UNIVERSIDADE D
COIMBRA

Daniela do Nascimento Vieira

Relatórios de Estágio sob orientação da Dra. Ana Leite e Silva e da Dra. Ana Margarida Andrade e Monografia intitulada *"Safety assessment of cosmetic products: a comprehensive approach of the regulatory affairs to promote the identification of gaps"* sob orientação da Professora Doutora Filipa Mascarenhas Melo, referentes à Unidade Curricular "Estágio", e apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

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Coimbra, 29 de agosto de 2023.

Daniela do Nascimento Vieira

(Daniela do Nascimento Vieira)

Agradecimentos

À Karina, Eduarda e Sara, por muito mais do que a amizade, são irmãs de coração que a vida me presenteou.

Aos "CF dealers + adotados", porque juntos fomos e somos mais fortes. Nunca esquecerei dos desafios que ultrapassamos e memórias que criamos.

Ao Antonio, por segurar a minha mão e ser apoio sempre quando precisei.

À Dra. Ana Leite, pela direção ao longo do estágio na Farmácia Coimbra.

À Dra. Ana Margarida Andrade, pelo apoio durante o estágio na OWLPharma, que me guiou até a minha ambição profissional.

À Professora Doutora Filipa Mascarenhas Melo, pela disponibilidade e impecabilidade na orientação da monografia.

À minha família por tornar esta conquista possível.
Aos meus pais, pelo exemplo de dedicação, resiliência e perseverança.
Aos meus avós, que sempre foram suporte e torceram por mim, tanto em vida quanto estrela.
Aos meus irmãos, que são os abraços nos momentos de necessidade.

À Coimbra, pelos ensinamentos e segredos que levarei comigo para a vida.

Obrigada por embarcarem comigo nos altos e baixos desta montanha-russa e manterem-na andando para a frente.

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Parte I

Relatório de Estágio em Farmácia Comunitária

Abreviaturas

AINE – Anti-Inflamatório Não Esteroide

FFUC – Faculdade de Farmácia da Universidade de Coimbra

MICF – Mestrado Integrado em Ciências Farmacêuticas

MSRM – Medicamento Sujeito a Receita Médica

SWOT – *Strenghs, Weaknesses, Opportunities and Threats*

1. Introdução

O percurso académico no Mestrado Integrado em Ciências Farmacêuticas (MICF) da Faculdade de Farmácia da Universidade de Coimbra (FFUC) finaliza-se com a realização de um Estágio Curricular em Farmácia Comunitária. Sendo a intersecção entre a esfera académica e o ofício, o estágio revela-se como uma oportunidade para a consolidação dos conhecimentos adquiridos ao longo dos últimos cinco anos, assim como fortalecer atributos pessoais essenciais no ambiente de trabalho. Valências interpessoais e comunicativas, otimização do tempo de trabalho, gestão da carga de *stress*, desenvolvimento de pensamento clínico crítico e a capacidade de aplicar a teoria de forma prática são alguns dos muitos pontos que os meses de estágio em Farmácia Comunitária proporcionam abordar.

O presente relatório de estágio em Farmácia Comunitária foi realizado no âmbito da unidade curricular Estágio Curricular, no período de 9 de janeiro e 11 de abril de 2023, na Farmácia Coimbra, localizada na Avenida Mendes Silva 211/251 (Coimbra Shopping, loja 119/121), sob orientação da Dra. Ana Leite e Silva. A elaboração do relatório assenta numa análise SWOT, que compreende a descrição e análise das tarefas realizadas e os conhecimentos adquiridos aquando da sua realização. A análise SWOT engloba as *Strengths* (Forças), *Weaknesses* (Fraquezas), *Opportunities* (Oportunidades) e *Threats* (Ameaças) que me deparei ao longo do tempo como estagiária (Tabela I)[1]. Serão apresentados, por fim, cinco casos práticos, a título exemplificativo.

2. Análise SWOT

Serve a seguinte análise SWOT (*Strengths, Weaknesses, Opportunities and Threats*) para descrever e desenvolver a avaliação crítica do meu estágio curricular em Farmácia Comunitária do MICF.

Tabela I – Análise SWOT dos pontos observados durante o período de estágio curricular.

Forças	Fraquezas
• Estruturação faseada do plano de estágio. • Sistema de dispensação de medicamentos automatizado por um robô. • Fluxo intenso de pessoas na farmácia. • Diversidade de produtos disponíveis para venda. • Prestação de serviços farmacêuticos.	• Gestão dos *stocks* existentes. • Falta de autonomia na interpretação de receitas manuais.
Oportunidades	**Ameaças**
• Iniciativa de formação contínua. • Pluralidade de pessoas atendidas.	• Quebra do *stock* de medicamentos essenciais. • Desafios na coordenação e integração de uma equipa técnica grande. • Encomendas mensais desajustadas à demanda local. • Furtos frequentes aos produtos expostos ao público.

2.1 Forças

- Estruturação faseada do plano de estágio

O estágio curricular define-se como o primeiro contacto entre o futuro profissional de saúde e o mundo profissional, destacando-se a importância de uma boa orientação. A equipa da Farmácia Coimbra é formada por pessoas altamente competentes e profissionais, que não hesitaram em responder a todas as dúvidas que me foram surgindo ao longo do tempo.

A estruturação do estágio, idealizada pela minha orientadora e diretora técnica, foi concebido com o intuito de otimizar a minha aprendizagem durante este período. Uma vez que cada membro da equipa tem as suas tarefas específicas delineadas, estive sob supervisão de diferentes pessoas consoante a fase do estágio em que me encontrava.

A primeira semana foi dedicada à apresentação dos colaboradores da farmácia e das suas respectivas funções, bem como a entender a organização da farmácia. Nesta fase, desenvolvi funções na organização dos lineares e reposição de produtos, destacando a zona do balcão, onde se encontravam prateleiras designadas a produtos com a mesma indicação terapêutica numa determinada ordem enquanto nas gavetas eram guardados os restantes

produtos que não estavam expostos por razões internas de marketing. Numa segunda fase, iniciei a realização das tarefas de *back-office* que se mantiveram até ao final do tempo de estágio, com a finalidade de conhecer as ferramentas disponíveis no sistema informático utilizado (*software* SIFARMA 2000®), ficar familiarizada com a gama e aparência dos produtos da farmácia e aprender as diferentes formas de rececionar encomendas. Quando a minha orientadora considerou que os conhecimentos anteriores estavam consolidados, a minha principal atividade passou a ser assistir aos atendimentos. Ao sentir-me segura nesta função, pude passar a atender e fazer aconselhamentos sozinha, sob supervisão de outra pessoa da equipa.

Esta estruturação do estágio contribuiu para aumentar a minha confiança durante o estágio e garantir que de fato aprendi a realizar cada uma das tarefas na sua totalidade. Para além disso, a disponibilidade da minha orientadora e da restante equipa em responder a dúvidas sempre que necessário foi crucial para o meu êxito nos desafios diários de um farmacêutico comunitário.

- Sistema de dispensação de medicamentos automatizado por um robô

Durante o estágio, bastante do tempo inicial foi para me familiarizar com o robô (Rowa Vmax), ferramenta essencial para o funcionamento normal da farmácia. Este equipamento agiliza o processo de dispensa dos produtos, uma vez que é bastante rápido selecionar o código da caixa de interesse no SIFARMA 2000® para que o robô o procure e o desarmazene. Outra vantagem do robô que constatei foi a possibilidade de controlar o *stock* dos produtos, uma vez que é de fácil visualização e permite correção de erros que possam ter ocorrido no processo de entrada de encomendas. Essa etapa de reposição de *stocks* do robô também foi vantajosa na medida em que permitiu conhecer a aparência dos laboratórios.

- Fluxo intenso de pessoas na farmácia

A Farmácia Coimbra encontra-se localizada no interior do Coimbra Shopping, sendo este um centro comercial com elevado fluxo de pessoas. A farmácia conta, portanto, com os seus utentes habituais somados aos clientes esporádicos que estão de passagem pelo centro comercial. Como consequência, são raros os momentos nos quais a farmácia não possui pessoas para atender, o que influencia positivamente o faturamento do estabelecimento. Particularmente, a questão de haver um número grande de pessoas para atender traduz-se numa maior exposição a casos clínicos diversos, melhorando a experiência do estágio.

- Diversidade de produtos disponíveis para venda

Como a farmácia atende muitas pessoas, é necessário que o estabelecimento esteja preparado para suprir as eventuais demandas que aparecerão. Desde produtos cosméticos e suplementos a medicamentos psicotrópicos, a gama de artigos disponíveis para serem aconselhados e dispensados é muito extensa e variável. Foi possível conhecer muito do universo farmacêutico, aprofundar os meus conhecimentos nas diversas marcas comerciais existentes assim como conhecer novos produtos.

- Prestação de serviços farmacêuticos

A Farmácia Coimbra conta com um gabinete reservado para a prestação de serviços farmacêuticos dentre os previstos no artigo 2º da Portaria n.º 1429/2007, do Decreto-Lei n.º 307/2007. Equipado em conformidade, este espaço é utilizado para a realização dos seguintes: testes profissionais de antigénio SARS-CoV-2, administração de vacinas e injetáveis pela equipa especializada, medições de tensão arterial e determinações de glicémia, do colesterol total e dos triglicerídeos, parâmetros importantes de serem rastreados. Após ser instruída para a realização de medições de tensão arterial e determinações de glicémia, do colesterol total e dos triglicerídeos, pude perceber que, nesse contexto, a relação entre o farmacêutico e o utente torna-se mais próxima e a comunicação fica mais natural. Como a transmissão de informações é mais fluida, a probabilidade de perceber falhas ou esclarecer alguma dúvida que condicionem a adesão à terapêutica aumenta. Foi possível, então, fazer um aconselhamento farmacêutico mais personalizado para os utentes com os quais tive este contacto, tanto relativamente às medidas farmacológicas quanto às não farmacológicas. Verifica-se, também, que o utente percebe essa atenção diferenciada que lhe foi dispendida e fideliza-se à farmácia para tudo o que precisar.

2.2 Fraquezas

- Gestão dos *stocks* existentes

Com o elevado fluxo de entrada e saída de mercadorias, vem o desafio da gestão do *stock* existente. Pude verificar que, às vezes, acontecia a seguinte situação: era requisitado pelo utente um produto que já tinha chegado, mas que ainda não se encontrava inserido no sistema. Neste caso o *stock* estava a zero no sistema, no entanto, o produto era vendido e o *stock* passava a negativo. O oposto, por vezes, também ocorria, no qual era indicado que havia na

farmácia um produto que, na realidade, não havia. Considero esta situação um ponto fraco na gestão da farmácia, pois resulta num maior tempo dispendido por atendimento, levando a utentes impacientes, existência de filas de espera, e, em último caso, a perda de vendas.

- Falta de autonomia na interpretação de receitas manuais

As receitas manuais, aceitas nas condições excecionais previstas no artigo 8.º da Portaria n.º 224/2015, de 27 de julho, alterada pela Portaria n.º 390/2019 de 29 de outubro, possuem alguns elementos aos quais o farmacêutico deve ter atenção no momento da dispensação, como a assinatura do prescritor e validade da receita. Sendo assim, todas as vezes que dispensei uma receita manual, realizei a sua interpretação e, após o fazer, precisei pedir sempre a confirmação da minha supervisora de modo a assegurar que nenhum fator passou desapercebido. Considero a interpretação destas receitas um ponto fraco devido à dependência de dupla verificação com outra pessoa da equipa para poder finalizar o atendimento, tornando-o mais demorado.

2.3 Oportunidades

- Iniciativa de formação contínua

Na Farmácia Coimbra, decorriam sessões de informação médica com periodicidade semanal, promovidas por delegados de informação médica das diversas empresas cujos produtos eram vendidos na farmácia, como Sanofi, Tilman, Angelini, Heel, La Roche Posay, Neutrogena e Pierre Fabre Oral Care. Para além destas, também tive a oportunidade de integrar duas formações externas da Zambon, uma sobre o Fluimucil® e outra sobre o Spidifen®, que contribuíram muito para o aconselhamento apropriado em situações de expectoração e dor, respectivamente. Em complemento às iniciativas direcionadas à equipa regular da farmácia, a minha orientadora de estágio dedicou-se em promover sessões de esclarecimento quanto às situações mais frequentemente observadas no atendimento. Percebo claramente o valor dessas formações principalmente quando comparo a firmeza com que respondia a questões apresentadas pelos utentes anterior e posteriormente a tê-las assistido.

- Pluralidade de pessoas atendidas

O contacto com pessoas de diferentes nacionalidades, faixas etárias e géneros foi extremamente engrandecedor, na medida em que é possível ter uma perspectiva diferente da usual. Durante o estágio, tive a oportunidade de praticar com sucesso indicações farmacêuticas

em inglês e francês a turistas. O contacto com pessoas idosas, por outro lado, permitiu-me ter emotividade durante as habituais conversas durante o atendimento assim como desenvolver uma sensibilidade especial relativamente ao aconselhamento direcionado a esta faixa etária. A pluralidade de indivíduos que tive a possibilidade de atender, sem dúvidas, contribuiu para a construção de uma visão abrangente das terapêuticas existentes e da melhor maneira de aconselhar tendo em conta a individualidade de cada utente.

2.4 Ameaças

- Quebra do *stock* de medicamentos essenciais

Devido a problemas externos à farmácia, não foram raros os momentos nos quais os medicamentos que foram prescritos aos utentes não estavam disponíveis em *stock* e nem para encomenda nas distribuidoras. Embora tentasse sempre substituir apropriadamente ou fazer aconselhamentos favoráveis, muitas vezes o utente encontrava-se sem opções e acabava por sair da farmácia sem aquilo que precisava, por tempo indefinido. Tal problemática ameaçou, para além da continuidade no tratamento dos utentes, a fidelização destes com a farmácia, uma vez que acreditavam ser uma questão interna e ficavam insatisfeitos com o serviço prestado.

