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SOCIO-LEGAL CONSIDERATIONS IN ADVANCED THERAPY MEDICINAL PRODUCT REGULATION: A REVIEW OF THE EVALUATION LITERATURE

Abstract. *Advanced Therapy Medicinal Products (ATMPs) represent a pivotal advancement in healthcare, offering potential solutions for severe and life-threatening diseases. However, the dynamic landscape of ATMP development poses challenges in regulatory frameworks, necessitating comprehensive evaluation. This study aims to explore socio-legal perspectives on ATMPs, assessing risks and benefits within regulatory paradigms. A thorough literature review spanning 2009 to 2023 was conducted, synthesising empirical research to comprehend ATMP utilisation and regulatory approaches' impact on patient health. Employing multiple sampling strategies, 58 relevant studies were identified, with eight meeting inclusion criteria for qualitative analysis. Perspectives from clinicians, researchers, and industry experts underscored ATMPs' potential to address high unmet medical needs while highlighting concerns regarding clinical safety, efficacy demonstration, and long-term effects. Risk assessments highlighted uncertainties surrounding clinical safety, treatment benefits, and manufacturing consistency, underscoring the multifaceted nature of ATMP risk evaluation. The study advocates for a nuanced regulatory approach, allowing sufficient time to address uncertainties and ensure patient safety. In conclusion, while ATMPs offer promising therapeutic avenues, their complexity necessitates hard regulatory frameworks informed by empirical evidence and stakeholder perspectives to optimise patient outcomes and mitigate potential risks associated with ATMP utilisation. The article proposes amendments to EU legislation regarding the manufacturing practice of ATMP, and further incorporation of these changes into Ukrainian legislation.*

Keywords: *advanced therapy medicinal products, patient health impact, orphan diseases, risk assessment methodology, clinical safety uncertainties.*

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СОЦІАЛЬНО-ПРАВОВІ АСПЕКТИ РЕГУЛЮВАННЯ ЗАСОБІВ ПЕРЕДОВОЇ ТЕРАПІЇ: ОГЛЯД ОЦІНОЧНОЇ ЛІТЕРАТУРИ

Анотація. *Лікарські засоби передової терапії (ATMP) є важливим досягненням у сфері охорони здоров'я, що пропонує потенційні рішення для лікування важких і небезпечних для життя захворювань. Однак, стрімкий процес впровадження ATMP створює проблеми в регуляторному аспекті, що вимагає всебічної оцінки. Це дослідження має на меті проаналізувати ATMP з соціально-правової перспективи, оцінити ризики та переваги в рамках регуляторних механізмів. Було проведено ретельний огляд літератури за період з 2009 по 2023 рр., в якому узагальнено емпіричні дослідження для розуміння впливу використання ATMP та регуляторних підходів на здоров'я пацієнтів. Використовуючи декілька стратегій вибірки, було визначено 58 релевантних досліджень, вісім з яких відповідали критеріям включення для якісного аналізу. Погляди клініцистів, дослідників та галузевих експертів підкреслили потенціал ATMP для задоволення високих незадоволених медичних потреб, водночас висвітливши занепокоєння щодо клінічної безпеки, демонстрації ефективності та довгострокових наслідків. Оцінки ризиків виявили невизначеності, пов'язані з клінічною безпекою, терапевтичними перевагами та стабільністю виробництва, що підкреслює багатогранність проблематики оцінювання ATMP. Автори дослідження виступають за виважений регуляторний підхід, який надасть достатньо часу для усунення невизначеностей і забезпечення безпеки пацієнтів. Таким чином, хоча ATMP пропонують багатообіцяючі терапевтичні можливості, їх складність вимагає жорсткої регуляторної бази, що ґрунтується на емпіричних даних та поглядах причетних сторін, для оптимізації результатів лікування пацієнтів та зменшення потенційних ризиків, пов'язаних із застосуванням ATMP. У статті пропонується внесення змін до законодавства ЄС у сфері виробничої практики досліджуваних лікарських засобів, а також подальша інкорпорація цих змін в українське законодавство.*

Ключові слова: *лікарські засоби передової терапії, вплив на здоров'я пацієнтів, орфанні захворювання, методологія оцінки ризиків, невизначеності щодо клінічної безпеки.*

INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs), an advancement in healthcare, offer potential solutions for the treatment of severe diseases.Their novelty, complexity, and diversity necessitate tailored regulatory frameworks, addressing patient risks, benefits, and long-term safety uncertainties [1].

