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THIS ISSUE

Introducing APPI, the Association of Pharmaceutical Physicians of Ireland

The Association of Pharmaceutical Physicians of Ireland (APPI) was formally inaugurated on the 8th of November, 1989. It was formed to promote the development of Pharmaceutical Medicine in Ireland. Initially the APPI included many associate members who were not medically qualified. With a view to focusing on the development of Pharmaceutical Medicine as a medical speciality, membership was limited to medically qualified individuals from 2000.

The function of the association is to assist its members in keeping fully informed of advances in Pharmaceutical Medicine and related areas. In addition, the association aims to improve communication between pharmaceutical physicians, the medical profession as a whole and others involved in this exciting discipline. These goals are achieved primarily by holding regular meetings for members and in some cases guests, where topics relevant to the practice of Pharmaceutical Medicine are discussed and debated. Since 1993 the APPI has been affiliated to the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP).

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The APPI is a not-for-profit association and exists solely for the benefit of its members. Its only source of income is from subscriptions of its members of which there are currently 35.

The membership of the association is drawn from medical practitioners who have an interest in drug development and use whether their primary involvement stems from an industry, regulatory, academic, or clinical background. Membership to the APPI is currently open only to registered medical practitioners. Physicians in the association may work within the pharmaceutical industry, a clinical research organisation, a regulatory authority, or in academic or clinical research posts.

In 2005, the Minister for Health formally approved the recognition of Pharmaceutical Medicine as a medical speciality in Ireland. To date, members of the APPI educational subcommittee have achieved entry to the Specialist Division of the Medical Register in the speciality of Pharmaceutical Medicine, using the direct entry route. The evaluation process was undertaken by the Royal College of Physicians of Ireland (RCPI) on behalf of the Medical Council of Ireland and included external expert review.

Since the recognition of the speciality, the educational subcommittee of the APPI has been working with RCPI to establish a Higher Specialist Training (HST) programme for pharmaceutical physicians in Ireland. This proved to be a significant challenge to overcome the lack of awareness of the speciality amongst the clinical specialities. With persistence, resilience and ongoing education significant progress was made. The HST programme for Pharmaceutical Medicine was eventually approved in 2015. It contained speciality-specific training modules as well as the generic competences required for all Irish HST programmes, with an annual update to stay contemporary. In 2021, the first HST trainee is about to complete his final year on the programme, and a new trainee has been approved to commence in September.

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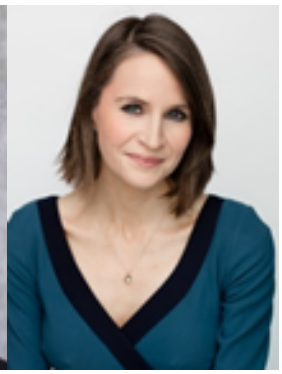
Dr Anthony Chan



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Medicinal Products for Children and Adolescents – *Still a Topic for Discussion?*

The EU Paediatric Regulation came into force in 2007 (1). The intention was and still is to avoid an off-label use of medicinal products in children and adolescents. By 2006, the European Commission referred to around 50% of all medicinal products given to minors as not authorised for patients below 18 years of age (2). The Regulation is structured around three main objectives: more medicines for children, better product information and more paediatric research.

The Regulation sets up a system of obligations, rewards and incentives. The obligation compromises that for new medicinal products the potential use in children should be investigated by a pharmaceutical company. The development plan, the 'Paediatric Investigation Plan' (PIP) must be presented and agreed by the European Medicines Agency, which is supported by its Paediatric Committee (PDCO). The obligation to develop a medicinal product for children can be waived. In the regulation, reference is given to two kinds of waivers.
Class waiver according to Article 11 of the Regulation: the requirement to submit a PIP is waived for specific medicines or classes of medicines that:

- are likely to be ineffective or unsafe in part or all of the paediatric populations;
- are intended for conditions that occur only in adult populations;
- do not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Product specific waiver according to Article 13 of the Regulation: an exemption from the obligation to acquire data, through a paediatric investigation plan, in some or all subsets of the paediatric population for a given condition, route of administration and pharmaceutical form of a specified medicine. The PDCO adopts product-specific waivers.

The EMA annual report (3) 2019 refers to 479 Paediatric Investigation Plans reviewed from 2015 to 2019. The table reports the data presented for the years 2015 – 2020.

Year	PIPs agreed	Full waiver [4]	Oncology
2015	71	54	8
2016	90	53	3
2017	86	83	15
2018	86	101	32
2019	95	117	34
2020	80	65	26 [5]

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Having a closer look at the years 2019 and 2020 the PDCO granted 161 full waivers (6).