- Desafios na coordenação e integração de uma equipa técnica grande

A equipa da Farmácia Coimbra é constituída por mais de dez colaboradores, que trabalham conjuntamente com o propósito de fazê-la funcionar da melhor forma possível. Embora seja plausível devido à demanda de trabalho, é desafiante ter tantas pessoas coordenadas num ambiente relativamente pequeno sem que os procedimentos estejam muito bem definidos. Constatei que a metodologia de trabalho, muitas vezes, envolvia seguir os conceitos próprios de prudência e, como consequência, colaboradores diferentes trabalhavam de formas diferentes. Este sistema funciona corretamente em muitas situações, no entanto, frequentemente aconteciam erros evitáveis devido à falta de comunicação. Acredito que ter um sistema de qualidade, com uma metodologia de trabalho organizada por procedimentos poderia ter sucesso a longo prazo para a farmácia.

Noutra perspectiva, a falta de pessoal também se faz sentir. Num curto período de tempo, no último mês do estágio, a farmácia ficou desfalcada em alguns colaboradores por motivos de demissões e férias, o que resultou numa ligeira sobrecarga de trabalho nos

restantes. Foi imprescindível um maior esforço e empenho para que não houvesse comprometimento da qualidade dos atendimentos e serviços farmacêuticos prestados.

- Encomendas mensais desajustadas à demanda local

A Farmácia Coimbra faz parte de uma rede de farmácias, que conta com uma gerência de topo. Essa gerência é responsável por fazer a encomenda mensal dos produtos que serão recepcionados e vendidos nas semanas seguintes. Essa encomenda, constituída por centenas de embalagens, pode não corresponder necessariamente à necessidade local, isto é, frequentemente existia uma quantidade de produtos superior à capacidade de armazenamento do robô, levando consequentemente ao armazenamento destes em locais improvisados. Para além disto, eram encomendados produtos que não correspondiam aos que a farmácia costumava vender, não satisfazendo desta forma as necessidades dos utentes. Esta questão foi muito significativa na problemática dos *stocks* errados.

- Furtos frequentes aos produtos expostos ao público

Embora câmeras supervisionassem a farmácia em toda a sua extensão, é difícil fiscalizar todas as pessoas que a frequentam. Favorecido pelo grande fluxo de pessoas, alguns indivíduos aproveitavam-se para furtar produtos, especialmente de dermocosmética, que depois refletia em prejuízo financeiro para o estabelecimento e falhas no *stock*.

3. Casos Práticos

Caso Prático 1

Um utente jovem veio à farmácia preocupado com a namorada que acordou com muitas náuseas e já havia vomitado duas vezes. Disse que havia pesquisado na internet que medicamentos contendo ondansetrom eram usados para tal, portanto, queria levar uma caixa de Zofran Zydis®.

Primeiramente, busquei compreender melhor a situação, uma vez que o Zofran Zydis® é um MSRM indicado para controlo de náuseas e vómitos induzidos pela quimioterapia e para prevenção das náuseas e vómitos no pós-operatório[2]. Ao questionar o utente sobre a causa da sua sintomatologia, ele revelou que a namorada ficou assim depois de ter ingerido bebidas alcoólicas na noite anterior.

O aconselhamento prestado nesse caso foi:

- Expliquei as indicações terapêuticas do ondansetrom e que só poderia ser comprado mediante apresentação de receita médica. Considerando a mais provável causa da sintomatologia, não se justificava a toma do medicamento que pediu.
- Fiz questões de modo a compreender o contexto clínico: Não se verificava presença de sangue, bile ou muco nos vómitos; a senhora não faz medicação crónica; se trata de uma mulher saudável em idade fértil.
- Recomendei que ele lhe levasse o Antimetil®, suplemento alimentar com extrato de gengibre padronizado a 10% de gingeróis, que tem ação antiemética rápida e segura. Normalmente é indicado para situações de enjoo do movimento, gastroenterites e indigestão[3], portanto, era um produto mais apropriado no caso desse utente.
- A posologia habitual é dois comprimidos, até ao máximo de oito comprimidos diários, durante o tempo que precisasse até se sentir melhor[3].
- Como ela também havia vomitado algumas vezes, reforcei a necessidade de hidratação frequente com água e sais minerais, de modo a evitar desequilíbrios hidroeletrolíticos. Recomendei a toma de Eletrolit®, uma solução oral para reidratação.
- Caso o suplemento alimentar não resultasse, aparecesse algum outro sintoma ou a duração das náuseas e vómitos se prolongasse por mais de 48 horas, seria preciso consultar um médico.

O utente era cliente habitual da farmácia e, na semana seguinte, tive a oportunidade de lhe perguntar como que a namorada estava após o ocorrido. Após a primeira toma de dois comprimidos, já não havia mais vomitado e, uma hora depois da segunda toma de dois comprimidos, já estava bem-disposta.

Caso Prático 2

Uma menina, aparentando ter 16 anos de idade, queixava-se de dores abdominais explicando que se encontrava no primeiro dia da menstruação. Referiu que não havia tomado nenhum medicamento em casa.

O aconselhamento prestado neste caso foi:

- Questionei se ela apresentava algum problema de saúde e se tomava algum medicamento, pelo que ela referiu que tomava apenas suplementos alimentares multivitamínicos todos os dias desde criança.

- Recomendei um medicamento genérico contendo ibuprofeno na dosagem de 400 mg, que tem atividade anti-inflamatória e analgésica, sendo eficaz no alívio das cólicas menstruais[4].
- Referi que a aplicação de calor na zona da barriga é uma medida não farmacológica que costuma funcionar para relaxar a musculatura e aliviar a dor[5].
- Como ela aparentava estar aflita com a dor, aconselhei que tomasse Spidifen EF® 400 mg em saquetas com granulado para solução oral. Por serem formulados sob a forma de arginato de ibuprofeno, o tempo até o início de ação é menor, portanto, ela terá o alívio das dores mais rapidamente[6].
- A saqueta deveria ser diluída em 50-100 ml de água e tomado de imediato após as refeições, de modo a melhorar a tolerabilidade e evitar problemas gastrointestinais.
- Por se tratar de um anti-inflamatório não esteroide (AINE), a recomendação é tomar até 3 vezes ao dia e não tomar duas doses com intervalo inferior a 4 horas[6].

A menina levou o medicamento aconselhado e disse que passaria a tomá-lo quando tivesse cólicas menstruais.

Caso Prático 3

Um rapaz jovem, aparentando ter cerca de 20-30 anos de idade, veio à farmácia, às 20h, com a mão enfaixada devido a um corte profundo por um copo de vidro quebrado. Encaminhado das emergências do hospital, apresentou a seguinte receita médica:

- Flexiban® em SOS, até 3 comprimidos diários.
- Betamox® de 12 em 12 horas, durante 8 dias.

Queixando-se que o médico não lhe havia explicado exatamente o que constaria na receita eletrônica sem papel que recebeu por mensagem, o utente pediu para que eu lhe explicasse quais medicamentos estavam na receita e como os tomar.

O aconselhamento prestado nesse caso foi:

- Mencionei que na receita consta o Flexiban® (ciclobenzaprina 10 mg), que teria como função aliviar os espasmos musculares e as dores localizadas causadas pela lesão. O médico referiu a posologia para toma em SOS, ou seja, seria para tomar quando as dores estivessem muito intensas, até os 3 comprimidos diários. Aconselhei que o tomasse de 8 em 8 horas nos primeiros dias de forma preventiva, para evitar que passasse muito tempo com dor.

- Para além do relaxante muscular, também consta na receita o Betamox® (amoxicilina 500 mg + ácido clavulânico 125 mg), que deveria ser tomado rigorosamente de 12 em 12 horas até ao fim da caixa de 16 comprimidos. Aconselhei que iniciasse a toma do antibiótico imediatamente e mantivesse a toma sempre às 20h e às 8h para assegurar a eficácia do antibiótico.
- O utente referiu não tomar nenhuma outra medicação, não ter problemas gástricos e nem hipersensibilidade às penicilinas, cefalosporinas ou outros beta-lactâmicos.

Após a explicação de como fazer a medicação, o utente saiu da farmácia confiante de que conseguiria fazê-lo bem. Para além dos dois medicamentos da receita médica, o utente também adquiriu as compressas estéreis para fazer a limpeza da ferida como recomendado pelo médico. Não tive a oportunidade de fazer o acompanhamento do doente após este aconselhamento, era uma pessoa que estava apenas de passagem pela cidade.

Caso Prático 4

Uma senhora dirigiu-se à farmácia com o objetivo de comprar um produto de dermocosmética que a ajudasse com as recentes borbulhas que apareceram no rosto. Revelou ter 39 anos, que a questão hormonal está bem controlada e monitorizada pelo seu médico de família e que nunca tinha tido problemas de pele.

O aconselhamento prestado nesse caso foi:

- Primeiramente, perguntei à senhora relativamente aos seus hábitos de limpeza na pele do rosto, uma vez que a sujidade é uma das principais causas para o aparecimento de pústulas, as tais "borbulhas", no rosto. A resposta à pergunta foi que ela não tinha essa preocupação e lavava o rosto apenas com água quando tomava banho.
- Ao questionar sobre o tipo de pele da senhora, obtive a resposta de que ela não tinha pele oleosa, mas estava num processo de obras em casa e, neste momento, vivia num ambiente com muito pó. Expliquei, portanto, que esse pó poderia estar ficando acumulado na pele e bloqueando a saída da oleosidade natural dos folículos pilosos, resultando numa inflamação local.
- A utente revelou não ter quaisquer sintomas indicativos de alergias ao pó das obras, Como prurido ou dificuldade em respirar.
- O primeiro passo para evitar que aparecessem novas lesões inflamatórias seria a lavagem regular da pele com um produto específico. Como ela não tem pele oleosa, recomendei que utilizasse um gel de limpeza suave para o rosto duas vezes ao dia para

remover impurezas e os resíduos de células mortas da superfície da epiderme de forma suave, de forma a também não provocar o ressecamento.

- Como ela aparentava estar incomodada com a "borbulha", também lhe recomendei que utilizasse um produto de cuidado específico sobre ela que fosse à base de ácido salicílico, um beta-hidroxiácido lipossolúvel, porque a faria sumir mais rapidamente.
- Ressaltei, por fim, que os cuidados com a pele devem ser complementados com hidratação e fotoproteção.

A senhora pareceu satisfeita com as recomendações, dizendo que não havia associado que as reformas em casa poderiam ter sido a causa dessa questão. Comprometeu-se em ter mais atenção com a pele e adquiriu os produtos recomendados da marca Bioderma®, que era a de sua preferência, com exceção do protetor solar, que disse já ter em casa.

Caso Prático 5

Um senhor, aparentado ter cerca de 60-70 anos, pede algum xarope para a tosse, referindo que está com muita expectoração e dor na garganta.

O aconselhamento prestado nesse caso foi:

- Antes de selecionar o xarope, fiz perguntas para compreender o contexto clínico: o senhor era diabético e referiu não apresentar patologia ulcerosa péptica.
- Sendo assim, aconselhei a toma de Fluimucil® 40 mg/ml solução oral, uma vez que é composto pelo agente expectorante acetilcisteína e não contém sacarose na sua composição[7].
- Como o produto é fluidificante do muco, era preciso tomar bastante água para auxiliar na expulsão das secreções da mucosa respiratória. Alertei que era esperado aumento da expectoração e da tosse durante o início do tratamento[7].
- O senhor deveria tomar o xarope até aos 15 dias que sucedem a abertura do frasco, na posologia recomendada de 15 ml diários, numa única toma ou dividido em três tomas de 5 ml[7].
- Para as dores na garganta aconselhei a toma das pastilhas Strepsils® sabor morango sem açúcar, que contém álcool diclorobenzílico 1,2 mg e amilmetacresol 0,6 mg na composição. Essas pastilhas teriam ação antisséptica e analgésica local. O senhor poderia tomar uma pastilha a cada 2-3 horas, mas sem exceder as 12 diárias[8].
- Referi que era preciso observar a garganta para ver se não apareciam placas esbranquiçadas, uma vez que poderia ser sinal de infeção. Para além disso, se as dores

na garganta persistissem por 2-3 semanas ou piorassem, seria preciso verificar com o médico de família alguma causa subjacente.

O senhor era utente habitual da farmácia e, ao retornar à farmácia para sua habitual medição da glicémia, tive a oportunidade de lhe perguntar se a tosse havia melhorado. O senhor disse que a tosse havia melhorado em cerca de 5 dias com o xarope e ainda tinha sobrado algumas pastilhas na caixa de 16 unidades.

4. Conclusão

Com o fim do Estágio Curricular em Farmácia Comunitária, pude compreender o caráter fundamental desta etapa na minha formação académica. Ainda que relativamente curto, esse período forneceu uma bagagem profissional que me permitiu aperfeiçoar os conhecimentos teóricos e sociais, de modo a entrar no mundo profissional apta a enfrentar as principais adversidades intrínsecas ao setor.

É imensurável o quanto a Farmácia Coimbra contribuiu para o meu amadurecimento como farmacêutica. Este estágio não só me permitiu elucidar como ocorre o funcionamento prático de uma farmácia para além da literatura, mas também exigiu o meu máximo empenho para contribuir com a saúde e bem-estar das pessoas que me cruzaram o caminho. Levo desta experiência, que finalizou meu percurso no MICF, exemplos e inspirações da profissional que ambiciono ser.