The European Medicines Agency's «CAT quarterly highlights and approved ATMPs» (January 2023) reveals a dynamic ATMP approval landscape from 2009 to 2022 [2]. Initial progress was limited, with only two approvals, including Glybera, the first Gene Therapy Medicinal Product (GTMP) [3]. Subsequent years witnessed a significant increase, reaching 24 approvals by December 2022, with expectations of further growth. Despite concerns about a slight decline in European clinical trials, the EU made substantial progress in ATMP approvals [4]. Growing pharmaceutical manufacturing investment in Europe created a favorable environment for ATMP development [5].

The December 2021 introduction of the European Commission's Health Technology Assessment (HTA) Regulation aims to streamline ATMP evaluation, enhancing patient access [6]. According to this regulation, ATMPs will have to undergo joint clinical evaluations, which will allow to abandon the procedures used during the HTA at the national level, avoiding duplication and discrepancies.However, the increasing trend in ATMP approvals raises concerns about evidence quality, long-term effects, cost-effectiveness, and ethical considerations.

Given the growing trend of approval of new ATMPs, the EU has some concerns about the quality of the evidence base, long-term effects, cost-effectiveness and ethical implications, as reported by scientists such as Elsallab et al [7]. The regulation of ATMPs, poses unique challenges that require careful consideration of the appropriate regulatory approach. It is necessary to know which approach will be more effective when taking into account the nature of ATMP, its therapeutic benefits and risks. For example, hard regulation typically involves strict rules and directives within the framework of legal and ethical constraints on individual activities, while soft regulation relies more on guidance and stakeholder engagement without restricting the freedom of action of the market economy and scientific freedom to innovate [8]. Finding the right balance is crucial to fostering innovation and ensuring patient safety. Therefore, the literature review in this section aims to explore comprehensively the socio-legal perspectives on ATMPs, with a particular focus on identifying and analysing risks and benefits.

A systematic approachwas adopted to review studies that have assessed the use of ATMPs in the context of their risks and benefits [9]. The review begins with a description of how searching for studies across the spectrum of ATMP use was undertaken. After a qualitative analysis of the authors' views, assessment is made in light of the reviewed evidence as to which regulatory approach to ATMPs appears most effective in balancing risks and benefits.

The review was not limited to specific categories of ATMPs, but included stakeholder perspectives on each of the four categories of ATMPs defined in Regulation 1394/2007/EC. This study delves into socio-legal perspectives on ATMPs, evaluating risks and benefits in regulatory frameworks. A comprehensive literature review examines stakeholder views, emphasizing an understanding of ATMP use and regulatory approaches for their impact on patient health. The review, spanning all ATMP categories, aims to ascertain the efficacy of «hard» or «soft» regulatory approaches in balancing risks and benefits.

1. MATERIALS AND METHODS

Inclusion and exclusion criteria. This review includes the risks and benefits of using ATMP for therapeutic purposes. It excludes studies of other medicines or therapies that do not involve ATMPs. The review focused exclusively on empirical studies that used data collected from experiments or observational studies and was not limited to specific categories of ATMPs, but included the views of authors and other stakeholders on each of the four categories of ATMPs defined in Regulation 1394/2007/EC.

The inclusion criteria cover the period from 2009 to 2023, which ensures an up-to-date understanding of perspectives. The inclusion period could not predate 2007, as this is when ATMPs were legally approved in the EU, namely by Regulation 1394/2007/EC, which was adopted and entered into force on 30 December 2007. However, in order to evaluate the benefits and risks not on a theoretical level, but in terms of direct practical use for therapeutic purposes and understanding the real consequences for patients, it is necessary to start from the date of the first use of a drug approved as an ATMP, so the starting period from 2009 was selected, as this is the year when the first ATMP, Chondrocelect, was approved.