Year	No	Class waiver	Product waiver	Thereof Combination medicinal product
2019	96	38	58	13
2020	65	20	45	8

In 2015 the EMA updated the list of class waivers (7), with the intention to overcome insufficient opportunities for the PDCO to consider the potential benefits of individual medicinal products for the paediatric population at large (8). According to the snapshot given above, it seems that further discussion on this topic is necessary.

The 10-year European Commission (EC) report, State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation (9) refers for 2007-2016 that over 260 new medicines for use by children (new marketing authorisations and new indications) were authorised, most of them linked to the Paediatric Regulation's requirements.

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Updating this information with a publication date of 30 March 2021 German vfa ("Die forschenden Pharma-Unternehmen"; research-based pharma companies) published (10) for the year 2017 thirty-seven, for the year 2018 forty-eight, for the year 2019 thirty, and for 2020 fifty new medicinal products and application aids receiving a marketing authorisation. New in the meaning of a product with the active substance or the presentation/formulation was available only for older age groups or adults before. Since 2016, 165 new medicinal products have been available for the treatment of children and adolescents, with the restriction mentioned above. That means overall since 2007 425 medicinal products more are on the EU market with the target to treat children and adolescents.
Even if some improvements can be recognised, additional support is needed to make a big step forward for the treatment of children and adolescents.

The EC, the EMA and their PDCO agreed on an action plan (11), also outlined in status/progress report, to further improve the situation for children and adolescents by:

An EU network of networks of investigators and trial centres carrying out paediatric research;

An EU inventory of paediatric needs;
A public database of paediatric studies;
A requirement for companies to submit any existing paediatric studies on authorised medicinal products for scrutiny by regulatory authorities.

In this status/progress report, dated December 2020 and mentioned above, amongst others, information on the topics identifying paediatric medical needs and increasing transparency around paediatric medicines are given as in progress.

Additionally, the EC published a road map (12) regarding the EU rules to incentivise the development of medicines for children and for people with rare diseases, which have been in place for nearly 20 years. This revision addresses shortcomings identified in a recent evaluation, aiming to ensure that:

- products addressing the specific needs of children and patients with rare diseases are developed;
- these groups have timely access to medicines;
- there are efficient assessment and authorisation procedures.

An outcome of this initiative is foreseen in the first quarters of 2022.

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Overall, the regulation is a reliable instrument to improve the situation for children and adolescents in respect to the treatment of their diseases. Nevertheless, a continuous review of the implementation of the Paediatric Regulation is necessary to make a real change in the provision of medical care for minors.

Dr. Birka Lehmann, Senior Consultant in Regulatory Affairs, Germany

References

(1) EUR-Lex - 02006R1907-20140410 - EN - EUR-Lex (europa.eu)
(2) 2017_childrensmedicines_report_en.pdf (europa.eu)
(3) 2019-annual-report-european-medicines-agency_en.pdf
(4) The EMA class waiver guideline was up-dated in July 2015. European Medicines Agency decision CW/0001/2015 of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council
(5) According to EMA data base Medicines | European Medicines Agency (europa.eu)
(6) The EMA data base (date 12 04 2021) presents
(7) European Medicines Agency decision CW/0001/2015 of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council (europa.eu)
(8) EMA/PDCO Summary Report on the review of the list of granted Class Waivers (europa.eu)
(9) 2017_childrensmedicines_report_en.pdf (europa.eu)
(10) Arzneimittelzulassungen für Kinder in Übersicht | vfa
(11) Progress report - Action plan on paediatrics (europa.eu)
(12) Medicines for children & rare diseases – updated rules (europa.eu)

Summary Report of the COVID-19 Webinar Held on April 14, 2021 with Presentations from Switzerland, Austria and Germany

This webinar was chaired by Dr Ghazaleh Gouya, Austrian member of the House of Delegates, and Dr Martin Traber, President of the Swiss Society of Pharmaceutical Medicine. Dr Marco Romano, IFAPP President, summarised the event at the end and provided an outlook for the upcoming events.