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Parte II

Relatório de Estágio em Assuntos Regulamentares

OWL
PHARMA CONSULTING

Abreviaturas

AIM – Autorização de Introdução no Mercado

AR – Assuntos Regulamentares

CNMI – Congresso Nacional de Medicina Interna

CSI – *Core Safety Information*

DADI – *Digital Application Dataset Integration*

DCP – Procedimento Descentralizado

EMA – Agência Europeia do Medicamento

FV – Farmacovigilância

MedDRA – *Medical Dictionary for Regulatory Activities*

MRP – Procedimento de Reconhecimento Mútuo

QRD – *Quality Review of Documents*

SOP – *Standard Operating Procedures*

SPOR – *Substance, Product, Organisation and Referentials*

SWOT – *Strenghs, Weaknesses, Opportunities and Threats*

1. Introdução

Estudar Ciências Farmacêuticas implica a aquisição de conhecimentos globalizados e generalizados sobre a saúde e de seus intervenientes, o que o torna capacitado para executar quaisquer tarefas a eles relacionadas[1]. Da mesma forma que esse aspecto é positivo por dar margem a grande variedade de saídas profissionais, também pode ser um obstáculo, devido à baixa especificidade do profissional recém-formado. O fato de haver a oportunidade de realizar um estágio ao fim do curso, especialmente um que difira do habitual em farmácia comunitária, permite que uma pessoa com inclinação a outras áreas de atuação do farmacêutico possa se assegurar da sua ambição profissional e desenvolver alguma habilidade mais específica.

Sendo do meu interesse a área de Assuntos Regulamentares (AR), optei pela realização de um estágio curricular que me pusesse em contato com o contexto real de uma empresa especializada nesse serviço, como é o caso da Owlpharma – Consulting Lda. Com essa oportunidade, pude verificar como o farmacêutico que trabalha na área de AR é fundamental como intermediário nos pontos críticos do ciclo de vida do medicamento, desde sua concepção e produção até a fase pós-comercialização, de modo a garantir que os requisitos estão sendo sempre em conformidade com a legislação aplicável e não há desvios de qualidade[2].

O presente relatório de estágio em Assuntos Regulamentares foi realizado no âmbito da unidade curricular Estágio Curricular, no período de 05 de maio e 31 junho de 2023, na Owlpharma – Consulting Lda., empresa de consultoria farmacêutica com sede em Coimbra, no departamento de AR, sob orientação da Dra. Ana Margarida Andrade. A elaboração do relatório assenta numa análise SWOT, que compreende a descrição e análise das tarefas realizadas e os conhecimentos adquiridos aquando da sua realização. A análise SWOT engloba as *Strengths* (Forças), *Weaknesses* (Fraquezas), *Opportunities* (Oportunidades) e *Threats* (Ameaças) que me deparei ao longo do tempo como estagiária (Tabela I)[3].

2. Consultoria Farmacêutica

Fundada em 2013 na incubadora do Instituto Pedro Nunes e, atualmente com escritórios localizados em Coimbra e Lisboa, a Owlpharma é uma empresa que fornece consultoria farmacêutica à indústria farmacêutica, quer a nível nacional quer internacional, tanto no que toca a medicamentos, quanto a produtos cosméticos, dispositivos médicos e suplementos alimentares. A organização interna da Owlpharma é estruturada por 5

departamentos: Assuntos Regulamentares, Farmacovigilância, Garantia de Qualidade, Médico e Científico e Auditorias, que são cooperativos entre si.

Trata-se de uma empresa em crescimento contínuo, que foi distinguida em 2019, 2020 e 2021 pelo prêmio Gazela, concedido pela Comissão de Coordenação e Desenvolvimento Regional do Centro às empresas com menos de 5 anos de criação que já conseguem demonstrar prosperidade. Essa gratificação foi um dos resultados da competência da empresa, que é focada no atendimento às necessidades emergentes dos seus clientes e na valorização de seus colaboradores[4].

3. Análise SWOT

Tabela 1 – Análise SWOT dos pontos observados durante o período de estágio curricular.

Forças	**Fraquezas**
• Integração numa equipa jovem e dinâmica • Diversidade das tarefas realizadas • Processos e procedimentos determinados por SOPs	• Imprevisibilidade da carga de trabalho diária • Eventuais falências informáticas
Oportunidades	**Ameaças**
• Possibilidade de participar de projetos relevantes • Desenvolvimento de habilidades com ferramentas informáticas • Conhecimento e prática linguística (inglês) • Formação e treinamento contínuo • Introdução no mercado de trabalho	• Tempo curto de estágio

3.1 Forças

- Integração numa equipa jovem, dinâmica e competente

Já nos primeiros dias, a minha orientadora de estágio (Ana Margarida Andrade) me apresentou as instalações da empresa e à equipa, tanto a que estava presente no escritório quanto a que se encontrava em teletrabalho, através de uma videoconferência do departamento de AR. Esta ação favoreceu a que eu me sentisse integrada à equipa e estivesse mais confortável a me dirigir a alguém caso de dúvidas, que foram sempre prontamente atendidas.

- Diversidade das tarefas realizadas

Sendo a base do trabalho de uma consultora o atendimento à necessidade dos clientes, a gama de tarefas a serem realizadas é muito diversa, permitindo o ganho de conhecimento mais abrangente.

No contexto de AR, desempenhei as seguintes tarefas: traduções inglês-português de textos de informação do produto (Resumo das Características do Medicamento, Folheto Informativo e Rotulagem) segundo o template *Quality Review of Documents* (QRD) atualmente em vigor; preparação de formulários e *cover letters* para a submissão de alterações aos termos de Autorização de Introdução no Mercado (AIM) ao INFARMED, I. P.; comparações de Core Safety Information (CSI) de diversos medicamentos; criação e atualização de bases de dados no projeto *Digital Application Dataset Integration* (DADI) prevista pela Agência Europeia do Medicamento (EMA) para entrar em vigor em 2023/2024. Para além disso, também tive a oportunidade de cooperar com a equipa de Farmacovigilância (FV) na análise dos *hits* presentes nos artigos apresentados no Congresso Nacional de Medicina Interna (CNMI) de 2023.

Todas essas tarefas permitiram adquirir conhecimentos sobre as áreas de AR e FV propriamente ditas, mas também de desenvolver competências a nível do conhecimento de ferramentas informáticas e gestão de tempo e prioridades.

- Processos e procedimentos determinados por SOPs

A empresa é sustentada por um Sistema de Garantia de Qualidade (SGQ), no qual os processos e procedimentos são determinados por *Standard Operating Procedures* (SOPs). As SOPs são documentos escritos que irão indicar exatamente como executar as atividades da rotina, o que garante que a empresa entrega resultados consistentes e de qualidade aos seus clientes. Considero como um ponto forte da empresa, uma vez que a padronização dos processos minimiza a chance de erros durante sua execução e não deixa margem para confusão ou interpretações.

3.2 Fraquezas

- Imprevisibilidade da carga de trabalho diária

Como a carga de trabalho está dependente das demandas dos clientes da Owlpharma, esta torna-se imprevisível. Há momentos com sobrecarga de tarefas e outros em que é mais fácil a gestão das tarefas a realizar, instigando o desenvolvimento da gestão de prioridades e

proatividade aquando da execução das tarefas. Como esta foi a origem de uma dificuldade que experienciei no início do estágio, considero-a um ponto fraco.

- Eventuais falências informáticas

Alguns dos projetos em que estive envolvida eram dependentes da consulta de informação em bases de dados informáticas como Infomed, *Medical Dictionary for Regulatory Activities* (MedDRA), EUDRA-GMP e *Substance, Product, Organisation and Referentials* (SPOR), que por vezes ficam temporariamente inacessíveis. Embora seja um fator externo à empresa, este constitui um ponto fraco na medida em que acaba diminuindo a produtividade ou impedindo a execução de algumas tarefas.

3.3 Oportunidades

- Possibilidade de participar de projetos relevantes

Durante o tempo de estágio, tive a oportunidade de integrar um projeto baseado na SPOR *master data*, gerido pela EMA. O projeto SPOR-DADI, consiste na criação de uma base de dados que reúne as principais informações de todos os produtos do portifólio de um dos clientes da Owlpharma, organizando-as de modo a serem enviadas para a EMA e sustentarem a submissão de novos pedidos de alteração aos termos da AIM[5]. Foi um trabalho muito moroso, mas que me permitiu ter acesso a documentação relevante e diversificada para analisar e, também, aprimorar as competências no programa informático Excel.

- Formação e treinamento contínuo

A especialização dos colaboradores é muito valorizada na Owlpharma, sendo a eles proporcionado um protocolo de formação e treinamento. Como estagiária, fiz as formações de "Alterações aos termos da AIM – Procedimentos Nacional, Descentralizado (DCP) e Reconhecimento Mútuo (MRP)"; "Preparação da documentação do módulo 3 no formato CTD"; "Preparação da informação do produto: RCM, FI e ROT"; "Publicidade de medicamentos"; "Avaliação da segurança de produtos cosméticos"; "Formação inicial em farmacovigilância". Essas formações foram, sem dúvidas, cruciais para a boa execução das tarefas propostas durante o estágio, especialmente no que toca à autonomia e ao pensamento crítico.

- Introdução no mercado de trabalho

A oportunidade de um estágio em AR é uma porta de entrada ao mercado de trabalho nesta área da profissão farmacêutica. O conhecimento prático através da tentativa e erro gera conhecimentos para além dos que poderiam ser obtidos na faculdade e, também, sentido de minuciosidade e atenção ao detalhe. Dessa forma, considero o estágio como uma oportunidade para quem tem ambição de seguir carreira em AR, como no meu caso pessoal.

- Conhecimento e prática linguística (inglês)

A prática de AR requer a análise e interpretação de muita documentação em inglês devido a muitas bases de dados estarem disponíveis apenas nessa língua ou para permitir a comunicação universal entre os clientes, para além dos trabalhos de tradução. A necessidade de praticar a língua em contexto profissional foi uma oportunidade de aperfeiçoamento e aprimoração do idioma.

3.4 Ameaças

- Tempo curto de estágio

Embora seja diferenciador a oportunidade de fazer um estágio em AR, sinto que 3 meses de experiência ainda é pouco para capacitar um profissional desta área. Tratando-se de um trabalho rigoroso, detalhado e pouco abordado no plano curricular do curso de ciências farmacêuticas, considero que o tempo de estágio curricular, unicamente, é curto para estar confiante no próprio trabalho, autônoma e tão qualificada quanto o restante da equipa.

4. Conclusão

A experiência que ganhei durante o período de estágio foi extremamente valiosa para mim como futura profissional na área de Assuntos Regulamentares. O contacto com pessoas qualificadas e o conhecimento da metodologia de trabalho contribuiu para a aquisição de competências práticas, teóricas e pessoais que dificilmente seriam desenvolvidas de outra maneira. Ao fim deste estágio, nutro sentimento de gratidão à Faculdade de Farmácia da Universidade de Coimbra pela oportunidade de realizá-lo ao fim do curso e, principalmente, à equipa da Owlpharma pela disponibilidade, atenção prestada, transmissão de conhecimentos e exemplo de profissionalismo.

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Parte III

Monografia

"*Safety assessment of cosmetic products: a comprehensive approach of the regulatory affairs to promote the identification of gaps*"

Safety assessment of cosmetic products: a comprehensive approach of the regulatory affairs to promote the identification of gaps

Abstract

Authorities have increasingly legislated cosmetic products, especially at the European level. Since 2013, when the Cosmetic Regulation came into force, cosmetic products have been subject to even higher quality requirements than under the preceding 1976 legislation. The core goal of the implementation of this regulatory framework is to ensure the safety of consumers using cosmetic products for any intended purpose. In practice, however, there are still some gaps to be addressed in the regulation, and thus there is still scope for more efficient protection of human and environmental health. Considering the aforementioned, this work aims to provide an overview of the current Cosmetics Regulation, highlighting the weakest cornerstones that represent the missing link keeping the core objective to being achieved. The reliance on data obtained from the currently banned animal studies for the safety assessment, the lack of appreciation of environmental concerns, the preoccupation not to restrict manufacturers' access to the market and the flawed surveillance system are some of the factors that favor the placing and maintaining of hazardous cosmetic products on the European market. Legally non-compliant – or perhaps compliant but unknowingly dangerous – products may be used by people who relativize them as inherently safe, leading to adverse events. Whether caused by an underlying disease or purely by the chemical's toxicity, these may never come to the attention of the authorities as they are generally under-reported, making it unfeasible to implement corrective or preventive measures to address their root cause. To illustrate, non-compliant products that have been detected by the Portuguese authority INFARMED, I. P. from January 2018 to August 2023 are mentioned, which were found to be potentially dangerous to human health and, therefore, withdrawn from the market.

Keywords

Cosmetic regulation; safety assessment; cosmetovigilance; quality defects; regulatory affairs; animal testing.