Published full articles from peer-reviewed journals were under consideration. Consultation with Information Skills Librarians from London South Bank University (LSBU) Southwark Campus Library helped to improve the search for relevant literature, which allowed the review to be as comprehensive as possible. Given the limited number of methodologically sound studies identified during the search phase, the inclusion of studies in this systematic review was not limited to randomised, controlled trials and studies that used data at the local (e.g. district), regional, state, national and international levels.

Search for Relevant Studies. Table 1 lists the databases canvassed. These covered the fields of healthcare, law, politics and administration, and economics. In addition, the British Library databases were used. In particular, Information Skills Librarians from the LSBU Southwark Campus Library helped to interrogate the British Library's online databases to access research that was not available in the LSBU database.

Table 1. List of Databases Searched in the Review

Academic Search Complete
APA PsycArticles
APA PsycInfo
Business Source Premie
CINAHL Complete
CORE
LexisNexis
Westlaw
MEDLINE
PubMed
Regional Business News
Sage journals

ScienceDirect
SocINDEX with Full Text
SpringerLink
Taylor & Francis Online
The Allied and Complementary Medicine Database
Trip Medical Database
Wiley Online Library

To identify studies that were not found through the database search, the references of all collected articles were searched and relevant papers that met the selection criteria were also used as a source of potential studies.

A number of UK and international websites covering the use of ATMPs were also searched, for example, European Medicines Agency https://www.ema.europa.eu/en; Labiotech https://www.labiotech.eu; European Federation of Pharmaceutical Industries and Associations https://www.efpia.eu; Legislation.gov.uk https://www.legislation.gov.uk [10; 11; 12; 13].

The keywords used in database searches are listed in Table 2. To narrow the search, the keywords in combination (e.g., a combination of «ATMP» and «risks» and «empirical research») were utilised, or to facilitate the search process, the keywords were replaced with their abbreviations, synonymous meanings, generic (subclass) names (e.g. «ATMPs» or «GTMPs» or «TEPs» or «SCTMPs» or «gene therapy medicinal products» or «tissue-engineered products» or «somatic cell therapy medicinal products» for the search «Advanced therapy medicinal products» in combination with the words «hazards» or «threats» or «uncertainties» or «risks», etc.)

Table 2. Keywords Used in the Search

Advanced therapy medicinal products
ATMP
ATMPs
Benefits
Empirical research
Gene therapy medicinal products
GTMPs
Hazards
Opinions
Perspectives
Risks
SCTMPs
Somatic cell therapy medicinal products
TEPs
Threats
Tissue-engineered products
Uncertainties
Views

If a minimal number of results were obtained from keyword searches containing multiple terms (e.g. «ATMP» and «threats» and «empirical research»), the number of terms was either reduced or searched for the terms independently in separate searches.

The search process was iterative, starting with broad search terms such as «ATMP» and «empirical research» and then moving to more detailed search terms. Although the early stages of the search yielded a large number of results (most of which were irrelevant), the broad search approach was found to be the most comprehensive approach, followed by a thorough sifting process to ensure that the articles retrieved met the pre-defined inclusion criteria.

The assessment of eligibility was initially based on a careful review of the abstracts; however, when the abstract did not provide sufficient information to determine the eligibility of the study, the full text was obtained.

To collect and evaluate the views of the research authors, 4 sampling strategies were used according to the Typology of sampling strategies in qualitative inquiry, namely «Maximum variation sampling» to document a variety of views and identify important common patterns; «Theory based sampling» to find examples of a particular theoretical concept of the benefits or harms of ATMP and thus develop and explore this concept; «Stratified purposive sampling» to illustrate subgroups of individuals (e.g. respondents) in terms of their position on ATMP and to make comparisons between these subgroups; «Criterion based sampling» to find and characterise those cases (views/positions) that meet a certain criterion, for example, to find those views that are relevant to support only a «hard» regulatory approach to ATMP [14].

2. RESULTS AND DISCUSSION

Initially, 58 studies were identified, and 8 met inclusion criteria for a qualitative review of ATMPs. This review offers a comprehensive exploration of ATMP regulation, covering risks and benefits. However, limitations in research design, like small sample sizes and the absence of significance testing, affect result reliability.

Selected eight studies, encompassing 100 participants, examined perspectives from clinicians, laboratory researchers, company representatives, and academics involved in the field of Regenerative Medicine (RM). They focused on ATMPs' impact on patient health.