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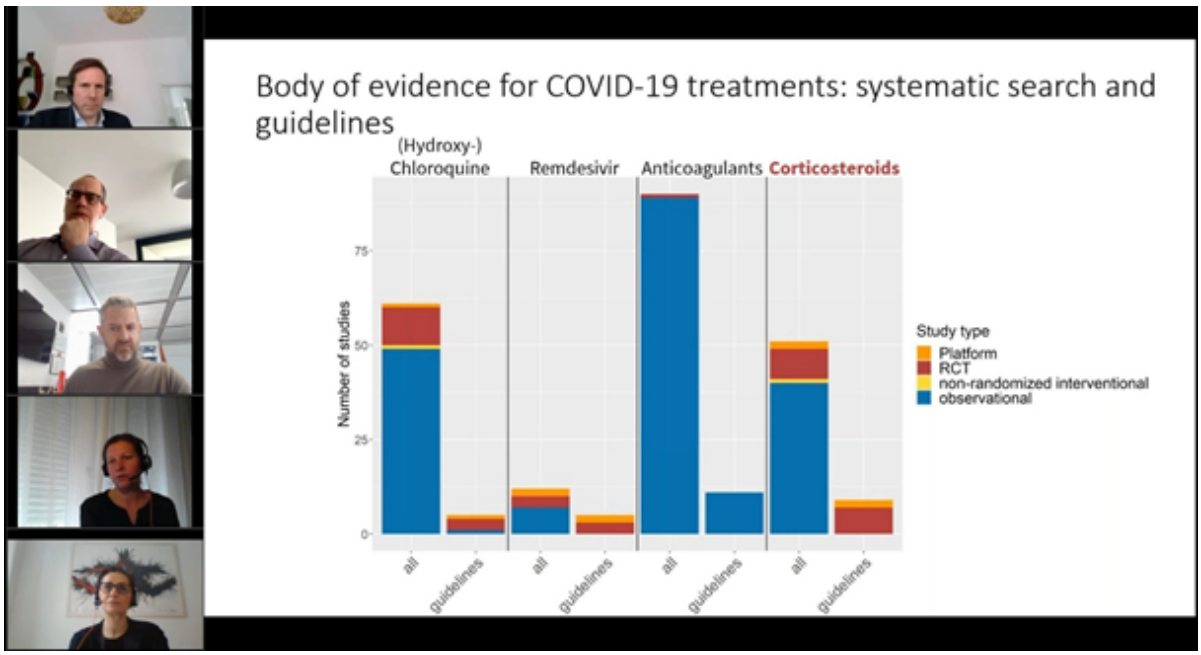

Top to bottom: PD Dr Johannes Pleiner-Duxneuner (Roche Austria, President elect GPMed), Dr Martin René Traber (SGPM President and Global Medical Lead F. Hoffmann-La Roche), Prof. Dr Milo Puhan (Professor of Epidemiology and Public Health at the University of Zurich), Dr Stefanie Wüstner (Head of Business and Scientific Innovation AMS Advanced Medical Services), PD Dr Ghazaleh Gouya Lechner (Gouya Insights, GPMed Board member). Presentation of a slide from Stefanie Wüstner on body of scientific evidence from potential treatment option in COVID-19.

A very high level of interest for this webinar was already shown in advance with 500 clicks on the registration link, 237 registrations and 154 attendees who also took the survey. The mean rating of the event was 4.16 in favour (out of a total of 5.00). Most of the participants came from national member associations in Germany (54), Austria (26), and Switzerland (9). The remaining attendees were from the USA and UK, with at least one person from Kuwait, Egypt, Côte d'Ivoire, Indonesia, Australia, Canada, India, Ukraine, China, and Latin American countries.

The presentations on the COVID-19 situation in these three countries focused on different aspects. Whilst we learned from epidemiological insights and an extensive and impressive research network in Switzerland established during the pandemic, the Austrian presenter spoke about successful collaboration in public-private partnerships and lessons learned with regard to online tools. The German speaker provided an insight into the existing body of scientific evidence of COVID-19 treatments and implementation into the German COVID-19 treatment recommendations.

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1 Switzerland

Prof. Dr. Milo Puhan, Professor of Epidemiology and Public Health at the University of Zurich presented Corona Immunitas (www.corona-immunitas.ch), the national research project of the Swiss School of Public Health, a Switzerland-wide programme to assess the spread and impact of the pandemic. Fourteen universities and health organisations, more than 40 studies throughout Switzerland with 50,000 study participants.

There are repeated cross-sectional and cohort studies to determine seroprevalence, all enrolled in a digital follow-up, and additional site-specific studies. All Swiss cantons are involved, and it could be shown that seroprevalence increased by more than twice the percentage numbers from summer 2020 to winter 2021. In early 2021, thanks to the nation-wide vaccination programme, seroprevalence increased in the older (>65 years) when compared to the younger population. Based on a study by Zsac (1) (prospective population-based cohort of PCR+ persons) it was shown that 15% of the infected persons do not develop antibodies (which was more likely after a mild course of the disease as well as in women and in smokers). Ninety percent still have detectable antibodies after >6 months. The total number of infected persons is currently about 2 million in a total population of about 8.7 million.