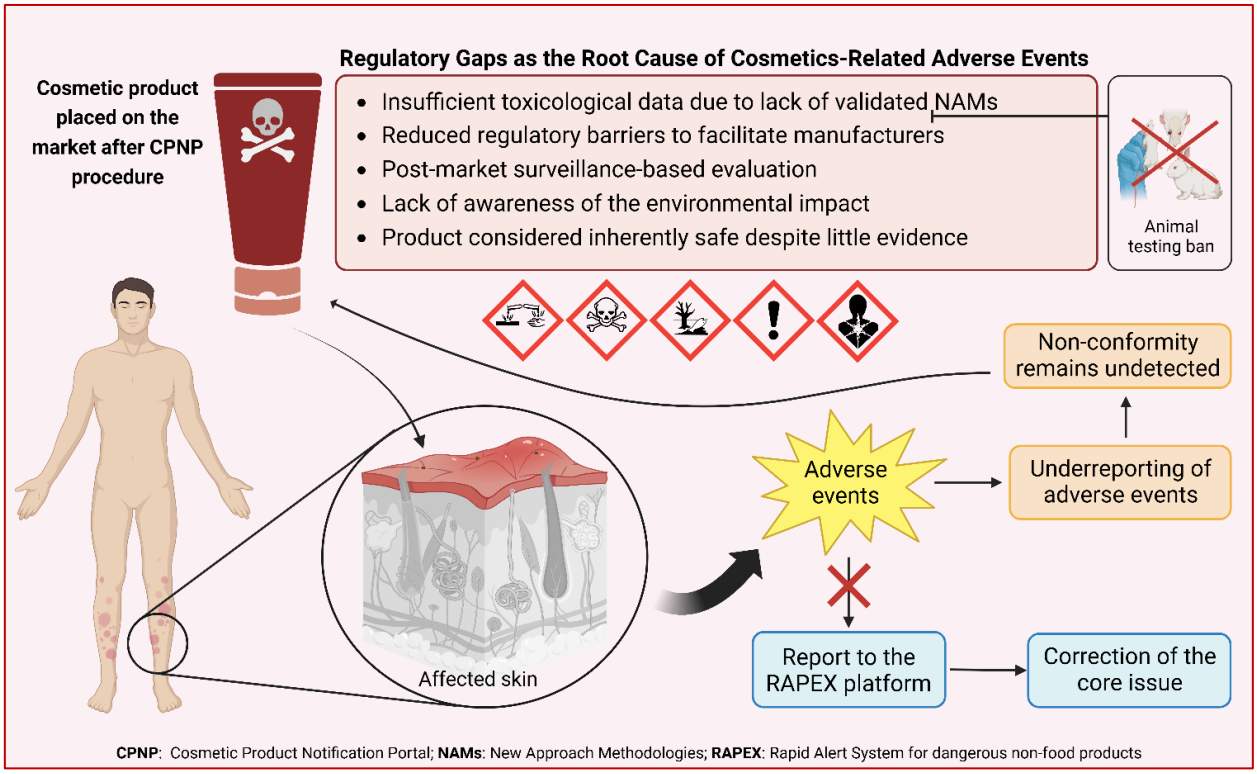
Resumo

As autoridades têm legislado cada vez mais sobre os produtos cosméticos, especialmente a nível europeu. Desde 2013, ano em que entrou em vigor o Regulamento dos Cosméticos, os produtos cosméticos estão sujeitos a requisitos de qualidade ainda mais elevados do que na legislação anterior, de 1976. O principal objetivo da implementação deste quadro regulamentar é garantir a segurança dos consumidores que utilizam produtos cosméticos, seja qual for o fim pretendido. Na prática, porém, ainda há algumas lacunas a colmatar no regulamento, pelo que ainda há margem para uma proteção mais eficaz da saúde humana e do ambiente. Face o exposto, este trabalho tem como objetivo fornecer uma visão geral do atual Regulamento dos Cosméticos, destacando as fragilidades que representam aquilo que falta para que o objetivo principal seja alcançado. A dependência de dados obtidos a partir de estudos em animais atualmente proibidos para a avaliação da segurança, a falta de apreciação das questões ambientais, a preocupação em não restringir o acesso dos produtores ao mercado e o sistema de vigilância defeituoso são alguns dos fatores que favorecem a colocação e manutenção de produtos cosméticos nocivos no mercado europeu. Os produtos não conformes com a legislação - ou talvez conformes, mas desconhecidamente perigosos - poderão ser utilizados por pessoas que os relativizam como inerentemente seguros, conduzindo a eventos adversos. Quer sejam causados por uma doença subjacente ou puramente pela toxicidade do produto químico, estes podem nunca chegar ao conhecimento das autoridades, uma vez que são generalizadamente subnotificados, tornando impraticável a implementação de medidas corretivas ou preventivas para combater a sua causa raiz. Para ilustrar, são mencionados os produtos não conformes que foram detetados pela autoridade portuguesa INFARMED, I. P. de janeiro de 2018 a agosto de 2023, que foram considerados potencialmente perigosos para a saúde humana e, por conseguinte, retirados do mercado.

Palavras-chave

Regulamento dos cosméticos; avaliação da segurança; cosmetovigilância; defeitos de qualidade; assuntos regulamentares; ensaios em animais.

Graphical Abstract



Abbreviations

CA – Competent Authority

CLP – Regulation on the Classification, Labelling and Packaging of substances and mixtures

CMR – Carcinogenic, Mutagenic, or Toxic for Reproduction

CPG – Consumer Packaged Good

CPNP – Cosmetic Product Notification Portal

CPSR – Cosmetic Product Safety Report

CR – Cosmetic Regulation

EMA – European Medicines Agency

EU – European Union

GMP – Good Manufacturing Practices

INCI – International Nomenclature of Cosmetic Ingredients

MoS – Margin of Safety

MS – Member State

NAM – New Approach Methodology

NOAEL – No Observed Adverse Effect Level

NoG – Notes of Guidance

PBT – Persistent, Bioaccumulative and Toxic

PIF – Product Information File

PoD – Point of Departure

QSAR – Quantitative Structure Activity Relationship

RA – Read-across

RP – Responsible Person

SC – Stratum Corneum

SCCS – Scientific Committee on Consumer Safety

SED – Systemic Exposure Dosage

TTC – Threshold of Toxicological Concern

UV – Ultraviolet

vPvB – Very Persistent and Very Bioaccumulative (vPvB)

1. Introduction

Cosmetic products result from the inclusion of cosmetic active ingredients in a vehicle that ensures the chemical, physical and microbiological stability to enable cleansing, protection, beautification and/or odor correction[2]. For the most diverse functions, the growing demand for the category leads to the development and implementation of new technologies, increasingly based on specialized scientific knowledge. It is estimated that currently the global cosmetics industry market already exceeds hundreds of billions of dollars [3; 4].

Formulation strategies in cosmetology prioritize meeting the new market trends, which lately have included more attention to skin care, sustainability, social beauty, customizability, and safety[5]. However, the claims made by the products, the marketing strategies, as well as the formulation itself are not always in accordance with what is pleaded by the Competent Authorities (CA)[6]. The distinguishing features between products acceptable to be placed on the market and those that cannot be sold due to safety or ethical concerns are well specified and harmonized within the European Union[2; 6], especially when compared to other countries on other continents[4].

The European method for the registration of cosmetics on the market, the applicable legislation and the cosmetovigilance system are primarily aimed at protecting public health against the risks associated with exposure to formulations considered as hazardous[2]. Although this system has evolved since the beginning of its development, it still reveals some gaps that hinder complete protection. These gaps are particularly visible in the assessment of adverse events whose causality can be attributed to the use of cosmetic products, individually or in combination, and their subsequent relationship with cases of non-compliance by manufacturers that led to their withdrawal from the market.

Originally conceived as preparations to enhance personal appearance through direct application to the skin, cosmetics have now taken on a new role in dermatology by supporting the management of many skin conditions. With the improved understanding of skin physiology and the development of technological advances in cosmetology science, it is now better known that cosmetics could change the aesthetic appearance and the well-being of the skin. As will be illustrated further, such category of products can alleviate discomforts caused by dermatological diseases, improve quality of life and self-esteem, and prevent diseases that may ultimately evolve into serious outcomes. Cosmetic formulations, for whichever purpose, are tailored to the consumer regarding their individual profile, such as age, tendency to have

sensitive skin, skin type and condition, and underlying dermatological issues. It is therefore justified that these products should be regulated with some stringency by the CAs to establish the quality criteria and ensure that they will not cause harm to human health if used correctly[7].

2. Cosmetics social relevance and impact on Human Health

The skin is considered the mirror of the soul[8], being seen socially as the symbol of a person's emotional and psychological behavior, representing physical and mental well-being[3; 9; 10]. In addition, people with attractive faces often receive positive personality attributions and receive special treatment in a variety of contexts. Beauty activates reward centers in the brain, motivating sexual behavior and the development of interpersonal alliances[11]. In the opposite scenario, the visibility of skin alterations can be a triggering factor for judgments and stigmatization, contributing to social exclusion and isolation of patients experiencing it due to feelings of shame and/or fear of discrimination[10].

Presenting beautiful skin is therefore one of the goals of a large part of the population, who are willing to invest in whatever promises this result: preventive measures, invasive procedures, topical and systemic therapeutic agents and, most commonly, cosmetic products[9]. Cosmetics and body care products are often the most accessible option for the public, and generally the safest. Although they have no systemic activity to treat diseases[2], these products can have a significant impact on the health of those who use them correctly, namely by providing comfort, reducing the need to take certain medications, or even preventing diseases. In the presence of certain pathologies, dermocosmetic adjuvant therapy can be a key factor in successful treatment[7].

2.1 Skin cancer

One of many examples of the importance of cosmetic products is the short- and medium-term benefits on the quality of life of cancer patients. Possibly all systemic cytotoxic therapies for cancer treatment accompany dermatological toxicity, with modifications to the skin, hair, and nails, which can be mitigated with cosmetic products[12; 13]. Typical reactions include folliculitis (rash), xerosis, pruritus, erythema of the hands and feet and an increased photosensitivity, possibly leading to dose reductions and treatment discontinuations[13]. Beyond the physical, these adverse effects can lead to psychosocial distress associated with appearance. Beauty care, such as the application of makeup, has been shown to reduce symptoms of depression and anxiety in cancer patients in the long-term, since the perception of self-image and self-esteem improves considerably[14].

Not only can dermocosmetics be positive for patients who already suffer from it, but it is also important in preventing the early onset of some types of cancer[15; 16; 17; 18]. Ultraviolet A (UVA) radiation (340-400 nm) plays an important role in the development of photodermatoses and hyperpigmentation, while ultraviolet B (UVB) radiation (200-290 nm) participates in the process of sunburn, cellular DNA damage and the development of skin cancer[15]. Although it is not possible to prevent them completely, evidence shows that the incidence of skin cancer is significantly reduced in the population that regularly uses photoprotection. The influence of radiation on skin carcinogenicity is evident in both melanomas and non-melanomas, such as keratinocyte cancers, basal cell carcinomas, and squamous cell carcinomas[15; 16; 18], mainly due to the cell mutagenicity of the rays penetrating the skin and their immunosuppressive effect, which prevents the natural immune defense against tumor growth[15; 17].

As the main motivation for people to use sunscreens is the prevention of sunburn, they tend to underestimate the risks and preventability of skin cancer, using the product only when they are in the context of excessive sun exposure, rather than daily. Furthermore, due to melanin's ability to attenuate radiation transmittance and protect the deeper layers of the skin, this problem is even more common in dark-skinned people[16]. A third explanation for the popular devaluation of the regular use of photoprotective methods is the belief that this habit would threaten healthy serum vitamin D levels[15], but this assumption is unfounded[15; 17]. Although solar UVB radiation is the major source of vitamin D, studies have concluded that sunscreen use has minimal influence on the body's vitamin D status[17].

Sunscreens are therefore cosmetic products that, despite having no systemic effects – although some percutaneous absorption of sunscreen ingredients has been observed[15] – can be of considerable interest in the prevention of serious oncological diseases[15; 16; 17; 18].

2.2 Dermatoses: Acne, Atopic Dermatitis, Seborrheic Dermatitis

Acne vulgaris, one of the most common dermatological diseases in the world [19], is an example of the relevant applicability of dermocosmetics[20]. Acne is a chronic inflammatory and immune-mediated disease of the pilosebaceous units, which manifests as lesions on the skin, either of inflammatory (papules, pustules, or nodules) or non-inflammatory (comedones) genesis, to be treated topically or systemically. When the disease has progressed to its more severe forms, pharmacological treatment is needed. There are, however, many pharmacological treatments available that cause dysfunctions in the integrity of the epidermal

barrier, with consequent increased transepidermal water loss, depletion of cutaneous vitamin C levels, inflammation, and reduced thickness of the stratum corneum[20; 21]. Depending on its genesis and severity, the therapy targeting the physiopathology of acne usually combines aggressive actives, such as hydroxy acids, antibiotics, tretinoins and/or benzoyl peroxide[19]. Topical application of benzoyl peroxide, for instance, should be alternated with retinoids[19; 22] because of its side effects: erythema, itching and burning sensation on the skin, which can be a reason to discontinue the treatment[21; 22]. A proper skincare routine that includes cleansing, moisturizing and photoprotection helps alleviate these effects, bring greater comfort and compliance to treatment[20; 21]. Acne-targeted cosmetic products include cleansing agents for oily or sensitive skin, sebaceous secretion regulators, anti-inflammatory actives, moisturizers, and sunscreen, both to manage the condition and for maintenance therapy[20]. In addition to the intrinsic distress caused by skin sensitization in such a context, there is another underlying complication: the prevalence of acne is associated with lowered appearance-related satisfaction, self-esteem, and self-confidence[20; 23], increased anxiety and depression issues[23; 24] and increased incidence of suicidal ideation, especially among adults [23].

Many epidemiological studies suggest that the prevalence of sensitive skin has increased over the years, although this analysis has some subjective bias considering differences in nationality, gender, and age. In any case, although of unknown cause, many factors can be triggers for uncomfortable sensations of sensibilization on the skin: physical factors (UV rays, heat, cold, wind), chemical (cosmetics, soaps, water, and pollutants), and sometimes hormonal or psychological factors. Besides acne, there are other dermatoses related to sensitive skin, including atopic dermatitis and seborrheic dermatitis.[25].

As a chronic inflammatory skin disease with cycles of remission and relapses, atopic dermatitis is characterized by scaly, pruritic, erythematous lesions located on flexural surfaces[26]. These manifestations are the result of dysfunctions in the structure and function of the stratum corneum, which has its physical barrier function against the environment, allergens, and pathogens impaired[27]. A person's risk of atopic dermatitis has been shown to be related to mutations in the gene encoding filaggrin, a protein that aggregates intermediate keratin filaments, which is also associated with immune dysregulation[26; 27]. Because skin lesions can cause impactful discomfort on an individual's quality of life, rebuilding its barrier function is essential. Pharmacological treatment with topical application of corticosteroids and calcineurin inhibitors is reserved for moderate to severe manifestations of the disease, with first-line treatment being the maintenance care through dermocosmetics[26]. Cosmetic care can prevent allergies, reduce the incidence of infections, ease the discomfort caused by sensitive

skin, and increase the interval between relapses. Atopic skin displays reduced natural moisturizing factors, as well as an imbalanced lipid matrix - mainly composed of cholesterol, free fatty acids, and ceramides - resulting, therefore, in a very pronounced transepidermal water loss. Evidence shows that the use of soap-free, dye-free, and fragrance-free cleansers[26] and emollient or occlusive moisturizers are effective in retaining skin moisture and reducing the need for pharmacological therapy[26; 27].