The beneficial impact of ATMPs is primarily seen in their potential to repair damaged or diseased tissue, which distinguishes them from drugs and therapeutic medical devices [15] and their use in serious and life-threatening diseases, in particular the treatment of orphan diseases, and mainly serving patients with high unmet medical needs [16; 17].

In general, authors from the clinical field note that the main therapeutic areas include haematological malignancies, monogenic diseases and cartilage diseases [16]. However, other clinicians have also argued for the important potential of ATMP to treat a much wider range of diseases including various forms of cancer, visual impairment, spinal muscular atrophy, autoimmune conditions, hereditary diseases, diabetes, neurological diseases (including Parkinson's, Alzheimer's, Huntington's disease, heart disease, etc.),

and thus has the potential to drastically change patient care in the 21st century [15; 18; 19; 20].

In terms of the main therapeutic focus, clinician-researchers Bengt Jönsson et al note that many ATMPs are aimed at severe conditions that cannot be effectively treated, but these diseases affect only a small proportion of patients [21]. Nevertheless, it is worth considering that even if the number of people in the world suffering from such conditions is small, this does not mean that they are not entitled to better treatment (if the current treatment is not effective) and gives rise to a moral, if not necessarily legal, obligation to seek ways to cure them or improve their health or quality of life.

Several concerns related to risks to patients' health were identified in the studies: uncertainty about the clinical safety of the product lack of treatment benefits lack of or insufficient demonstration of efficacy, risk of serious side effects for the patient (toxic effects, tumourigenicity, difficulties with biodistribution and engraftment), uncertainty about the long-term benefits, risks associated with immunogenicity**,** risk of different patient responses to a particular drug [15;16;18;21;22]. The analysed studies did not consider other risks, for example, to the environment or other people.

In particular, some authors noted that the uncertainty of clinical safety is associated with the risks of bias and uncertainty about the size of clinical effect estimates, which stems from the specifics of ATMP clinical trials (more non-randomised, non-blinded studies, involving a much smaller number of patients) [16;21].

For example, in the study by Hofer, M. P et al, cited by Bengt Jönsson et al, 49% of the main objections of the Committee for Medicinal Products for Human Use to marketing authorisation were related to the clinical safety of the product (27% – the risk of serious side effects for the patient) [21]. Despite this, 104/157 marketing authorisations were granted. However, the limitation of this study is that it refers to orphan products in which the share of «biologics» (which includes ATMPs) was minimal compared to both «new chemical entity» and «known substances».

For a more comprehensive understanding of ATMP risk assessment, it is also worth noting the work of the authors, who, despite the quantitative limitations of their study of comparison medicines, note that the success rate for orphan ATMPs is 59%, but for non-orphan ATMPs the chances of success are only 50% [16]. Thus, it can be argued that authorisation can be granted if the risks associated with ATMPs, especially orphan ATMPs, are borne by the patient.

ATMPs such as GTMPs often face the following objections related to insufficient demonstration of efficacy, as well as claims of efficacy based on non-specific post hoc analyses [16]. For example, the importance of collecting evidence of efficacy and safety throughout the life cycle of a medicinal product is emphasised by Bengt Jönsson et al and Carolina Iglesias-Lopez et al as essential to determine whether a marketing authorisation should be maintained, modified, suspended or withdrawn [16; 21].

However, the question arises as to how the risks of ATMPs not being effective can be properly assessed in the absence of a comparable drug. Indeed, another author reports

that, mainly due to the frequent lack of alternative medicines (for comparison with ATMP) in the treatment of similar diseases, it may be difficult to collect clinical evidence to assess the risks of ATMP [21]. Other clinician-researchers emphasise that the small sample size of approved drugs undergoing HTA, due to their limited number, has led to recommendations for the same drug differing in different jurisdictions [17]. This, in turn, creates new risks to the patient's health and life when the therapeutic procedure does not fully take into account all aspects of the nature of the drug, and also affects the effectiveness of the ATMP itself.

