuesday 19 July, which would include the chairs of ACPM and PBAC. The purpose of the workshop was to support consistent and best practice management of declarations of interest by committees.

It was hoped that the workshop would develop practical examples of conflict of interest rulings; however, it was understood that some variations between committees would exist. The workshop also aimed to build an evidence-based approach to managing declarations, including taking into account how conflicts of interest can potentially influence decisions made by a committee, consumer perceptions of conflicts of interest, and TGA requirements. The Chair invited members to provide examples of scenarios for consideration at the workshop.

The Chair met with the UK Medicines and Healthcare Products Regulatory Agency (MHRA) about the establishment of an early post-market symbol scheme for prescription and non-prescription products entering the market in Europe. The model used in the UK applied a black triangle to the packaging of new products to indicate that additional monitoring was being undertaken. New European legislation included criteria linked with specific details of the RMP for the product. While the existing UK program was voluntary and aimed at health care

professionals, the intention was to mandate the use of a symbol across Europe as a communication tool for both consumers and health care professionals. The MHRA had invited Australia to provide suggestions for the design of the symbol and the Chair extended this invitation to the committee. Members noted that this issue was being considered as part of the TGA transparency review and would be discussed further at Item 7.1.

The Chair advised that she had been invited to join the Horvath review governance working group to consider options for the establishment of a vaccine safety committee.

6.2 Report from the Office of Product Review

The secretary advised the committee that the process for the appointment of new members to ACSOM was progressing. TGA planned to appoint six new members to ACSOM, including a general practitioner, biostatistician, pharmacist, psychiatrist, neurologist and nephrologist. One membership to ACSOM was left vacant for the recruitment of a cardiologist. The committee were advised that the appointment process was due to be completed in August 2011 and that the new members would hopefully attend the following meeting in September 2011. It was planned that all 15 ACSOM members would attend each meeting. The expression of interest process attracted 46 potential members of a high calibre, which also served to identify potential experts for ACSOM to seek additional advice on an ad-hoc basis in areas such as haematology and anaesthesiology.

The committee was advised that Dr Katherine Gray would be the replacement secretary of ACSOM for 12 months during Elspeth Kay's absence. The committee thanked Elspeth for her work and expressed their best wishes.

6.3 Outcomes of recent safety investigations

Outcomes of recent safety investigations were provided for information. TGA staff offered to relay any questions or comments back to the authors of each for response at the next meeting or out of session.

This report was comprised of the most recent PRR report, the OPR activity report, and copies of recent safety filters/reviews that were not referred to ACSOM for advice. In addition to the PRR and OPR activity reports, members were provided with the following:

- Safety filter of fluticasone and epistaxis
- Safety filter of TNF Inhibitors, azathioprin, mercaptopurine and hepatosplenic T cell lymphoma
- Safety filter of venlafaxine and spontaneous abortion

The committee also noted the following:

- The status of dextropropoxyphene had not changed since it was discussed at ACSOM. Additional information had been received from the sponsor that was being considered.
- An update was provided on pioglitazone and bladder cancer, including that the Dear Healthcare Provider Letter (DHCP) had been published.
- The PIs for Yaz and Yasmin (containing drospirenone) had been updated to refer to risk of venous thromboembolism (VTE) risk.
- Cladribine, as indicated for Multiple Sclerosis, had been withdrawn from the market.

6.4 Publishing of ACSOM advice

The Secretary advised that ACSOM is obliged to publish advice under the existing regulations, but had not yet done so. The Secretary informed the committee that it was likely that the TGA transparency review would include recommendations relating to publishing advice from ACSOM, however, there was no progress to report on this since the last meeting.

Item 7 General Business

7.1 ACSOM submission to the TGA Transparency Review: Requirements for implementing an early post-marketing symbol

TGA staff updated the committee on the progress of the TGA transparency review, which was being considered by the Parliamentary Secretary.

The committee discussed its submission to the transparency review regarding the introduction of an early post-marketing symbol and options for its implementation.

The TGA requested the following advice from ACSOM:

What would be required to effectively implement an 'early post-marketing symbol' risk communication scheme, such as that described in ACSOM's submission to the transparency review? The committee may wish to comment on the following:

- Aims of the scheme
- Communications – audiences, messages, tools/channels
- Criteria for including medicines in the scheme
- Potential linkages with other organisations or information providers
- Evaluation of the scheme

Aims

The committee advised that the aim of the early post-marketing symbol was to:

- improve spontaneous reporting by consumers and health professionals, particularly by providing a clear signal of drugs for which reports of adverse drug reactions were particularly requested;
- provide an incentive for sponsors to conduct appropriate post-marketing safety monitoring;
- alert health professionals and consumers to medicines for which the full safety profile was unknown; and
- trigger discussion between consumers and health professionals about new medicines.

Communications

The committee advised that implementation of such a scheme should be accompanied by a communications program that explained the meaning of the symbol, with information tailored to consumers and health professionals. Health professionals particularly needed information about what sorts of events to report as it appeared that a current barrier to reporting was uncertainty about this. However, it was important that health professionals were not told to avoid reporting any sort of event, but that they were encouraged to use their judgement about the events they reported.

The committee advised that the TGA seek input from stakeholder groups to ensure that a broad range of health professionals and consumers would have a clear understanding of the purpose of the symbol. The committee advised that it would then be appropriate to initiate a consumer-focused education campaign similar to that of the National Prescribing Service (NPS). The TGA should also seek expert advice about developing a social marketing campaign.