Dandruff and its more serious manifestation, seborrheic dermatitis, are also dermatoses that, although not curable, need an appropriate cosmetic approach[28]. This condition is triggered by the excessive proliferation of the fungus *Malassezia globosa*, which will produce active metabolites responsible for the hydrolysis of the triglycerides in sebum. The released free fatty acids lead, in susceptible individuals, to inflammatory reactions, epidermal hyperproliferation and disruption of the skin barrier, resulting in pruritus, erythema, skin flaking and dryness. If left unmanaged, it can cause a significant degree of discomfort for individuals with the condition[29; 30]. In addition to physical discomfort, seborrheic dermatitis has negative impacts on quality of life due to psychological distress and the tendency to instigate low self-esteem[30]. People with seborrheic dermatitis should not use all kinds of cosmetics, as some, such as oils/comedogenic ingredients, can worsen the condition. To treat the disease, there are topical drugs formulated as shampoos whose composition includes non-steroidal anti-inflammatory agents and antifungals, but there are also non-pharmacological alternatives: cosmetic products with nicotinamide in low concentrations, vitamin E and hyaluronic acid are to be considered in the seborrheic dermatitis management[28].

2.3 Infectious Diseases

One of the ways in which bacterial, viral, fungal, and parasitological infections are prevented from spreading is frequent and effective hand washing. The use of soaps and water is recommended above other types of non-cosmetic hand sanitizers, both those that are alcohol-based and those with other antimicrobial agents, such as benzalkonium chloride. The advantage of hand washing is a result of various factors, such as the elimination of a wider spectrum of pathogens and chemicals, and the removal of the bioburden on dirty hands[31]. During the COVID-19 pandemic, the frequency of hand washing was increased in an attempt to interrupt the chains of transmission in direct and indirect contact, thereby infecting fewer people. Although justified, such excessive washing can induce hand dryness and disruption of the skin barrier, resulting in more vulnerable skin for pathogens to penetrate[32; 33]. Since soap removes the hydrolipidic barrier involved in preventing transepidermal water loss, the lack of

adequate hydration of the SC will affect the elasticity of the skin and cause structural changes in the epidermis, making it appropriate to use a moisturizer[33]. Furthermore, studies show that people who wash their hands with soap regularly and after contact with excreta are less likely to get diarrhea due to a lower incidence of enteric infections, compared to those who wash only with water[34; 35; 36]. Soaps, even though they are classified as cosmetic products, are fundamental for the maintenance of human health due to the property of emulsifying skin impurities and contaminants into smaller particles, allowing them to be detached and then removed from the skin surface[37].

2.4 Oral Diseases

Bacterial colonization of the dental tissues results in the accumulation of supragingival plaque, which culminates in the initiation of gingivitis. If not controlled, this condition can evolve into periodontitis, which is an inflammatory infection leading to the destruction of the teeth-supporting apparatus[38; 39; 40]. Multiple studies have shown that periodontal disease is associated with negative impacts on the quality of life of those affected, including regarding their esthetic appearance, proportionally to the severity of the disease[39; 40]. When periodontitis is in advanced stages, the therapeutic approach includes antibiotics, tooth mineralizing agents, tooth extraction procedures, treatment of any subsequent caries and/or other adjunctive therapies for example laser therapy. These outcomes are serious, requiring regular maintenance care and attention to avoid recurrence[40]. The foundation for the prevention of this condition is the regular brushing and flossing of teeth, with the aid of cosmetic dental hygiene products [38].

2.5 Other conditions

In addition to the previously mentioned, there are several other conditions in which the use of cosmetics can be beneficial, highlighting them as being important elements for human health. Discomfort and chronic itching may be manifested by other inflammatory and/or autoimmune dermatological diseases besides atopic and seborrheic dermatitis, including psoriasis, pemphigus vulgaris, dermatitis herpetiformis dermatomyositis, morphea and vitiligo. In these cases, due to the negative impact on the quality of life, administration of an antipruritic therapy may be justified[41]: although systemic therapy with oral medications may be appropriate, the foundation of pruritus management is the application of daily moisturizers, especially the ones containing urea, glycerol, propylene glycol and lactic acid as active ingredients[41; 42].

The use of cosmetics is not only valid in situations of illness, esthetic dermatology with emotional benefits is also relevant. Anti-aging treatments, aiming to achieve healthy, smooth, blemish-free, translucent, and resilient skin, are increasingly the subject of specialized studies. Skincare, sun protection, topical use of selected active ingredients, such as antioxidants and retinoids, and lifestyle choices are proving to be more and more effective in preventing the formation of wrinkles and age spots[43].

3. Regulatory Framework for Cosmetics in Europe

Aiming to guarantee safety and quality, the European CA established a set of standardized norms that outlines the threshold of acceptability for cosmetic products to be placed on the market within the European Union. The main requirements and definitions are mentioned in Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of November 30, 2009 on cosmetic products – also called the Cosmetics Regulation (CR) – which entered into force on July 11, 2013, replacing the obsolete Council Directive 76/768/EC of July 27, 1976. The primary points of the legislation are the following:

- Cosmetics products are defined as "*any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours*".

- Manufacturers are required to conduct a safety assessment for each cosmetic product to predict any potential risks to human health arising from its use. It is required that they maintain a Product Information File (PIF) containing the relevant data consistent with the most recent scientific information available, which must be kept for a period of 10 years after the latest batch of the product has been marketed.

- Manufacturers must comply with the Good Manufacturing Practices (GMP) for cosmetics to ensure the quality, safety, and stability of cosmetic products throughout their production, packaging, storage, and distribution. To demonstrate compliance with GMPs, one way is through ISO 22716:2007 certification.

- Before the product is placed on the market, manufacturers are required to notify the responsible authority. The notification is a charge-free procedure and is submitted via the Cosmetic Product Notification Portal (CPNP). It allows relevant product information to

be available electronically to CAs for market surveillance, market analysis, review, and consumer information purposes. Once notified on the portal, there is no need for periodic renewals or additional steps at the national level of any of the European countries. There is no specific timetable for it, only being specified in the CR that it should be prior to placing the product on the market - unless it contains nanomaterials, in which case it needs to be at least 6 months in advance.

- Products must be traceable within the supply chain.
- Manufacturers and distributors have a responsibility to report adverse events caused by their cosmetic products.
- In line with the prohibition of animal testing, the CR proposes alternative testing methods and encourages their implementation.
- The notion of a Responsible Person (RP) is developed as the person within the EU who is committed to ensuring compliance with all obligations mentioned in the legislation and acts as a point of contact for the authorities for each product placed on the market.
- The competent authorities undertake market surveillance actions to ensure compliance with the mentioned legislation.
- Annexes to the regulation, usually updated once a year:

    i. Minimum information to be mentioned in the Cosmetic Product Safety Report (CPSR). The CPSR is a part of the PIF written by the qualified person designated as a safety assessor, who will ensure the safety of the product under normal and reasonably foreseeable conditions of use. It is divided into two parts: the relevant information about the cosmetic product (part A) and the conclusion of the safety assessor based on part A (part B).

    ii. Substances that have been prohibited for being considered unsafe for use in cosmetics by the Scientific Committee on Consumer Safety (SCCS).

    iii. Restricted substances, in the sense that they can be included only under conditions set regarding concentration and mandatory labelling.

    iv. List of authorized colorants.

v. List of authorized preservatives.

vi. List of authorized UV filters.

vii. Labeling requirements: cosmetics should be labeled in a designated form, containing the composition in descending order of concentration and in the International Nomenclature of Cosmetic Ingredients (INCI), the presence of nanomaterials, the batch number, the date of minimum durability and RP contact information.

viii. Mention and description of the validated approaches to replace animal testing in safety assessments.

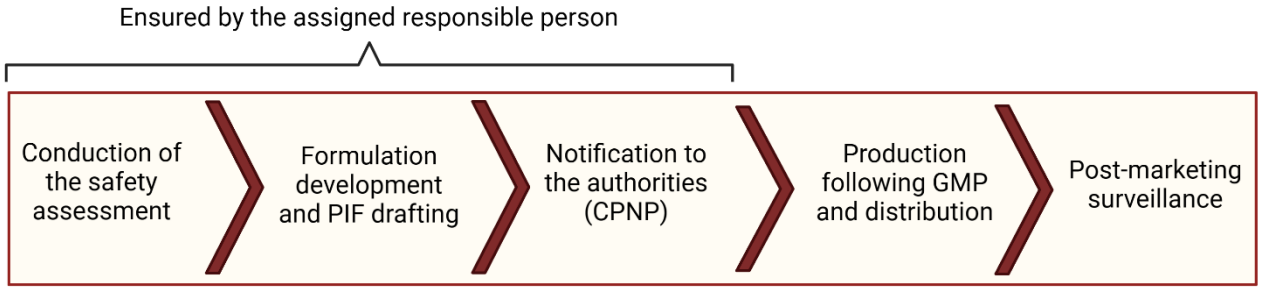


Figure 1 – Schematic representation of the requirements for the placing of cosmetic products on the market in the European Union under Regulation (EC) No. 1223/2009.

4. Safety Evaluation of Cosmetic Ingredients

The European regulatory framework for cosmetic products requires a safety evaluation to be performed prior to its placing on the market. Cosmetic product safety is established by assessing the toxicological profile of each of the ingredients in the formulation, both independently and in combination with the others[44]. The cosmetic formulation, in general, is a compilation of chemical compounds in direct contact with the skin and mucous membranes, which can be absorbed to some extent through the dermis[45]. By controlling which substances are used, their chemical structures, toxicological profiles, and exposure patterns, it is possible to manage the overall safety of cosmetic products circulating in Europe. It is particularly important to consider the long-term picture, since these are products used extensively throughout an individual's lifetime, including those with easily sensitized skin[44].

The Scientific Committee on Consumer Safety (SCCS) is the organization responsible for advice on the ingredients listed in the Annexes of the CR, on which the assessment is based. The main function of the experts on this committee is to provide technical advice on policies and proposals relating to health and chemical, biological, mechanical, or physical

hazards associated with non-food consumer goods or services, such as cosmetic and body care products. The SCCS Notes of Guidance (NoG) for the Testing of Cosmetic Ingredients and their Safety Evaluation is a document that aims to provide practical support for the preparation of the PIF in accordance with the requirements of the CR, namely the description of the proper methods for assessing the risk of chemicals and the provision of updated scientific information. It is to be noted that this guide may be subject to revision based on scientific advances in toxicology, validated alternative methods, or changes in legislation, for which the periodicity is undetermined[44].

The process of risk assessment, in general, can be outlined in four major steps (see Figure 2)[46; 47; 48; 49]:

a. Hazard identification: research of the intrinsic properties of substances to uncover what adverse effects they may cause, through epidemiological, clinical, *in vivo*, *in vitro*, *in silico*, physicochemical and literature studies.

b. Dose-response assessment: to establish the relationship between the dose and the incidence and severity of the adverse effect by determining the No Observable Adverse Effect Level (NOAEL).

c. Exposure assessment: determination of which amount of the substance will be in contact with the human body and for which duration, resulting in the calculation of the Systemic Exposure Dosage (SED).

d. Risk characterization: A probability of occurrence of harm converted into a value of Margin of Safety (MoS), including uncertainty analysis.

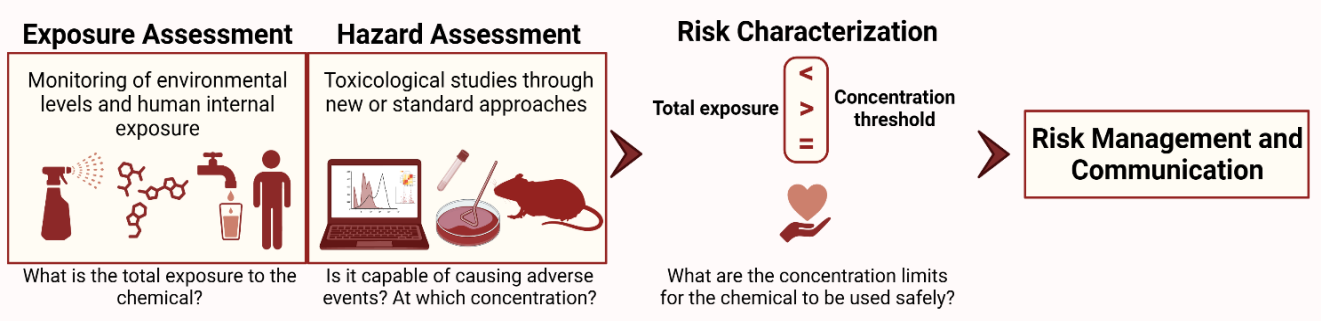


Figure 2 – Steps of risk management of cosmetic ingredients.

Traditional toxicological studies have used animal models to investigate the effects of chemicals on the metabolism of living organisms. Following the ongoing ecological trend, as

well as encouraged by REACH Regulation (EC) No 1907/2006, chemical risk assessment has been transitioned in the EU to be handled through alternative and innovative *in silico* or *in vitro* methods, known as the New Approach Methodologies (NAMs)[46; 50; 51; 52]. The CR defines as prohibited, since 2013, the marketing of cosmetic products that have been or contain ingredients tested on animals[2], regardless of the availability of satisfactory alternative resources for the toxicological evaluation of these formulations[53]. The technical difficulties relate mainly to repeated-dose toxicity, reproductive toxicity, and toxicokinetics, for which there are no alternatives yet defined[2; 46; 47]. Given that this information is necessary for the assessment of cosmetics, it is imperative to develop improved methods based on non-animal models that will ensure equal or better safety[47; 53]. The *in vitro* tests currently accepted by regulatory agencies concern skin sensitization, and skin irritation and corrosivity, eye damage and eye irritation[46; 50; 52]. There is, therefore, a lack of alternative means for performing the required studies of acute toxicity, dermal absorption, sub-chronic toxicity (such as 90-day oral toxicity in rats, NOAEL, repeated use toxicity), DNA damage, phototoxicity and photomutagenicity, human data, reproductive toxicity, and carcinogenicity[44] (see Figure 3). If repeated use toxicity data are not included in the submission of a new cosmetic ingredient to the SCCS, it is considered that the risk assessment of the compound in question is not viable[44].