An important component is the use of a properly thought-out and unified methodology for risk assessment, in which the theoretical aspect is as close as possible to the practical one. Thus, in the study by John Gardner and Andrew Webster, conducted in the UK, clinicians were particularly aware of the need for pragmatic negotiations between clinicians and regulators to develop quality and safety protocols that more fully take into account the practical aspect of risk assessment in the clinical use of ATMPs [15].

A similar position on a more individual and nuanced approach is also held by such authors as Carolina Iglesias-Lopez et al, who in a study of the risks of serious side effects of ATMP for patients due to the unique nature of ATMP stated that conventional approaches to toxicity testing are not adequate means of risk assessment [16]. The instability and potential tumorigenicity of living cells and tissues, especially those derived from pluripotent cells, creates additional safety concerns [15].

For example, in the case of the GTMP called Glybera, proof of concept in animal studies failed to translate effectively into consistent pharmacokinetic and pharmacodynamic properties in the clinical setting [16]. Similarly, certain toxic effects associated with CAR T cell therapy, such as cytokine release syndrome and neurological toxicity in tumour/non-tumour events, have not been fully predicted by non-clinical studies [16]. Biodistribution and engraftment pose additional risks that require careful evaluation in animal models that mimic the clinical route of administration [22].

The number of patients for the types of diseases targeted by many ATMPs is small, resulting in a lack of robust clinical trial evidence, but when it is possible to extend treatment to a wider population, manufacturing challenges make it difficult to ensure consistency between batches [15; 16; 21; 23]. This is because the expansion of production does not allow for a proper assessment of the comparability between the different manufacturing processes that existed before the expansion and those that existed after the expansion. This leads to the need to collect additional clinical data or to question the validity of previously collected data (e.g. ATMPs: Kymriah and Zolgensma), which in turn can change later versions of a particular ATMP [16]. Consequently, later patients may not receive the same medicinal product as patients in phase 2 and 3 trials.

Thus, in addition to the side effects that may be detected due to the extension to a wider, more diverse population, the efficacy of the drug may be affected, and potentially even small changes in the drug may pose new risks to patients.

Another feature of ATMPs is their arguably sustained effect. While scientists such as Carolina Iglesias-López et al, Jesper Jørgensen & Panos Kefalas note that one or a limited number of ATMP treatments (e.g. GTMP Glybera) can potentially provide benefits for the patient's lifetime, should refer to the position of other authors ten Ham et al and note such statements as a form of extrapolation of evidence to model the benefits of treatment that are not fully proven [18; 23]. Thus, these scientists rightly criticise those statements that do not substantiate the claims of a sustained (therapeutic) effect that exceeds the available clinical data [17]. In addition, if the sustained effect does not justify itself, treatment cannot be stopped for the patient in this case (due to the side effects of treatment interruption).

In summary, despite the controversy of HTA Regulation, which aims to speed up the process of ATMP approval, and the risks that arise, it should be recognised that this will first allow not only to avoid duplication of evaluation procedures but also to achieve convergence, unification of testing requirements based on joint clinical assessments. For example, the excessive scope of comparative studies increases the discrepancy in the results of ATMP evaluation, which in turn creates safety and efficacy risks when launching the production of the latter [24].

As mentioned earlier, before the implementation of the HTA Regulation, which will be effective as of January 2025, the assessment process follows a differentiated approach. This approach involves assessments conducted both at the national level and within the European Union. This, in turn, posed a risk not only of a dubiously evaluated ATMP entering the market, but also of precedents for qualifying medicinal products as illegal in the EU common market, even though a valid marketing authorisation for a particular medicinal product was granted under national law [25].

However, on the other hand, with the reduction of the number of verification procedures, it becomes expedient to regulate a more thorough evaluation of ATMPs within the framework of HTA, i.e., the use of a «hard» regulatory approach, which may slow down the pace of ATMP approval, but increase the evidence base of the latter's proven effectiveness.

One of the possible options for using a «hard» regulatory approach in the framework of ATMP application is, first of all, changes in the manufacturing process of ATMP, in particular, first at the EU level (for example, the " Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products», introduced on June 26, 2018), and then at the level of national legislation [26].

For example, a broader utilisation of the risk-based methodology outlined in the Guideline on the risk-based approach by annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products. Critical parameters within the manufacturing process should be prioritised, identifying which process steps and working conditions are essential for achieving the desired product quality, and determining the necessary conditions to attain this objective [27].