Evaluation

The committee advised that it did not seem possible to implement the scheme in a way that would provide a control group to allow for comparison. Possible evaluation questions could include awareness of and understanding of the scheme amongst prescribers, dispensers and consumers; whether adverse reaction reporting shifted towards including more drugs included in the scheme; and whether the symbol might be used as a marker of judicious prescribing of new medicines.

Criteria for inclusion in / graduation from the scheme

The committee explored criteria for inclusion in the scheme and when a medicine would 'graduate' from the scheme. It suggested that inclusion in the scheme could be linked to the period for which a sponsor was required to submit Periodic Safety Update Reports to the TGA for a drug, as this was an indicator of the period for which the TGA considered that closer monitoring was warranted. Selected drugs with risk management plans could be included, such as those with additional pharmacovigilance activities or that were new chemical entities. The committee discussed whether the size of the population in which the drug would be used should be a criterion for inclusion, concluding that utilisation should not be a factor in determining the need for transparency. Marketed drugs for which a new safety issue was identified and would be monitored could also be included.

The committee also queried the scope of the scheme, including whether it would be structured to include listed, over-the-counter and/or complementary medicines. It was determined that it was not likely to be appropriate for listed medicines to be included because they are, by definition, lower risk medicines.

The committee suggested that the TGA investigate the criteria used in the European scheme to inform development of criteria appropriate for an Australian scheme.

Consultation/collaboration

The committee suggested that the TGA consider the following groups or organisations to be stakeholders in the scheme:

- NPS
- Consumers Health Forum

- Pharmacy organisations
- Health professional groups such as colleges and societies
- State and Territory health departments
- Industry
- Aged care sector
- Media
- Training organisations and universities

Item 8 Correspondence

8.1 Letter to the Australian Council on Healthcare Standards — 2010 Clinical Indicator Report

The committee noted the letter from ACSOM to the Australian Council on Healthcare Standards (ACHS) regarding the 2010 clinical indicators report about the 2010 clinical indicator set, which was considered at ACSOM's May meeting. Also at the May meeting, the committee discussed the utility of the indicator set more broadly, and considered what value it could add to the set in future. In part, the committee concluded:

Aside from indicator area 1, other indicator areas were focused on medication safety, with the goal of driving improvement in systems and practice to help avoid preventable harms from medicines. It was agreed that comments and guidance on these indicators would probably be better addressed by a group with a focus on quality use of medicines in the hospital setting, such as the various state-based therapeutic advisory groups, and the Australian Commission on Safety and Quality in Healthcare. The committee discussed whether it should be involved in the future, and came to the conclusion that it would be beneficial to remain involved, but for more limited purposes than previously.

Since the May meeting, the Chair, secretary and another ACSOM member had held a teleconference to discuss future involvement in the indicator set. In that discussion it was agreed that:

- it was no longer appropriate for ACSOM to be seen as the 'owner' of the indicator set and be asked for comment about the interpretation of the data, as the indicators are focused more on medication safety than adverse event reporting.
- it may, however, be appropriate for the TGA to seek experts from ACSOM to be involved in the ACHS working party, to provide input about the indicators relating to adverse drug reaction reporting.
- given that the current indicators relating to adverse drug reaction reporting are difficult to interpret, it was worth suggesting to ACHS that they amend these to process-oriented indicators (eg percentage of healthcare organisations with a policy/established process for reporting) rather than attempting to quantify the number or proportion of adverse drug reactions reported.
- if ACHS wished to seek comment about the data relating to the ADR reporting indicators in the future, it would be most appropriate that this be sought from a TGA officer in the first instance, as they have access to the relevant data about reporting rates and other aspects. The TGA may then wish to seek advice from ACSOM about practical issues such as barriers to reporting to inform its response to ACHS.

A letter is planned to be sent to ACHS explaining the points above.

Item 9 Papers for information

The following papers were provided for information only.

- 9.1 Safety advisories from other regulators
- 9.2 Medicines Safety Update, August 2011 (proof)
- 9.3 ACPM 275th Meeting ratified minutes
- 9.4 ACPM 276th Meeting ratified resolutions
- 9.5 Hélène Théophile, Ghada Miremont-Salamé, Philip Robinson, Nicholas Moore, Bernard Bégaud & Françoise Haramburu. Relevance of a “Dear Doctor letter” to alert healthcare providers to new recommendations for vitamin D administration. Eur J Clin Pharmacol 2011;67(7):681–6.

10 Other Business

A member informed the committee that Poisons Information Centres were undergoing a review, particularly to consider whether they should be combined into a single national service. Poisons centres were potentially valuable source of information about adverse reactions for the TGA, because they received a large volume of calls, 5% of which (approximately 10,000 calls) were related to adverse drug reactions. This compared very favourably with the volume of reports generated by the Adverse Medicines Events line funded by NPS, which took approximately 1,000 calls per year, and reported only a proportion of these adverse events to the TGA. The member advised that calls to the Poisons Information Centres were mainly received from consumers, however, reports from general practitioners and aged care staff were also common. The member suggested that the TGA consider whether it could use data from Poisons centres in its postmarket monitoring program – possibly by resourcing Poisons Centres to consider the value of its data to pharmacovigilance, or pursuing a TGA–Poisons Centre partnership grant to investigate whether Poisons centre data could generate safety signals of use to the TGA. A recent Canadian publication had considered a similar question, and might be informative for the TGA. It was noted that a TGA officer and a senior pharmacist from the NSW Poisons Information Centre had been discussing whether reports captured by the Poisons Information Centre might be of value to the TGA, and had been asked to provide a recommendation to the Head of the Office of Product Review, which would be conveyed to ACSOM.

The meeting closed at 16:00.