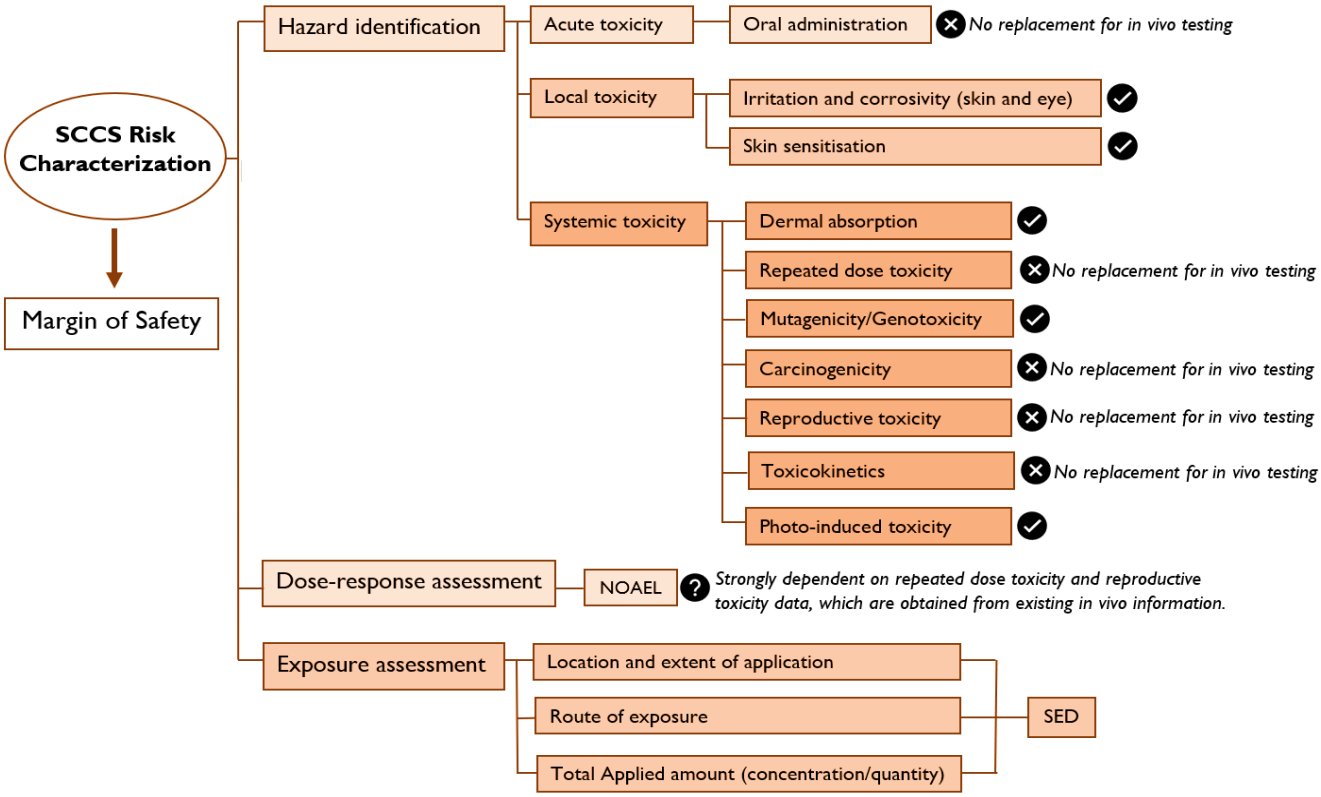


Figure 3 – Schematic representation of the current reliance on animal testing in risk assessment.

One of the *in silico* tools under investigation is the Threshold of Toxicological Concern (TTC), which establishes a maximum exposure value below which a given chemical would have negligible impact on human health, based on existing toxicological information from known substances (see Figure 4). The TTC then relies on consolidated toxicological data from various classes of chemicals for the prediction of the minimum exposure that would cause adverse effects in humans. This approach was considered scientifically acceptable by the SCCS for cosmetics, but should not be generally used for all ingredients, as these should be evaluated on a case-by-case basis[53]. When the TTC is not possible, studies suggest the application of a 10-step read-across (RAX), which consists of using relevant information from analogous substances to predict the properties of a test substance. In other words, a health reference value would be calculated for that substance by adjusting the toxicokinetics of another substance that has animal toxicity data and is similar in chemical structure, physicochemical properties, or biological activity[54]. Both *in silico* NAMs mentioned remain dependent on animal research data, which represents a barrier to the safety assessment of novel ingredients. Extrapolation of *in vitro* data to *in vivo* and variability between species may be at the root of potential mistakes that could escalate to human health impacts[53; 54].

Another relevant method for chemical evaluation is Quantitative Structure Activity Relationship (QSAR), which is an *in silico* method that mathematically relates the similarity between chemical structures (see Figure 4). In this way, it is possible to predict the toxicity and biological effects of a given chemical under study by comparing it with another that is already known, supposing they would have the same activity *in vivo*. This tool, however, does not have SCCS regulatory acceptance. The drawback of this method is that the lack of a structural alert does not mean that the chemical is guaranteed to be non-toxic; it could simply indicate a knowledge gap[47].

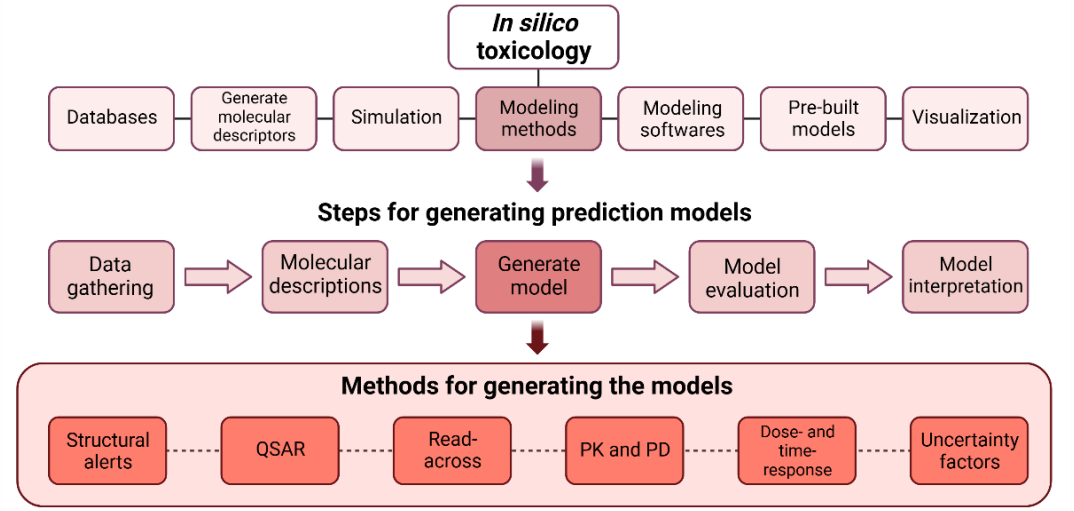


Figure 4 – *In silico* toxicology tools, steps to generate prediction models, and categories of prediction models (adapted from [55]).

The cosmetics industry perceives as a marketing opportunity the use of ingredients not mentioned in the annexes, as there is no evidence that they will be unsafe, as opposed to others that have a well-established toxicological profile. If there is any endpoint that cannot be tested, it will be at fault, which does not prevent the safety assessment of the ingredient[47; 56]. These ingredients may, however, be unknown allergens and pose a risk[47]. Some ingredients are controversial such as parabens – extensively used and known preservatives – which tend to be replaced by less controversial yet less tested and possibly unknowingly unsafe alternatives[57].

4.1 Carcinogenic, Mutagenic or Reprotoxic Ingredients and Other Special Concerns

There are ingredients that raise a special concern over human health (notably fragrances, colorants, preservatives, and UV-filters)[58], mainly in relation to the potential endocrine disrupting or Carcinogenic, Mutagenic and/or Reprotoxic (CMR) effect they may have. Article 15 of Regulation (EC) No 1223/200911 establishes that the use in cosmetic products of substances that have been classified as CMR substances of category 1A (confirmed effects), category 1B (claimed effects) or category 2 (suspected effects) in Part 3 of Annex VI to Regulation (EC) No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP) is prohibited, unless evaluated and found safe by the SCCS[2; 59]. This classification is based on the overall exposure an individual will have to the substance – including in cosmetics, chemicals, food, and medicines and can undergo changes over time[59].

The human exposure to the chemicals in the formulation is calculated taking into consideration the stated function of the cosmetic product according to the location and extent of application, the normal and reasonably foreseeable route of exposure and the target population, along with the estimated daily applied amount, considering the quantity applied, frequency of use and retention factor. Skin corrosion, for example, is a non-expectable property for a cosmetic product, unless it is due to production error or misuse by the consumer. In contrast, an ingredient that has the intrinsic quality of corrosion is not necessarily excluded from being formulated in cosmetics: it will all depend on its final concentration and overall context[2; 44].

Except for CMR ingredients, the evaluation of the concern only considers the use in the respective cosmetic product, although the exposure may be increased when considering chemicals present in non-cosmetic products, such as the ones used for cleaning purposes[44].

Another concern to be taken into consideration is the cocktail effect: the synergistic potential between substances that interact when applied simultaneously, and the additive effect, which refers to increased exposure to a particular ingredient because it is present in multiple products, leading to a higher probability of an unexpected toxicity[60].

In addition to being classified as potential CMRs, cosmetic ingredients can also be classified as sensitizers or non-sensitizers. The subcategory, which would classify them according to sensitizing potency is only possible if there is sufficient data for it, which is determined by animal testing - usually by murine local lymph node assay. Currently, there is no single NAM that can provide this information. Multiple methods need to be integrated to assess the mechanisms of toxicity and reflect the ability of the substance to induce allergic contact dermatitis and inflammatory responses[61].

4.2 The Need for a Case-by-Case Study

During the recent years, much progress has been made in the development and validation of alternative methods for the testing of chemicals in the context of cosmetic products. Despite these efforts, these tests are currently best defined for risk identification in the context of local toxicity and short-term testing. This means that to obtain quantitative information regarding systemic toxicity, risk potency or long-term effects, the methodology is still highly dependent on the results of animal testing. Without such data, the systemic NOAEL information is lacking and, consequently, it will be impossible to calculate the MoS, resulting in incomplete safety information[47]. It is to be noted that, in the context of cosmetics, the use of safety data obtained in territories outside the European Union is prohibited, according to the REACH regulation[51].

Therefore, it is not clear from the legislation exactly how to proceed in these cases, which causes serious problems for the safety assessment of new cosmetic products or new cosmetic ingredients. The practical interpretation of the regulation by the SCCS adapts it by excluding the need for cosmetics to have this complete information unless there is a need to verify the risks of occupational exposure – in these cases, there is increased potential hazard, as in the example of nail and hair salon workers[62]. The approach suggested by the SCCS is phased, but still emphasizes that a case-by-case study of all the data obtained is necessary to have a critical view of the applicability of the alternative methods. This approach involves the integration of different strategies, which implies the need to, besides the individual validation,

establish the relationship between them and comprehensively validate the study model, in order to be accepted by the regulatory organizations and considered effective [52; 63]

Although there is no data requirement for absorption, distribution, metabolization and excretion of cosmetic ingredients in most cases, these are relevant for the extrapolation of *in vivo* and *in vitro* findings to humans. In the case of systemic exposure via sprays, aerosols and products that contact the oral mucosa, there are some suggested approaches from the SCCS, but no formally validated methods. Currently, dermal absorption of 50% is considered for all substances included in the annexes of the CR in the scope of the calculation of the margin of safety[44].

4.3 Environmental Concern

The chemical safety assessment also includes the environmental hazard assessment and the assessment of persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) risks[51]. This assessment is not required for cosmetic ingredients in the European Union[44], although some could have an important environmental impact, such as some UV filters[64].

An important example is Benzophenone-3, a widespread cosmetic ingredient that raises special safety concerns. Compounds of the benzophenone group have bioaccumulation properties and thus can be detectable in aquatic environments and in the organism of animals higher up the food chain. One possibility that might be overlooked, but should not be dismissed, is human exposure to the substance through ingestion of water or contaminated fish. In addition to the increased exposure to humans, the aquatic ecosystem might also be harmed by inducing adverse effects on animal and vegetal species, and therefore threatening ecological safety[65; 66; 67].

The link between UV filters and coral bleaching and damage to marine life has been increasingly studied and documented. The loss of color in corals is a result of the loss of zooxanthellae (*Symbiodinium spp*), which are algae that are resident within coral polyps and support marine life (see Figure 5) – thus coral bleaching has detrimental impacts throughout the ecosystem[64].