Paula Salmikangas et al. suggest that this approach will facilitate a comprehensive examination of the crucial process stages It will also facilitate the identification of the optimal conditions for these stages, thereby ensuring the development of a consistent product eligible for marketing authorisation [28].

The next step involves mandating the use of multiple analytical methods for quality control. Specifically, this entails employing several independent analytical methods for characterisation to assess a single ATMP. These methods must demonstrate suitability for intended use during early development and be fully validated upon submission of the marketing license [28]. Additionally, in case of production changes, employing diverse analytical tools enables a more robust comparison between previous and new drugs.

When working with cells as crucial components of ATMPs in autologous settings, it's essential to extend beyond standard scientific requirements. Defining the specifications for each type of ATMP should include representative cells from healthy donors, especially considering the potentially limited availability of patient material [28]. This can be achieved by combining in vivo and in vitro methodologies to demonstrate biological activity, and to determine dosage and regimen selection [29]. To enhance control over the viability of autologous starting materials, it's preferable to utilise allogeneic primary cell sources [30]. Additionally, specialised cell banks should be established for the storage of such biomaterial [31]. Stockpiling allogeneic cells can further aid in reducing variability between donors, thereby minimising variability in treatment outcomes [32].

Regarding the manufacturing process, biological starting materials like growth factors and cell lines undergo initial risk analysis per the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products EMA/CAT/80183/2014 [29]. These materials, known for introducing product quality variability, necessitate thorough examination. Therefore, this initial risk analysis should also be extended to other ATMPs to guide efforts in pharmacovigilance mitigation.

In light of these recommendations, it is feasible to enact the proposed amendments to Ukrainian national legislation, specifically regarding the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products 42–4.9: 2020 [33]. Additionally, it is essential to enhance collaboration between scientific institutions, pharmaceutical manufacturers, and international organisations, such as the European Medicines Agency. This collaboration would not only facilitate access to scientific and technical support and advice for drug developers [34] but also drive further enhancements in ATMP assessment procedures [35].

CONCLUSIONS

This comprehensive review of ATMPs emphasizes their complexity, highlighting the need for a nuanced regulatory strategy to address risks and benefits effectively.

Concerning the balance of risks and benefits in terms of the impact on patients' health, it should be noted that both risks and health benefits are conditional, as they are

mainly aimed at the long-term perspective. It cannot be said with assurance that the need for long-term treatment will be fully eliminated, or that the quality of life will improve, or that the rate of disease progression will slow down. Similarly, there is no complete certainty that medicines will necessarily lose or reduce their effectiveness, or that serious side effects will occur for patients. Therefore, even if the current use of ATMPs is particularly effective compared to other conventional medicines, due to the «novelty» feature and all the consequences that it entails (e.g., insufficient evidence base), it will not be possible or appropriate to determine whether the benefits outweigh the risks or vice versa.

Therefore, a hard regulatory approach to balance the benefits and risks of ATMPs would appear proportionate. It provides the necessary time to address uncertainties regarding health effects on patients effectively.

Several amendments are suggested to the EU Good Manufacturing Practice specific to Advanced Therapy Medicinal Products to enhance assessment procedures. These proposed changes are intended to be integrated into Ukrainian legislation, specifically, Good Manufacturing Practice specific to Advanced Therapy Medicinal Products 42–4.9:2020. Furthermore, it is crucial to foster stronger collaboration between pharmaceutical manufacturers and international organisations.

RECOMMENDATIONS

The article's scientific value lies in its comprehensive examination of Advanced Therapy Medicinal Products (ATMPs) and their impact on patient health. By synthesizing empirical research and diverse stakeholder perspectives, it offers valuable insights into ATMPs' potential to address medical needs while addressing concerns about safety and efficacy. Overall, the scientific value of the article lies in its contribution to understanding the complexities of ATMP utilization and the development of hard regulatory frameworks to ensure patient safety and efficacy in healthcare interventions. The article is recommended for legal professionals in the field of law, including scientists, teachers and students, practitioners and all others who are interested in finding and applying new approaches to research on the legal regulation of innovative medicines.

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