The approved vaccines in Switzerland so far are those from BioNTech/Pfizer and Moderna. The cantons have to report a minimal required data set on the number of vaccinated persons (→15% at least once by 9th April 2021), age and sex (→around 50% of over 75-year old to be fully vaccinated).

Follow-up data on attitude towards the vaccinations, side effects, vaccination status by educational level, by household income, by underlying chronic disease as well as data on antibodies differentiating between infection and vaccination and more are expected throughout the upcoming year.

2 Austria

For Austria, the presentation was given by Dr Johannes Pleiner-Duxneuner, the President of the Austrian Association of Pharmaceutical Medicine, GPMed, with the title “Public Private Partnerships in Times of COVID-19, The Austrian Story”.

Funding from federal ministries (2) of 26 million Euros for the Corona Emergency Call were processed by the Austrian Research Promotion Agency (FFG) in a fast-track evaluation for forty-five projects being finally awarded in the following topics in COVID-19: vaccines (2), diagnostics (18), prevention/infection control (4), prevention/ protective materials (8), prevention/disinfection (3), prevention/safety (1), and therapeutics (9). Among the many projects Dr Pleiner-Duxneuner provided a few examples of research activities, e.g., with APN01, a recombinant human Angiotensin Converting Enzyme 2 (rhACE2) under Phase-2 clinical development, and solnatide, a synthetically produced peptide.

(1) ZSAC https://www.isrctn.com/ISRCTN14990068/ and Dan et al https://science.sciencemag.org/content/371/6529/eabf4063

(2)The Federal Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (BMK) and the Federal Ministry for Digital and Economic Affairs (BMDW)

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Online events and online trainings were organized throughout the past 14 months, stakeholders from academia, industry and regulatory have come closer during the pandemic organizing multiple virtual events on “Clinical Trials during the COVID-19 Pandemic” and other similar hot topics. An online course on “Introduction to Medical Affairs and Pharmaceutical Medicine” was successfully launched fully virtually and held in English in the first quarter of 2021 with planned annual courses to be held all online.

A guidance document for usage of RWD/RWE (Real World Data/Real World Evidence) is under development in a joint effort of public-private stakeholders, ethics committees and the regulatory agency. Important topics on quality criteria for RWD for primary and secondary use, the legal requirements and guardrails, overview on existing data sets/registries and which datasets to use for which analysis to be used for which analysis will be elaborated to set common recommendation on the use of RWD.

The crisis during the past months was accompanied by an enormous effort from all stakeholders in pharmaceutical medicine to collaborate.

3 Germany

Dr Stefanie Wuestner and Sara Hogger, both at AMS Advanced Medical Services in the field of HTA (health technology assessment) preparing documents for the German AMNOG-Process (Arzneimittelmarkt-neuordnungsgesetz "Pharmaceuticals Market Reorganisation Act"), presented their project which is performed in collaboration with Friedhelm Leverkus from Pfizer as well as collaborators from Amgen and Novartis. The title of their talk was ”Good enough? – Evaluating Evidence Generation for Treatment Recommendations on Pharmaceutical Therapies during the COVID-19 Pandemic”, dealing with the question: what kind of clinical data had strongest impact on patient care based on its uptake in German treatment recommendations.

Clinical data with increasing level of certainty became available over time. All analysed treatments followed the following chronological pattern, since they were available early due to repurposing and compassionate use and were analysed in large platform trials:

1. General treatment practice
2. Observational trials, cohort studies
3. Single-centre studies, interventional trials, randomised clinical trials
4. Multi-centre studies, adaptive platform trials (3)

In the current project, studies of four treatments with the most comprehensive evidence from published data and guidelines available end of 2020 ([hydroxy-]chloroquine, remdesivir, anticoagulants and corticosteroids) were evaluated to understand the pattern of evidence generation and uptake into German treatment guidelines. Due to the limited time, the example of remdesivir was not presented in the webinar.

The following sources were used to generate the body of evidence for the assessment: Studies referenced in the German guidelines for hospitalized/critically ill patients (primary studies, reviews, meta-analyses) and systematic search for treatments in MEDLINE (Dec 1, 2020).

Systematic overview of the design and characteristics of the studies as well as features regarding the communication and publication of study data were shown for (hydroxy-) chloroquine (the dismissed first choice – proven to be not effective), anticoagulants (the obvious treatment based on expert consensus), and corticosteroids (the big surprise with evidence towards mortality benefit).