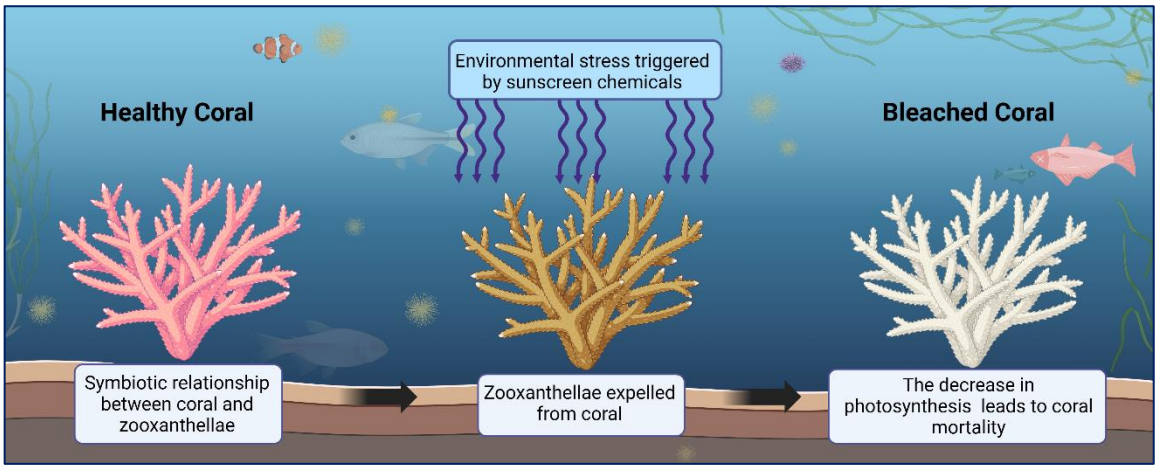


Figure 5 – The link between coral bleaching and ocean pollution with sunscreen ingredients.

5. Market Surveillance and Cosmetovigilance

Member States (MS) should not deny, prohibit, or restrict the availability of cosmetic products on the market if they are compliant with the requirements of the CR, as mentioned in article 9. The exception to this rule is determined in article 27: the MS may temporarily and immediately withdraw from the market a product believed to be responsible for serious risks to human health, informing the other MS and the European Commission of the reasons thereof[2].

Cosmetics, being classified as Consumer-Packaged Goods (CPGs), deal with a very competitive market and limited shelf space. Moreover, factors such as territorial supply constraints and regulatory barriers play an important role in the fragmentation of the European single market concept, hindering the economic prosperity of stakeholders[68]. Intending to attenuate this impact, the CPGs are regulated by an in-market control system, rather than by pre-market approval procedures. Cosmetic products, therefore, do not undergo a prior rigorous analysis by the authorities to confirm that the minimum quality parameters have been fulfilled[2; 47], like those performed for the administrative authorizations issued for medicines[69].

The current regulatory framework only requires that the RP guarantees compliance with the legislation and that the respective product is notified on the CPNP platform, which raises an issue: there is a margin for potentially health-damaging products to be sold indiscriminately without consumers or the authorities being aware of the threat. Penalties may be issued to the RP if the requirements are not properly met, but there is no guarantee that those are being identified. There is no filter external to the manufacturers that will eliminate non-compliant products, all products will be regularized independently[2; 47].

Although the structuring of the standards for the Cosmetic Regulation has been carried out at a centralized level by the European Medicines Agency (EMA), they are not responsible for their execution and supervision. The checking task is delegated to the MS in which the product is registered. As stated in article 22, the authorities of each European Member State carry out the market surveillance actions they deem appropriate to supervise the finished products already placed on the market, attempting to find possible quality defects[2]. They typically do so through suspicions triggered by consumer complaints, inspection activities to ensure the principles of good manufacturing practices, and laboratory control actions based on adequate samples, but these operations are not harmonized.

The CR states that cosmetic products must not cause harm to human health when used under normal or reasonably foreseeable conditions[2]. As with any pharmaceutical product, however, in spite of their safety and tolerability, they can lead to unexpected undesirable effects in the short or long term, even if they comply with all the requirements set by the authorities[70; 71; 72; 73]. Regulation (EC) No 765/2008 of the European Parliament and of the Council of July 9, 2008, foresees the need for collaboration between MS, as well as the possibility of enforcement actions in case of non-compliance verified in market surveillance activities. Serious safety issues regarding the use or misuse of a product require rapid intervention, which may involve withdrawing the product, recalling it, or prohibiting it from being made available on the market. In those situations, it is necessary to have access to a system of rapid exchange of information between Member States and the Commission[74; 75].

For medicinal products, a pharmacovigilance system is implemented, backed by three pillars: a national system for reporting suspected adverse reactions and providing information on medicinal products; a system for detecting and analyzing signals; a system for communicating safety information to the public that is considered relevant for risk minimization[70]. Similarly, but far less developed, a cosmetovigilance system for cosmetic products surveillance is available in Europe, to assure public health[71].

5.1 RAPEX Platform

Under article 12 of the Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 – also known as the General Product Safety Directive – there is mention of the Rapid Alert System for dangerous non-food products (RAPEX) for the improvement of market surveillance activities including the risk assessment, testing of products, exchange of expertise and scientific knowledge, execution of joint surveillance

projects and interventions[75], which has proved its effectiveness and efficiency[74]. The main objective of RAPEX is to involve Member States and the European Union actively in the reporting of products posing a serious risk for the consumer and sending additional notifications about the outcome in response to the initial notifications[76; 77].

This cosmetovigilance system, however, has some limitations to overcome. The number of notifications submitted is highly variable depending on the reporting country, influenced by several factors: in addition to market size and import volumes, historical differences in risk assessment perception and population awareness play an important role[77]. The notifications of adverse events, when carried out by users on their own initiative, are proportional to the degree of knowledge of the population about the detection of the signs of adverse events and awareness of the reporting platforms, which might not be intuitive[78]. Undesirable effects attributable to cosmetics are generally under-reported[71; 72], and can include distressing symptoms (see Figure 6) [25; 73; 79; 80].

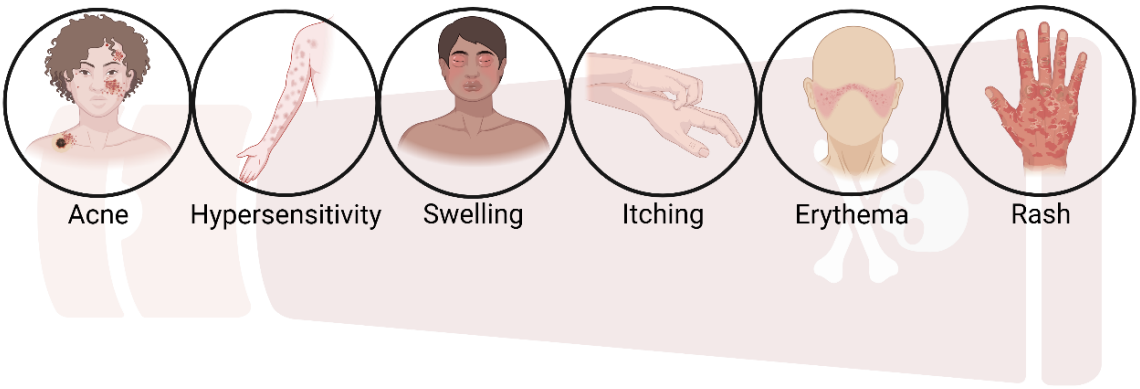


Figure 6 – Some clinical manifestations of sensitized skin that may be associated with the use of cosmetics and qualify as an adverse event.

Moreover, even when identifying the adverse reaction, users often intuitively discontinue the use of the product, thereby removing the cause without going through any adverse effect reporting procedure. Hence, RAPEX is unable to operate to its full potential, since its core function encompasses bringing unexpected negative outcomes of products to light and thus taking appropriate measures, either by analyzing the cause and/or by restricting the marketing of the product[72; 81]. When appropriate, corrective measures and the dissemination of information should be undertaken to reduce the likelihood of the recurrence of a serious undesirable effect, aiming at the protection of the health and safety of cosmetics users[2].

6. Revision of the Safety Information for Cosmetic Ingredients

For a substance characterized as CMR category 1A or 1B to be formulated as a cosmetic ingredient, it must be considered safe following a safety assessment performed by the SCCS[59]. This opinion is not permanent and may be subject to modification as new scientific evidence is made available to the public, while the market will need to adapt to the new guidelines.

6.1 From Widely Available to Prohibited

Butylphenyl Methylpropional, also known as Lilial, is a substance that was very commonly used as an intense floral fragrance in cosmetics, regulated by Annex III of the CR, i.e., it was part of the list of ingredients that could be incorporated if it complied with the concentration limits and mentions described[2]. Although one of the most frequently found in cosmetic products, this fragrance already had a well-known sensitizing potential and was listed as a contact allergen by the SCCS[82; 83]. New studies showed, however, signs of possible reproductive toxicity and endocrine disruptive effects[83]. Acute toxicity studies in various routes of application (oral, dermal, intraperitoneal and inhalation), however, showed signs of systemic toxicity in rats, mice, and rabbits, including by inhalation. Irritation of the skin, eyes and respiratory mucosa of the animals studied were also reported as consequence of exposure to Lilial. Aspects such as mutagenicity and carcinogenicity could not be conclusively answered, but adverse effects on the reproductive system of rats were consistently reported in repeated dose toxicity studies and in reproductive toxicity studies. These studies were submitted to the SCCS, which gave an unfavorable opinion on the ingredient[84]. Moreover, this ingredient was not only used in cosmetic products: it was also occurring in household cleaning products, which may result in a higher aggregate exposure than initially anticipated resulting in a higher likelihood of toxicity reactions[60; 85]. While Lilial was once considered safe in individual products, it is now banned, as it is prevalent for the same consumer to use simultaneously several formulations containing it[85]. Its prohibition due to being classified as toxic to reproduction (CMR 1B) therefore means its deletion from Annex III of the CR and inclusion in Annex II, relating to prohibited substances[2; 86]. The outcome, on a practical note, was the immediate suspension of the marketing of these cosmetics. Any entities that still provide them should not market them, and any consumers who still own these products should not use them[84; 86]. This new scientific information was based on numerous animal tests[84], which are now banned for cosmetic purposes[2]. Data on acute toxicity, referring to the side effects observed after dermal, oral or inhalation exposure to one or multiple doses of the substance[59], are not mandatory

for the safety assessment, as there are no NAMs for such an evaluation[44]. The need for a reconsideration of the hazard of Lilial could be a consequence of the lack of prior studies being performed.

As with Lilial, products containing Zinc Pyrithione were banned from being marketed after the ingredient was classified as CMR 1B by the SCCS. Previously, Zinc Pyrithione was often formulated as a preservative in rinse-off products, being regulated by Annex V of the CR, and as an anti-dandruff active ingredient in rinse-off hair products, being regulated by Annex III. The SCCS opinion for this ingredient resulted in the same outcome, but for a different reason: it was not established that there were no safer alternatives, and therefore the alternatives should be prioritized[86]. It is, however, relevant to critically consider the safety of these substitutes, as there are few advantages to public health if they are considered safer solely because of being less extensively tested. Zinc Pyrithione is well studied, being discovered in the late 1950s as an effective antifungal agent for the relief of the discomfort caused by the overgrowth of the scalp fungus, in the context of dandruff and seborrheic dermatitis[29].

Although Regulation (EC) No. 1223/2009 has been amended accordingly, in practice non-compliance is observed for many brands installed on the market. As an example, the Portuguese CA, INFARMED, I. P., carried out market surveillance actions in the year following the ban on the use of Buthylphenyl Methylpropional and Zinc Pyrithione (2022) which detected many irregularities. Attempting to alert the population and reduce potential harm, the authority issued circulars to bring this situation to light, stating that these were products considered unsafe by the SCCS87-102. Similarly, other examples of products identified as non-compliant following market surveillance actions are listed in Annex 1, comprising cases reported by INFARMED, I.P. between 2018 and June 2023. These products have fortunately been identified and have been recalled to meet the requirements of the authorities, however, it is unclear whether all irregularities have been spotted. The majority of those that were, featured formulations containing banned or undeclared allergen ingredients and misclassification as a cosmetic product.

6.2 Specific Cases of Permitted although Restricted Substances

Annex III of the CR mentions specifically the substances that could be included in cosmetic formulations if they follow specific requirements[2]. Mandatory labeling and concentration thresholds for the corresponding intended use are part of the requirements, as

the inclusion in this Annex is justified due to the dose-dependent toxicity of that ingredient or the potential to induce adverse events[60].

Methyl salicylate (methyl 2-hydroxybenzoate) is a fragrance that, since it is found in multiple cosmetic and cleaning products, can lead to toxicity reactions through aggregate exposure. This ingredient, which was already known to be a skin sensitizer and eye irritant[103] but not previously mentioned in the regulation, was considered CMR 2 by the SCCS in 2021[86; 104; 105]. This considers the information available on salicylic acid, since methyl salicylate is its metabolite and is significantly absorbed through dermal application, to an extent dependent on the carrier of the product. Such an exposure could cause harm to human health through the endocrine disruption and reproductive toxicity potential of salicylic acid[104]. It was then established by the SCCS that the chemical would be safe for use in cosmetic formulations as a preservative up to a maximum concentration of 0.5%, and for non-preservative uses to a maximum concentration of 3.0% for cosmetic rinse-off hair products, 2.0% for non-cosmetic use in other product types except for body lotion, eye shadow, mascara, eyeliner, lipstick and roll-on deodorant applications, which are limited to salicylic concentrations up to 0.5%. Thereby, the exposure to salicylic acid remains low and it is generally believed that there would be no important risks[104; 105].

Another example of safe substances with restrictions is UV filters, however these are not regulated by Annex III: the allowed UV filters are described in Annex VI of the CR[2]. Benzophenone-3 is a UV-absorbing chemical widely present in non-mineral sunscreens and is generally accepted by the public. Exposure to this compound, however, raises concerns over its endocrine disruptive potential and CMR, particularly due to evidence of high systemic absorption[66; 67; 106]. These concerns, as well as dose-dependent neurotoxicity, have been demonstrated through several studies, with the toxic impact varying depending on the substituents of the benzophenone chemical structure[66]. A systematic review involving older studies had, however, shown that current evidence does not strongly support a causal relationship between systemic Benzophenone-3 level and adverse health outcomes in humans[67], not to exclude the environmental harm [65; 66; 67]. The SCCS reassessment of the safety of Benzophenone-3 has determined in 2021 that its formulation in cosmetic products is safe, but at a lower concentration than previously approved. This restriction was established after concluding that there was a potential risk to human health from the use of this substance at the previously approved concentrations[106; 107]. SCCS, in its assessment, does not address environmental aspects[107], which could possibly change the perspective on the safety and restrictions to be imposed for this ingredient. Given the frequency of application required for

the prevention of skin cancer[15; 16; 18], it is assumed that exposure to the ingredients of sunscreens will be substantial, so it is appropriate that an extensive analysis of their safety is conducted, preferably staying on the side of caution.