(3) Definition of platform trials: Master protocol, multiple treatments, flexible features, e.g., studies like SOLIDARITY, RECOVERY, and REMAP-CAP

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The response to the question “Good enough evidence?” is that coordination by a well-connected, multinational organisation, early communication and cooperation with experts (e.g., senior investigators) and harmonisation and standardisation of study protocols and study procedures provide robust evidence and timely conclusions (good example: meta-analysis for corticosteroids by REACT Working Group).
Evidence from large platform trials, especially with adaptive design (e.g., REMAP-CAP, SOLIDARITY) allow timely and robust conclusions and spare resources.

Take-home Message of the Webinar: **Work together, learn fast as the game is not yet over!**

With special thanks to the speakers who approved the texts

Brigitte Franke-Bray, IFAPP Board Member, Switzerland, and Ghazaleh Gouya Lechner, Gouya Insights, GPMed Board Member, Austria

Plasma Against COVID-19: Neither Reduction of Deaths nor Reduction of Respiratory Distress

AIFA (the Italian Drug Agency) concluded the analysis of the results of the “Tsunami” clinical trial, which investigated the use of convalescent plasma in patients affected by the COVID-19 infection. The study was randomised and controlled, and its results indicate that convalescent plasma does not produce beneficial effects regarding both the reduction of the worsening of respiratory distress and patients’ death, in the initial thirty days of the disease. The clinical trial was sponsored by both AIFA and the Italian National Institute of Health (Istituto Superiore di Sanità).

487 Patients

The study compared the effects of convalescent plasma with high neutralising antibody titre (≥1:160), associated to the standard therapy, versus only standard therapy, in patients with a lab proven COVID-19 infection and pneumonia with a mild to moderate respiratory distress (defined as a ratio PaO2/FiO2 from 350 to 200). The study was performed at 27 clinical sites all over Italy and recruited 487 patients.

The two groups of patients were comparable in terms of demography, concomitant diseases, and concurrent therapies. Out of the 487 patients recruited into the study, 241 were randomised to the plasma and standard therapy arm (231 were evaluable) and 246 were randomised to the standard therapy arm (239 were evaluable). The results indicate no significant difference among the two groups in the primary endpoints (need of invasive ventilation, defined after a ratio PaO2/FiO2 < 150, or death within thirty days from randomisation). The experimental treatment was well tolerated, but adverse events were more frequent in the patients receiving convalescent plasma and standard therapy.

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Subgroup analyses did not identify any significant difference between the two groups: only in patients with a less severe respiratory distress (ratio PaO2/FiO2 ≥ 300 at randomisation) it was possible to demonstrate a favourable trend for the convalescent plasma therapy, without however reaching a statistically significant difference (p=0.059). This finding may suggest to further investigate the possible role of convalescent plasma in patients with a mild to moderate COVID-19 infection, or in the very early stage of the disease.

The Comparison with International Studies

AIFA underlines that these results are comparable to those published from additional international trials: most studies indicate negative results, with the only exception of trials which either recruited patients at a very early stage of the disease, or with the administration of convalescent plasma with very high antibody titre. In thanking all sites which collaborated in the "Tsunami" study (clinical centres, virology labs and blood transfusion centres) AIFA underlined the importance to perform well-controlled studies with an adequate sample size, in order to reach definitive conclusions.

AIFA press release available at www.aifa.gov.it

Note: this study will be published, and its reference will be communicated when available.

(Translated into English by Domenico Criscuolo, MD, PhD, GFMD)

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Newsletters from National Associations

"NMA TODAY"

This new series is to introduce newsletters of National Member Associations (NMAs) of IFAPP reporting of their activities, and the first one is from Japan. Please contribute your newsletter to follow suit.

Newsletter of JAPhMed

JAPhMed (Japanese Association of Pharmaceutical Medicine) is among the founding organisations of IFAPP and has been publishing newsletters to all members and our online magazine followers. It is also posted on our website (https://japhmed.jp/) to invite potential readers as a part of our effort to promote pharmaceutical medicine in Japan. It has been published at least twice a year, topped by the message from the president followed by the reports of the committees and the news of the upcoming meetings. Please see the latest issue No. 34 published in February 2021' (https://japhmed.jp/news/_no34.html) and you can see our manuscripts are shown in both Japanese and English language.

We expect our newsletter can help us communicate with other IFAPP NMAs and hope their newsletters to be introduced in IFAPP TODAY so that we can learn from each other.

Hideki Oi, Director of the Board of JAPhMed for Public Relations

THE FLAG

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