7. Final remarks

The regulatory framework for cosmetic products is not as strict as that for other pharmaceutical products in many regards. Firstly, to be placed on the market, no prior assessment of the product is required, a notification on the CPNP portal is sufficient. Such a pre-market assessment could restrict the commercialization of the products, constituting a barrier to industries in an extremely competitive market of fast-moving consumer goods, so there are efforts by the authorities to prevent this from happening.

Furthermore, the surveillance of cosmetic products that have reached the market easily is ineffective and not very stringent. Consequently, non-compliance can remain undetected for a time sufficiently long to the point of causing unpredictable effects on consumers that could have been avoided. If more samples of more products were tested and inspected, more non-compliant products would be detected, and more interventions, either preventive or corrective measures, would be conducted.

Assuming that a product fully complies with the requirements imposed by the CR, there is no way to be certain that it will be safe for consumption. The safety assessment, even if performed precisely as defined by the SCCS, may lack toxicological information. The replacement of animal testing by NAMs was implemented before it was well enough developed to have regulatory acceptance on all endpoints. Instead, multiple assays need to be analyzed together, and evaluated on a case-by-case basis, to reach a conclusion about the safety of the ingredient. Also, it may not be possible to disclose the full information, as some criteria are still dependent on the data obtained from animal studies.

In the light of this lack of rigor, there is scope for many adverse events to occur with a sizeable percentage of users. These adverse events, however, are under-reported to the responsible authorities, making it easier for them to remain unidentified for longer and not bring to the surface the consequences of regulatory gaps. Furthermore, there is only provision for reporting serious events, keeping alive the possibility that non-serious events will perhaps never be analyzed. In a way, the lack of regulatory rigidity in the cosmetics industry, together with the absence of perception of the seriousness of the problem, ends up nurturing a cyclical

relationship that does not do justice to the importance and social impact that cosmetics have in sustaining people's health and well-being (see Figure 6).

Even though the legislation envisages ways of safeguarding the consumers, what can be seen in practice is somewhat different. In addition to the issues that are not covered by the regulation, some aspects don't operate to their full potential, putting CAs even further away from achieving the end goal of consumer protection (summarized in Table I).

Table I – Demonstration of regulatory gaps, comparing what is foreseen in the European regulation and what occurs in practice.

Expected	Reality
The RP holds a record of the CSR and the PIF demonstrating the product is safe by conducting a proper safety assessment.	Non-compliance with this requirement is unlikely to be detected.
Only products that are safe under normal and reasonably foreseeable conditions of use are present on the market.	Possible intentional overlooking by authorities to avoid harming industries or sales.
Guidelines issued by the SCCS to guide the testing of cosmetic ingredients and their safety evaluation.	There is a need for the SCCS to also give a practical interpretation of the guidelines, as it is hardly feasible to comply with all the proposed requirements.
Market surveillance actions undertaken by the regulatory authority of the MS to detect non-compliant products.	The non-standardized approach to market surveillance renders it ineffective.
For ethical and ecological reasons, the testing of cosmetic products and ingredients on animals is banned, being replaced by NAMs.	NAMs have regulatory acceptance on a limited number of endpoints and are not available for all risk assessment criteria. Safety information, especially involving new cosmetic ingredients, often remains incomplete.
Risk assessment is based on the concept of safe dose, establishing an ideal MoS.	The wider the knowledge gap, the more inaccurate the MoS calculation gets.
The SCCS regularly updates the safety information of cosmetic ingredients.	The SCCS re-evaluation has no defined periodicity and often involves animal studies.
The cosmetovigilance system is designed to protect the health of cosmetic product users by monitoring adverse events that may occur post-marketing.	Adverse events are under-reported, keeping the cosmetic surveillance system from working at its most optimal efficiency.

8. Conclusion

Given the function and area of application, the intrinsic risks of exposure are indeed considerably lower for cosmetic products than for pharmaceuticals, but still are not to be dismissed. They are chemical substances formulated into a product to come into contact with the skin and mucous membranes in potentially vulnerable and injured states, so they could have a systemic impact. The inclusion of prohibited substances in the formulation, misclassification of a product as a cosmetic and the overall non-compliance, as the examples presented in Annex 1, can be hazardous to human health and, therefore, deserve careful attention. It is possible that some dermatological adverse events associated with cosmetic products could have been avoided if authorities were more stringent in their implementation and monitoring of the regulation, and through efforts to address the safety assessment gaps, especially to cover all toxicological endpoints, and improve the cosmetovigilance system.

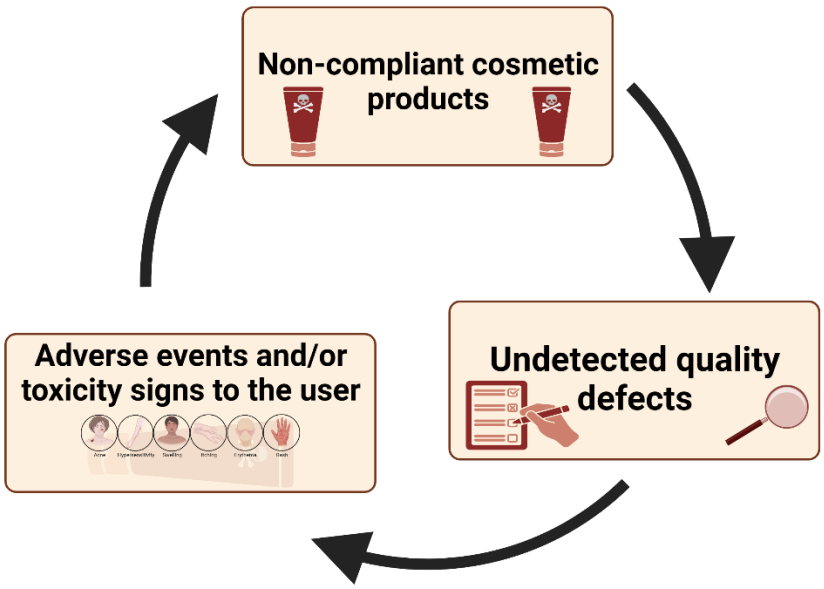


Figure 7 – Cyclic relationship linking regulatory gaps.

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Annex I

Examples of INFARMED, I. P. alerts regarding cosmetic products following market surveillance actions in the last 5 years (2018-2023).

Informative Circular N.º	Date (DD/MM/YYYY)	Title	Alert
083/CD/100.20.200	17/08/2023	Immediate suspension of marketing and withdrawal from the national market of all batches of Cannabiron CBD cream and Good Cannabis cream.	Contains prohibited ingredient (Cannabidiol)
035/CD/100.20.200	27/04/2023	Immediate suspension of marketing and withdrawal from the domestic market of all batches of the product Curcurinna Gel.	Misclassification as a cosmetic product and ingredient concentration above the threshold (methyl salicylate)
008/CD/100.20.200	19/01/2023	Immediate suspension of the commercialization and withdrawal from the national market of cosmetic products distributed by L'Oréal that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
131/CD/100.20.200	11/11/2022	Immediate suspension of marketing and withdrawal from the national market of all batches of all cosmetic products of the MANUBELA brand.	Non-compliance with the Regulation
108/CD/100.20.200	15/09/2022	Immediate suspension of the commercialization and withdrawal from the national market of lots of cosmetic products of the brand CIEN that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
096/CD/100.20.200	16/08/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brand A Nova Saboaria that have in the list of ingredients and/or in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
088/CD/100.20.200	01/08/2022	Immediate suspension of the commercialization and withdrawal from the national market of cosmetic products of the brand CNTENDENCE that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
082/CD/100.20.200	15/07/2022	Immediate suspension of the commercialization and withdrawal from the national market of cosmetic products of the brand ATL that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)

084/CD/100.20.200	15/07/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products marketed by the company RickiParodi - Moda e Acessórios Profissionais, S.A that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
081/CD/100.20.200	15/07/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brand Salon Line, whose Responsible Person is the company GPH - Laboratory Services, Lda. and which have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
074/CD/100.20.200	01/07/2022	Immediate suspension of the commercialization and withdrawal from the national market of cosmetic products of the brand Lola Cosmetics that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
066/CD/100.20.200	22/06/2022	Immediate suspension of the commercialization and withdrawal from the national market of cosmetic products of the brand Novex that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
050/CD/100.20.200	17/05/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brand Real Natura marketed by the company Real Natura, Lda. that have in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
049/CD/100.20.200	17/05/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brand Endocare, marketed by the company, IFC SKINCARE PORTUGAL - Produtos Dermatológicos, Unipessoal, Lda. which contain in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
048/CD/100.20.200	17/05/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brand VOIR marketed by the company Riscas Importantes, Lda. which contain in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
044/CD/100.20.200	11/05/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brand Gota Dourada that contain in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)

042/CD/100.20.200	04/05/2022	Immediate suspension of marketing and withdrawal from the national market of cosmetic products of the brands Real Natura, Salon Line and Gota Dourada, marketed by the company Pluricosmética S.A. that contain in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
041/CD/100.20.200	04/05/2022	Immediate suspension of the marketing and withdrawal from the national market of cosmetic products of the brand LADVANCE that contain in their composition the ingredient Butylphenyl Methylpropional.	Contains prohibited ingredient (Butylphenyl Methylpropional)
025/CD/550.20.001	23/02/2021	RAPEX Alert: Fructis by Garnier Hair Food - Shampoos and Conditioners*.	Need for corrective measures aimed at reducing the risk of ingestion
177/CD/550.20.001	19/11/2020	Voluntary withdrawal of the product Deliplus CATAPUM arnica stick.	Misclassification as a cosmetic product
035/CD/550.20.001	31/01/2020	Withdrawal from the market of the cosmetic product - Savon Gommant Exfoliating Soap of the brand Fair & White.	Contains prohibited ingredient (Mercury)
034/CD/550.20.001	31/01/2020	Withdrawal from the market of the cosmetic product - Lait AHA-2 of the brand Fair & White.	Contains prohibited ingrediente (Mercury)
033/CD/550.20.001	31/01/2020	Withdrawal from the market of the cosmetic product - Ultra moisturising body cream of the brand Fair & White.	Contains prohibited ingredient (Mercury)
160/CD/550.20.001	23/10/2019	Voluntary recall of sunscreen "Fotoprotector Isdin Pediatrics Transparent Spray Wet Skin SPF 50+.	Inconsistencies in SPF analysis
146/CD/550.20.001	03/10/2019	Voluntary recall of cosmetic products "Primer Water Watermelon" and "Primer Water Charcoal" from the Primark brand.	Microbial contamination leading to risk of infection
141/CD/550.20.001	12/09/2019	Immediate suspension of marketing and withdrawal from the market of the cosmetic product "D' Aveia Regenerador de Mamilos".	Contains prohibited ingredient (Triclosan)
068/CD/550.20.001	01/04/2019	Withdrawal of PaintGlow's Neon Eye Mascara from the market.	Contains prohibited ingredients (Butylparaben, Solvent Yellow 172, CI 45161, CI 45174, CI 74260)
063/CD/550.20.001	15/03/2019	Withdrawal from the market of the perfume EDP 100ml STREET LOOKS Ciao Babe.	Contains undeclared allergen ingredients (fragrances)

032/CD/100.20.200	08/02/2019	Herbal medicines wrongly classified as cosmetics.	Misclassification as a cosmetic product
163/CD/550.20.001	23/11/2018	Withdrawal from the market of batches of the cosmetic product Basiderma skin paste.	Contains prohibited ingredients (Methylchloroisothiazolinone, Methylisothiazolinone)
160/CD/550.20.001	14/11/2018	Withdrawal of the product AdniKid Gel Stick Bruises, Bumps, Swellings 15 g.	Misclassification as a cosmetic product
152/CD/550.20.001	19/10/2018	Withdrawal of the cosmetic Aqua Face and Bodypaint from the SuperStar brand.	Contains prohibited ingredient (Methylisothiazolinone)
151/CD/550.20.001	19/10/2018	Withdrawal of Wells Baby Face Cream cosmetic.	Contains undeclared allergen ingredients (Phenoxyethanol, Benzoic acid) and false claim
140/CD/550.20.001	26/09/2018	Withdrawal of Barral BabyProtect Face Cream.	Contains undeclared allergen ingredients (Phenoxyethanol, preservatives)
139/CD/550.20.001	26/09/2018	Withdrawal of INCA brand cosmetics.	Contains prohibited ingredients (Methylchloroisothiazolinone, Methylisothiazolinone)
132/CD/550.20.001	14/09/2018	Withdrawal of MoonGlow brand cosmetics.	Contains prohibited ingredients (colorants)
130/CD/550.20.001	14/09/2018	Withdrawal of PaintGlow brand cosmetics.	Contains prohibited ingredients (colorants)
094/CD/550.20.001	26/06/2018	Withdrawal of the cosmetic product Hydra-Suction Black Mask of the brand Pil'Aten.	Non-compliance with the Regulation (labelling)
057/CD/550.20.001	05/04/2018	Withdrawal of the cosmetic product "Day Protection SPF 10" of the brand Karin Herzog.	Contains prohibited ingredient (Methylisothiazolinone)
030/CD/550.20.001	15/02/2018	Voluntary recall of cosmetic products from the Plural brand.	Non-compliance with the Regulation (good manufacturing practices, safety evaluation, CPNP notification)
029/CD/550.20.001	15/02/2018	Withdrawal of the cosmetic product Tonic lotion, Leite de Colónia brand.	Contains prohibited ingredients (Sodium borate, Boric acid)

* No withdrawal from the market required.